Focus on Chronic Disease through Different Lenses of Expertise

Towards Implementation of Patient-Focused Decision Support Preventing Disability: The Example of Early Rheumatoid Arthritis

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At the Faculty of Arts and Science at Linköping University, research and doctoral studies are carried out within broad problem areas. Research is organized in interdisciplinary research environments and doctoral studies mainly in graduate schools. Jointly, they publish the series Linköping Studies in Arts and Science. This Thesis comes from the Swedish Institute for Disability Research at the Department of Behavioural Sciences and Learning.

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In memory of my grandfathers;

Sigvard Karlsson (1919-1994)

and

Tore Dahlström (1918-2008)
Abstract

Introduction: Rheumatoid arthritis (RA) is a chronic inflammatory disease. Treatment strategies emphasize early multi-professional interventions to reduce disease activity and to prevent disability, but there is a lack of knowledge on how optimal treatment can be provided to each individual patient. **Aim:** To elucidate how clinical manifestations of early RA are associated to disease and disability outcomes, to strive for greater potential to establish prognosis in early RA, and to facilitate implementation of decision support through analyses of the decision-making environment in chronic care. **Methods:** Multivariate statistics and mathematical modelling, as well as field observations and focus group interviews.

**Results:** **Decision support:** A prognostic tree that predicted patients with a poor prognosis (moderate or high levels of DAS-28) at one year after diagnosis had a performance of 25% sensitivity, 90% specificity and a positive predictive value of 76%. Implementation of a decision support application at a rheumatology unit should include taking into account incentive structures, workflow and awareness, as well as informal communication structures. **Prognosis:** A considerable part of the variance in disease activity at one year after diagnosis could be explained by disease progression during the first three months after diagnosis. Using different types of knowledge – different expertise – prior to standardized data mining methods was found to be a promising when mining (clinical) data for new patterns that elicit new knowledge. **Disease and disability:** Women report more fatigue than men in early RA, although the difference is not consistently significant. Fatigue in early RA is closely and rather consistently related to disease activity, pain and activity limitation, as well as to mental health and sleep disturbance. **Conclusion:** A decision tree was designed to identify patients at risk of poor prognosis at one year after the diagnosis of RA. When constructing prediction rules for good or poor prognosis, including more measures of disease and disability progressions showed promise. Using different types of knowledge – different lenses of expertise – prior to standardized data mining methods was also a promising method when mining (clinical) data for new patterns that elicit new knowledge.
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I.
Dahlström Ö, Timpka T, Skogh T, & Thyberg I. Prognostic components and predictive modelling of prognosis in early RA (manuscript)

II.

III.
Thyberg I, Dahlström Ö, & Thyberg M. Factors related to fatigue in women and men with early rheumatoid arthritis (the Swedish TIRA-study) (submitted)

IV.
Abbreviations
ACPA anti-citrullinated protein/peptide antibodies
ACR American College of Rheumatology
anti-CCP anti-bodies to cyclic citrullinated peptides
CDSS clinical decision support system
CRP C-reactive protein
CSCW computer supported cooperative work
DAS-28 28-joint count disease activity score
DMARD disease-modifying anti-rheumatic drug
ESR erythrocyte sedimentation rate
EULAR European League of Arthritis and Rheumatism
HAQ health assessment questionnaire
ICD-10 International Classification of Diseases, 10th revision
ICF International Classification of Functioning, Disability and Health
ICIDH International Classification of Impairment Disability and Handicap
MLR Multiple linear regression
NSAID non-steroidal anti-inflammatory drug
PCA principal component analysis
PGA physician's global assessment of disease activity
PPV Positive predictive value
RA rheumatoid arthritis
RF rheumatoid factor
ROC Receiver operating characteristics
TIRA Tidiga Insatser vid Reumatoid Artrit (Early Interventions in Rheumatoid Arthritis)
TNF tumor necrosis factor
ULR univariate logistic regression
WHO World Health Organisation
Outline
This thesis has its origins in three academic disciplines: medical informatics, disability research (which is the formal subject of the thesis), and rheumatology. In the first section of the thesis these three areas of research are introduced, together with other important and related subjects. The outline of this thesis is as follows. First medical informatics is described with a focus on clinical decision support. Second, the theoretical framework in relation to disability and rheumatoid arthritis is briefly outlined. Continuing with disability, models of disability and International Classification of Functioning Disability and Health (ICF) are described in two consecutive sections as framework and terminology for describing disability. Then rheumatoid arthritis (RA) is described as disease, and from a disability perspective including its relation to the framework provided by the ICF. Interventions in RA include medical interventions and rehabilitation initiatives. Treatment goals, treatment strategies and guidelines are followed by a section on prognosis.

After this introduction the aim of the thesis, including the aims of the studies conducted within the framework of the thesis, is described, followed by a methods section. Results are provided, and a discussion deals with the findings and their relationship to the aim of the thesis. Finally, a summary leads to the general conclusions of the thesis.

What is this box good for?
Boxes such as this one can be found on some pages in this thesis. The purpose of the boxes is to give non-scientific descriptions of or comments to different issues in the thesis. If you consider the texts in this thesis hard to understand, maybe a glance at these boxes will provide you with some cues.
Medical informatics

Medical informatics is the use and processing of data, information and knowledge in medicine, health care and public health (van Bemmel, 1998). Sometimes the term ‘health informatics’ is used since ‘medical’ can be considered too narrow. The term used in this thesis is ‘medical informatics’, since this is the most common term used, not the least in European settings.

Different areas in medical informatics as expressed by the subjects of the Medinfo2010 congress (www.medinfo2010.org) are, e.g. decision support systems, knowledge management, data and text mining, and electronic health records.

Some of the major aims in medical informatics as described by Haux (1997) are therapy, i.e. therapeutic interventions carried out virtually, early recognition and prevention, which has a large potential for disease prevention or early recognition, and knowledge-based decision support, i.e. formal representations of medical knowledge.

Medical informatics is interdisciplinary avant la Lettre, and is at best an ancillary discipline, existing for the benefit of health care (van Bemmel, 2008). This means first of all that research questions should preferably be based on clinical needs, and second that these needs should be met by using methods from multiple disciplines. In doing so, the interdisciplinary approach (as a characteristic) is a consequence of addressing complex research questions (van Bemmel, 2008). This collaborative approach between disciplines (Kuhn et al, 2008) in scientific, technological, personal and social problems (Altman et al, 2008) bridges gaps between different disciplines and cultures.

Why different lenses of expertise?

Lenses of expertise? Can lenses be experts in some manner? Well, let’s uses lenses as a metaphor! In this thesis the metaphor of lenses will be used to explain differences in things seen depending on prior knowledge, interest, motives, and other factors. Of special interest here are what experts in rheumatology see, or would be able to see if they were provided with some extra knowledge. Using this metaphor then, experts can be considered as having lenses that novices, such as you and I, don’t have; lenses of expertise! One idea is that if such lenses could be constructed, and provided a view that non-experts could understand, they could be loaned to anyone without prior knowledge and enable them to see really exciting or usable things.
Clinical decision support systems
Focusing on decision support with the help of electronic systems in clinical settings, i.e. Clinical Decision Support Systems (CDSS) the first studies on machines helping in the diagnostic process were published in the 1950s. The first computerized systems applied in clinical settings came late in the 1950s, and in the late 1960s a small breakthrough was made with the Leeds Abdominal Pain system. The system used Bayesian statistical theory and sensitivity, specificity, and disease-prevalence data for various signs and symptoms to calculate the probability of seven reasons for abdominal pain. The overall accuracy was 91.8% compared to an accuracy of 79.6% for the most senior member of the clinical team (Musen, et al, 2001; Mendonca, 2004; de Dombal et al, 1972). In 1966, the National Library of Medicine made an electronic version of Index Medicus, an index that helps to find medical papers, and called it the Medical Literature Analysis and Retrieval System. This system was later evolved into Medline. Medline uses Medical Subject Headings as a method for classifying papers by keywords (Hersh et al, 2001).

In the 1970s, cognitive approaches in the form of IF-THEN-rules, ‘production rules’, were introduced. MYCIN was a consultant system for infections, which from the rule-based approach helped physicians to find causes to some infections and suitable treatment (Musen, 1997). Few CDSSs were used in real-world clinical settings during the 1970s (Musen et al, 2001).

In the early 1980s, the MYCIN techniques were commercialized and met with a lot of enthusiasm, which by the end of the 1980s had decreased again. It proved to be very hard to develop and maintain the large rule-bases required to solve real-world problems (Musen, 1997).

In the 1990s, there was a separation between the ontologies and problem solving methods. OPAL was a tool that allowed oncologists to generate their ‘own version’ of the cancer therapeutic knowledge base ONCOCIN (Musen et al, 2001). Protégé is a more general tool in the same sense that it can be applied in a variety of different domains (Gennari et al, 2003).

Summarizing this brief historical overview, the development has gone from initially narrow and thereafter to wider expert systems during the 1970s and 1980s. During the 1990s
knowledge-based systems using different methods, and in the late 1990s combinations of different methods, came into focus.

Recently many different lines of research have been suggested and time will tell which lines will dominate. Striving to put 90% focus on the patient and 10% on the CDSS in clinical settings, and not the other way around, focus must be on making the CDSS ‘supportive’ and not ‘prohibitive’. There are lines of research that have switched focus from software and systems design to the interaction between systems and users (Kushniruk & Patel, 2004). Identifying standardized procedures and supporting them with guidelines is another area of research, nevertheless additional work is required before such guidelines will be used more in general, e.g. work on the standardization of formalism such as Health Level Seven (Jenders & Sailors, 2004).

Computer supported cooperative work
The area of Computer Supported Cooperative Work (CSCW) has meaningful insights to contribute here. First, taking incentive structures into account might prevent failures of the CDSS related to the CDSS not being compatible with issues at the institutional, organizational, or group level (Pratt et al, 2004; Orlikowski, 1992). It has been found that incentives of different hierarchical groups might compete with each other (Orlikowski, 1992). Incentives can cross through organization and small group levels in that there might be a mismatch between who does the work and who gains the benefits from it, e.g. if nurses feel that they have to put in extra work to use the CDSS, but only physicians gain from the CDSS.

Second, workflow reflects the process in an organization that coordinates the activities of different individuals to ensure the successful outcome of the work (Pratt et al, 2004). Clinical settings are of an exception-filled nature and this makes it difficult to build formal workflow models.

Third, awareness, as described by Dourish and Bellotti (1992) is an ‘understanding of the activities of others, which provides a context for your own activity’. Awareness of support in collaborative systems, e.g. an electronic medical record, greatly influences the efficacy of work (Pratt et al, 2004). Physical co-location is beneficial in many ways (Reddy et al, 2001). Different individuals can see both what and how other individuals are doing things and this makes it easy to ask others for explanations. Also knowledge from different individuals or
disciplines can be more effectively communicated. Using paper-based patient records makes clinicians aware of each others’ activities through interactions, such as when they meet each other in the corridor or at the bedside of a patient (Reddy et al, 2001). When co-location is not the case, the resulting loss of awareness can be helped by computer systems if awareness is incorporated into the system design. If information is decoupled from its representations (information can have different representations depending on the purpose of the user) it becomes accessible for people with different interests, concerns and work practices, e.g. people from different disciplines, and enables them to effectively work together (Reddy et al, 2001).

**Theoretical reflection – rheumatoid arthritis and disability**

Research can be conducted from a variety of perspectives, grounded in different philosophies of science, using a mixture of methods. The theoretical framework of this thesis is clarified in terms of and with examples from rheumatoid arthritis. It is mainly influenced by theory related to critical realism, see Danermark (2002) for an example with connections to disability research.

RA affects body functions, body structures, many different aspects of daily life activities, and possibly also participation in social events. Patients with RA have many different needs, and rheumatologic care is organized accordingly, including multi-professional approaches in clinical settings – physicians, nurses, occupational therapists, physiotherapists, receptionist nurses, secretaries (Petersson, 2005). The same is true for RA-related research – the research group in the Swedish TIRA project includes physicians, occupational therapists, engineers, and physiotherapists. Multi-professional cooperation is supported by the theoretical framework of this thesis, but it is extended by aiming for *inter-disciplinarity*.

Multi-disciplinarity exists, e.g. when a patient is seen by a physician, an occupational therapist, a physiotherapist all focusing on their discipline-specific areas. For instance, the physician may concentrate the optimal pharmacotherapy, the occupational therapist may concentrate on the best suited assistive devices to assist in cooking situations, the physiotherapist may focus on a training program to increase or maintain overall function and the social worker may support participation in society.
Inter-disciplinarity, in contrast, is, e.g. when the same professionals maintain their primary focus, but at the same time interact with clinicians from other disciplines, and patients, to better understand the overall living situation of the patient. A good response to pharmaceuticals prescribed by the physician may decrease inflammation and pain, thus making it possible for the physiotherapist to choose more possible exercises, and the assistive device prescribed by the occupational therapist may not be necessary anymore.

Inter-disciplinarity, as opposed to multi-disciplinarity, is in most clinical settings common practice, but to different degrees. In research, as compared to pure clinical settings, the situation is more multi- than inter-disciplinary due to many different aspects of academia, e.g. the academy’s organization according to faculties and disciplines. Working over disciplines is most often not facilitated by the physical separation of different disciplines, but nevertheless inter-disciplinary efforts, such as in the Swedish TIRA project, are more and more common.

One starting point is that a reality exists prior to our experience or knowledge of it, and therefore the characteristics of the reality determine how we gain knowledge of it. Two presumptions are nevertheless made:

First, the reality exists and is stratified into three domains. The empirical domain constitutes our experiences of what is actually happening, e.g. when an RA patient experiences inflammation in the form of swollen and tender joints. The actual domain constitutes all things that happen, irrespective of our experiences of it, e.g. a patient might have an inflammation in their joints even before he or she or a physician is able to experience it. The real domain is constituted by mechanisms with generative power. Research has the goal of discovering the mechanisms underlying empirically experienced manifestations.

Second, the reality is assumed to be ordered into hierarchical levels. A simple description is to divide the reality into biological, psychological and social levels. The levels can influence each other but each one has its own generative mechanisms. A person with early RA might be very depressed because of the uncertainty of what living with RA will be like. The mechanisms causing the inflammation in RA are determined by mechanisms at the biological level, but certainly have an effect on the psychological level (the experience of living with RA). Depression is however not determined by biological mechanisms, but by mechanisms at the psychological level, e.g. self-confidence.
Lenses above or under water?
The real world exists on different levels. Instead of talking about biological or sociological levels, we can take the example of a warm summer day at the beach. Being able to see different things on such days through different lenses for different situations would be suitable. Sunglasses would probably be necessary when you’re enjoying a cold drink and reading the latest book by J. K. Rowling. After a few minutes of reading, the sun will probably have made you really warm and you’ll want to have a swim and look at the beautiful fish under water. Then swim goggles would be suitable, enabling you to see the beautiful world under water.

When reading a book or swimming on a sunny day different lenses can help you focus on different things. We can think of experts in health care in the same sense. A physician might focus on your immunological system (compare this with watching fish under water) using all their prior experience and knowledge of its functions (think of their lenses of expertise as swim goggles) to decide which intervention is appropriate. An occupational therapist, in contrast, might focus on activities in daily living (compare this with reading J. K. Rowling) using all their prior experience and knowledge (think of their lenses of expertise as sunglasses) of how to assist daily living activities.

Mechanisms, as already mentioned, produce events. In interdisciplinary research, the focus is often on a phenomenon manifested empirically, and the aim is to find the mechanism(s) that produce(s) the phenomenon, e.g. when studying RA incidence in relation to smoking habits to examine whether smoking may be part of a causative mechanism. We can also start from assumed disease-causing mechanisms and study how they are manifested empirically, e.g. by assuming that inflammation has a direct effect on the erosion of bone and cartilage in patients with RA and examine how the erosion is manifested (Klareskog et al, 2009).

Context determines how generative mechanisms are manifested. Consider two women of the same age and with similar family situations, but where the first woman works as a telephone operator and the second is a cleaner. Both are early RA patients with swollen and tender joints in the upper extremities that especially affect hand strength. However, the generative (RA) mechanisms are manifested differently due to their ‘occupational contexts’. In other words, the telephone operator can (probably) more easily than the cleaner keep up with her occupation. Thus, the very same mechanisms constituting the disease are strongly manifested in the working-life of the cleaner, while they are not quite as clearly manifested in the working life of the telephone operator. Thus, even though body functions and body structures,
as well as activity limitations, can be considered to be similar for the two women, the participation restrictions on their daily working life, are manifested differently.

Empirical manifestations are not to be treated as causal proofs by themselves, but merely as tendencies. Taking the step from tendencies to causal explanation requires reasoning to rule out confounding factors or control of the confounding factors in a closed system experimental design. Closed systems are commonly assumed at the biological level, e.g. when evaluating immunological responses to certain pharmaceuticals in comparison to placebo, or when comparing novel and established pharmaceuticals (Sharp et al, 2000). These kinds of studies often use statistical analysis to draw conclusions out of small samples of corresponding populations. At the social level it is normally impossible to close a system, which implies research that acts in open systems, e.g. when examining prescription patterns of ‘biological’ pharmaceuticals in a Swedish community. A note here is that hardly any system can be treated as 100% closed since, in practice, no experiment can be repeated at the very same time in history at the exact same location. Rather the discussion of open and closed systems relates to how much the system of research interest can be expected to be closed or open, and thereby what can be assumed to be controlled and which confounders have to be ruled out by pure reasoning.

In clinical rheumatology settings as well as in rheumatologic research, inter-disciplinarity is often desirable. Thereby different levels of reality are to be included, and as an implication of this fact, different methods must be used to address concerns in clinical management and/or research questions. Integration, as an important aspect of inter-disciplinarity, cannot be achieved by finding a unifying method, but rather in the integration of the knowledge generated from different disciplines or different areas of research, using different methods, all gathered around a common phenomenon such as RA-related disability.

**Models of disability**

To understand the concept disability and the meaning ascribed to it in this thesis a historical view of the concept is motivated. Disability can be described in a variety of ways, and has been so during the twentieth century and into recent days. Here three different, but in literature agreed on, models will be briefly described.
The bio-medical model of disability focuses on body functions and body structures. Disability is here defined as an observable deviation from biomedical norms of structure or function, as a direct result of a disease, a trauma, or other condition (Bickenbach et al, 1999). This model has in recent history dominated our understanding of disability (Smart & Smart, 2006).

The social model of disability (or ‘socio-political perspective’) emerged in the 1970s developed by the Union of the Physically Impaired Against Segregation (formerly Disabled People’s International). It was a reaction to the exclusion of people from society according to their bodily functional or structural deficiencies (Masala & Petretto, 2008), and it was a reaction to what they called the ‘medical model of disability’. They defined impairment as ‘lacking part of or all of limb, or having a defective limb, organ or mechanism of the body’, and disability as a ‘disadvantage or restriction of an activity caused by a contemporary social organisation which takes no or little account of people who have physical impairments and thus excludes them from participation in the mainstream of social activities’ (Masala & Petretto, 2008). Similar approaches emerged in both the UK and the US. In the UK the focus was on social structures and their impact on people with disabilities, and in the US the focus was on social roles and attitudes. But common to both was that it is society that disables people.

The biopsychosocial model of disability, which is the focus of this thesis, is a synthesis of the bio-medical and the social model of disability (Bickenbach et al, 1999). It takes biological, psychological, as well as sociological considerations into account when considering disability. Disability can thereby be treated as caused by mechanisms at the biological level, e.g. a chronic disease such as rheumatoid arthritis. Disability can also be treated as caused by mechanisms at the psychological level, e.g. a person with rheumatoid arthritis who is so anxious about what living with rheumatoid arthritis will be like, that he or she is not able to do his or her full-time job anymore. And finally, disability can also be treated as caused by mechanisms at the sociological level, e.g. a person with rheumatoid arthritis who is anxious about what living with rheumatoid arthritis will be like making it hard to go to her or his full-time job, and who has a boss that cannot allow part-time work. To summarize, the biopsychosocial model of disability recognises all three aspects of disability and has the capability to show how mechanisms at different levels (biological, psychological, sociological) influence and cause what occurs at other levels, although the mechanisms cannot be reduced to another level (Danermark, 2002).
Disability models? Do I have to choose?

It might be confusing to think of different ‘models’ of something that in fact is a reality for most persons. Can the reality really be modelled? The awareness of different disability models is important when trying to express something about disability. First, what a person means by disability decides partly how he or she describes it. Second, the terminology used to talk about disability partly forms the view of it. So there is a bidirectional relationship between meaning and terminology. The example below will help shed light on this.

Imagine two persons watching a game of football. One is a real football-nerd (could be my supervisor) and the other may have no interest in sports at all (could be a colleague of mine). Asking these two persons for their views of the game would probably result in two very different sets of words used in their answers. The football-nerd would probably use words such as crosses and defending the box, while words like kicking and dashing would be used by the other person. So, a person’s knowledge and view of football determines the terminology they would use to describe it. This situation is much like the situation in disability research. From a biology perspective the terminology used would include words at the biological level (e.g. inflammation), and from a social perspective the terminology used

Disability in this thesis is treated as a phenomenon including persons in relation to biological, psychological, and social levels of the reality. Disability can therefore be a result of mechanisms at one or more levels of reality.

International classification of functioning disability and health – ICF

The WHO Constitution of 1947 requires that ‘Each Member shall provide statistical and epidemiological reports in a manner to be determined by the Health Assembly’ (Article 64) and ‘Each Member shall transmit upon the request of the Board such additional information pertaining to health as may be practicable’ (Article 65). Countries that are members of the WHO have traditionally reported population health in terms of mortality, e.g. by the International Statistical Classification of Diseases and Related Health Problems (ICD-10), but there has also been an increase in attention to the importance of reporting ‘non-fatal health outcomes’. Therefore, the WHO published in 1980 a tool for the classification of the consequences of disease, the International Classification of Impairments, Disabilities and Handicaps (ICIDH). Interestingly Philip Wood who revised the first version of the ICIDH at the 29th Assembly of the World Health Organization in May 1976 had a background in studies of rheumatoid arthritis (Masala & Petretto, 2008). He also (together with Elizabeth Badley) coordinated an analysis of an early model of disability by Amelia Harris and the Social
Survey Division in late 1960s together with colleagues at the Arthritis and Rheumatism Council Epidemiology Research Unit of the University of Manchester (Badley et al, 1978). The ICIDH was centralised around impairment, disability and handicap. Impairment was defined as ‘any loss or abnormality of psychological, physiological, or anatomical structure or function’. Impairments were in other words related to biomedical norms that are observable and measurable. Disability was defined as ‘any restriction or lack (resulting from an impairment) of ability to perform an activity in the manner or within the range considered normal for a human being’, implying a causal relationship from impairment to disability. In the same manner a causal relationship was assumed from impairment or disability to handicap, defined as ‘a disadvantage for a given individual, resulting from an impairment or a disability, that limits or prevents the fulfilment of a role that is normal (depending on age, gender and social and cultural factors) for that individual’ (Bickenbach et al, 1999). Measurements of the environment’s effects on individuals’ lives were not possible to describe within the ICIDH framework.

In 1993, a revision process of the ICIDH started. The first phase concentrated on the cross-cultural and linguistic applicability of the model and classificatory structure and language (Üstün et al, 2003). The second phase focused on questions of reliability and utility (Üstün et al, 2003). The final model was presented in May 2001. It was renamed International Classification of Functioning, Disability and Health (ICF). The title indicated the movement from the ‘consequences-of-disease’ approach, to a description of health domains.

ICF and ICD-10 are complementary since they together provide the tools for describing health states and experiences of health (ICF) and the codes for mortality and morbidity (ICD-10).

ICF is a framework for describing health conditions. It consists of five different components; body functions and structures, activities, participation, environmental factors, and personal factors (Figure 1). Environmental and personal factors are sometimes referred to as contextual factors, and activities and participation are sometimes referred to jointly. The relationships between the components in ICF are bidirectional (compared to the one-directional relationships in the ICIDH) (Stucki et al, 2002).
Health conditions can be described at different levels of detail, and in positive (body functions, activity, participation, or facilitators) or negative (impairments, activity limitation, participation restriction, or barriers) terms. The level of functioning or disability can also be notified. The ICF provides for a difference between capacity and performance. Capacity refers to a person’s functioning in a standard environment while performance refers to a person’s functioning (activity and participation) in a real world environment (environmental factors) (Üstün et al, 2003).

The ICF includes overall 34 codes on the first level, 362 codes on the second level, and 1424 codes on the third and fourth levels (ICF). Using ICF in a specific domain might be very time-consuming and complicated, and Stucki et al (2002) conclude that using ICF in its full version is hardly practical, and to be able to make comparisons of health conditions short-lists relevant for specific conditions, e.g. RA, are defined (Stucki et al, 2002). Core sets can be defined using ICF linking rules, (Cieza, 2005). Cieza (2005) brings some important clarifications to this process when separating the sometimes confusing use of terms such as functioning, quality of life, and health preferences. Functioning refers to limitations and restrictions related to a health problem. Quality of life refers to someone’s feelings about the limitations or restrictions, and health preferences refer to someone’s personal value given to these limitations or restrictions. When using ICF linking rules measures of functioning are...
ICF sounds Greek to me…

ICF is to my knowledge so far not available in Greek. However, ICF could be treated much like any language (could be Greek), but with the specific purpose of being useful when talking about health. ICF has been generated from existing opinions of how to deal with health (and disability), and has been imposed on persons dealing with health (and disability). In this way, it forces us to deal with health (and disability) from many different perspectives (through many different lenses of expertise).

chosen. That is, ICF provides a framework for ‘what to measure’ but does not tell us ‘how to measure’. This mapping of ‘what to measure’ to ICF terminology might also be a help in overcoming the ‘competition’ between assessment instruments and how to measure (Stucki, 2002).

Some of the critique of ICF, as expressed by Nordenfeldt (2003), is that ICF does not separate the capacity or possibility of an action from the will to make that action. What’s important to describe depends on what the describer chooses to describe.

Rheumatoid arthritis – chronic disease

RA is a disease characterized by chronic inflammation of synovial joints and subsequent permanent tissue damage, which often leads to disability of some kind (Scott et al, 2005). The term ‘rheumatism’ was used already in antiquity and was the term for any illness that weakened the body or afflicted the joints (Kimpel, 2005). In the seventeenth century the nosology of ‘arthritides’ started with the work of Sydenham, and RA was described for the first time in 1800 as a distinct entity by A.J. Landre’-Beauvais. The term ‘rheumatoid arthritis’ in reference to the disease was coined by A.B. Garrod in 1858 (Kimpel, 2005).

In a Swedish adult population the annual incidence of RA is estimated to 24/100000 (Söderlin et al, 2002) and the prevalence about 0.5% (Simonson et al, 1999). Several symmetrically swollen, tender/painful and stiff joints, primarily of the hands and feet, as well as fatigue and slight fever, are the most common symptoms reported by affected patients.

RA is described by the World Health Organisation (WHO) in ‘International Classification of Diseases’ (ICD-10) as a disease of the musculoskeletal system and connective tissues (WHO, 1997). A clinical diagnosis is usually concluded with a basis in the 1987 American College of
Rheumatology (ACR) classification criteria (Arnett et al, 1988) (Table 1). The criteria were established for classification purposes in prevalent cases of RA, and were not primarily intended to be used as a diagnostic tool. This fact implies that their utility may be limited in early RA, *i.e.* criteria 5 and 7 are generally not present at the time of diagnosis and/or initiation of treatment (Klareskog et al, 2009). The ACR criteria are nevertheless still used as the golden standard for the diagnosis of RA in research.

Table 1. The 1987 revised ACR criteria for classification of RA*.

<table>
<thead>
<tr>
<th>Criterion</th>
<th>Definition</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. Morning stiffness</td>
<td>Morning stiffness in and around the joints, lasting at least 1 hour before maximum improvement</td>
</tr>
<tr>
<td>2. Arthritis of three or more joint areas</td>
<td>At least 3 joint areas simultaneously have had soft tissue swelling or fluid (not bony overgrowth alone) observed by a physician. The 14 possible areas are right or left PIP, MCP, wrist, elbow, knee, ankle, and MTP joints</td>
</tr>
<tr>
<td>3. Arthritis of hand joints</td>
<td>At least 1 area swollen (as defined above) in a wrist, MCP, or finger PIP joint</td>
</tr>
<tr>
<td>4. Symmetric arthritis</td>
<td>Simultaneous involvement of the same joint areas (as defined in 2) on both sides of the body (bilateral involvement of PIPs, MCPs, or MTPs is acceptable without absolute symmetry)</td>
</tr>
<tr>
<td>5. Rheumatic nodules</td>
<td>Subcutaneous nodules, over bony prominences, or extensor surfaces, or in juxtaarticular regions, observed by a physician</td>
</tr>
<tr>
<td>6. Serum rheumatoid factor</td>
<td>Demonstration of abnormal amounts of serum rheumatoid factor by any method for which the result has been positive in &lt;5% of normal control subjects</td>
</tr>
<tr>
<td>7. Radiographic changes</td>
<td>Radiographic changes typical of rheumatoid arthritis on posteroanterior hand and wrist radiographs, which must include erosion or unequivocal bony decalcification localized in or most marked adjacent to the involved joints (osteoarthritis changes alone do not qualify)</td>
</tr>
</tbody>
</table>

* Criteria 1-4 must have been present for at least 6 weeks.

The aetiology of RA is the theory of the underlying factors and mechanisms initiating the disease. Although these mechanisms to a large extent remain elusive, the disease is believed to evolve in genetically susceptible individuals in whom environmental triggers cause immune reactions towards self-proteins. The relative contribution of genetic factors to the aetiology of RA is estimated at approximately 50% (MacGregor et al, 2000). Environmental and lifestyle factors constitute together the remaining 50% of risk not explained by genetic factors. Among environmental risk factors, cigarette smoking is the one most established (Klareskog et al, 2007). Other environmental risk factors suggested are silica dust, mineral oils, and airway exposures (Klareskog et al, 2009). Alcohol, in reasonable amounts, is a supposed protective environmental factor (Hazes et al, 1990; Pedersen et al, 2007; Källberg et
al, 2009). The pathogenesis is the description of the factors and mechanisms constituting the disease. In RA this involves functions in the immune system. Certain autoantibodies, i.e. antibodies directed against ‘self-antigens’ (native or modified macromolecules belonging to the organism) attract much interest in relation to RA, although they may occasionally occur also in other disease states and even in healthy individuals. Rheumatoid factor (RF) is a family of autoantibodies that occur frequently in RA and that are used to subdivide RA patients into ‘seropositive’ and ‘seronegative’ cases according to the 1987 ACR classification criteria (Arnett et al, 1988). Anti-citrullinated protein antibodies (ACPA), as measured using the anti-CCP test (test of antibodies to cyclic citrullinated peptides), have shown to be highly RA-specific, compared both to healthy controls (≥ 99%) and to other arthritides (≥ 95%) (van Gaalen et al, 1999; Zendman et al, 2006; van Venrooij, 2008). Tests of anti-CCP have also shown to be predictive of the disease course, and development and progression of joint damage (Kastbom et al, 2004; Forslind et al, 2004).

**Disability in rheumatoid arthritis using ICF**

From the disability perspective, RA is preferably described by the ICF framework. ICF in its full version is, however, not practical to use. To make it clinically relevant and practically manageable core sets have been constructed. These core sets include smaller and more relevant parts of the ICF framework according to the area applied. In RA, there are two core sets; one comprehensive and one brief core set (Stucki et al, 2004).

The ICF core sets for RA were created through a combination of a Delphi analysis, a systematic review, and empirical data collection (Stucki et al, 2004). The consensus procedure included 7 non-rheumatologist physicians, 7 rheumatologists, one nurse, one occupational therapist, and one physiotherapist. The comprehensive (brief) ICF core set included 76 (39) categories from the second level and 20 (no) categories from the third and fourth levels, and out of these 25 (8) body functions, 18 (7) body structures, 32 (14) activities and participation, and 21 (10) environmental factors (Stucki et al, 2004).

In a systematic review of measures and concepts in studies focusing on acute inflammatory joint disease Zochling et al (2006) showed that most of the concepts were linked to body functions (40.8%) and activity and participation (45.3%). Few were linked to body structures (10.6%) and very few were linked to environmental factors (3.3%). Of the environmental factors none were linked in more than 5% of the studies included.
The comprehensive ICF core set for RA was validated by Stamm et al (2005) in a qualitative study from the patient perspective. They identified 25 additional second level ICF categories to be added to the comprehensive ICF core set, e.g. fatigability and some aspects relating to side effects of drugs, e.g. psychic stability.

Uhlig et al (2007) validated the comprehensive ICF core set for RA and concluded that it had low to moderate reliability. Reducing the number of qualifiers was suggested, which raised the reliability. The mean intra-rater (inter-rater) agreement was 61% (55%) for body functions, 62% (55%) for body structures, 60% (51%) for activities and participation, and 52% (31%) for environmental factors. The low reliability might be due to the fact that the connection with the ICF category was made by two persons from different disciplines; one occupational therapist and one physiotherapist. The low reliability may be interpreted as a difference in focus and awareness between different disciplines. It is however possible that the very same clinicians would have a high inter-rater reliability after more experience of the ICF framework. The known low reliability when grading tender joints (Uhlig et al, 2000) might also have had an influence on the low reliability.

Most studies on living with musculoskeletal conditions do not use the ICF framework, since the framework was not introduced into the disability arena until 2001. For instance, Scott et al (2005) have described the consequences of early RA in three components similar to the ICF framework, although not identical. First physical consequences of arthritis, which relates to the component of body functions and structures, are described. Second, functional consequences of arthritis, which relates to the activity component, are outlined. Third, impact on society, which relates both to the component participation and the component environmental factors, is described. Interestingly patients and clinicians had quite different concerns about physical consequences (Table 2).
Table 2. Major concerns in RA related to ICF components (from Scott et al, 2005).

<table>
<thead>
<tr>
<th>Consequences / ICF-component</th>
<th>Major concerns</th>
<th>Comment</th>
</tr>
</thead>
<tbody>
<tr>
<td>Physical / Body functions and structures</td>
<td>Pain*</td>
<td>Dominant concern</td>
</tr>
<tr>
<td>Psychological impacts*</td>
<td>Has relation to pain</td>
<td></td>
</tr>
<tr>
<td>Fatigue*</td>
<td>Dominant factor in determining the quality of life (Suurmeijer, 2001)</td>
<td></td>
</tr>
<tr>
<td>Remission†</td>
<td>Key therapeutic target.</td>
<td></td>
</tr>
<tr>
<td>Disease activity†</td>
<td>Closely linked to other symptoms, e.g. pain.</td>
<td></td>
</tr>
<tr>
<td>Progressive joint damage†</td>
<td>Early DMARD key factor in determining radiological progression. Connection with inflammation.</td>
<td></td>
</tr>
<tr>
<td>Functional / Activity</td>
<td>Activity limitations linked to joint damage</td>
<td>Disability, linked to joint damage, has a relation to activity limitations, and is mainly a concern in ‘long-term’ RA. In early RA it is unclear what factors are of major concern.</td>
</tr>
<tr>
<td>Societal / Participation and Environmental factors</td>
<td>Costs (monetary and time)</td>
<td>In early phases of RA friends and families bear a majority of costs. In later phases of RA society bears an increased load precipitated by social care costs and interventions (‘biological’ DMARDs might, although expensive, change this).</td>
</tr>
</tbody>
</table>

* Major concerns of patients. † Major concerns of clinicians.

**Interventions**

**Medication**

Medication in early RA is mainly one of three kinds (Lambert, 2008) and is used for two main purposes, i.e. to reduce pain or to primarily interfere with the inflammation process and thereby to reduce consequences such as tissue destruction, pain, fatigue, stiffness, activity limitations and general well-being.

**Reduction of pain**

*Non-steroidal anti-inflammatory drugs (NSAIDs)* and/or paracetamol are very commonly used drugs used as symptomatic treatment, primarily to reduce pain in RA (Lambert, 2008).

**Reduction of inflammation process**

*Disease modifying anti-rheumatic drugs (DMARDs)* modify immunological mechanisms and thereby the disease course of RA. They constitute a heterogeneous group of pharmaceuticals (Lambert, 2008) and can be used as single therapy or in different DMARD combinations. Due to its high efficacy and tolerability, Methotrexate is the most commonly used ‘traditional’ DMARD for RA treatment.
Traditionally, glucocorticosteroids were considered merely as efficient symptomatic drugs with rapidly appearing anti-inflammatory properties. However, the glucocorticosteroids have also been shown to halt the disease process and reduce juxta-articular bone destruction in RA (Svensson et al, 2005), and should therefore actually be regarded as DMARDs.

‘Biological’ DMARDs (biologics) are proteins or protein constructs that specifically target molecules of importance for immunological/inflammatory processes (Lambert, 2008). Many, but not all, biologics are monoclonal antibodies. One group of ‘biologics’ targets free or cell-surface exposed cytokines or cytokine-receptors, for instance tumour necrosis factor (TNF-) inhibitors (e.g. etanercept, infliximab, adalimumab, golizumab, and certolizumab), interleukin-1 targeted therapies (e.g. anakinra), and IL-6 targeted therapies (e.g. tocilizumab) Other biologics are directed against molecules exclusively exposed on certain cell types, e.g. rituximab, a B-lymphocyte depleting monoclonal antibody, and abatacept preventing co-signalling in the interaction between antigen-presenting cells and T-lymphocytes.

Rehabilitation

Rehabilitation can be understood as one of four health care strategies (Stucki et al, 2007):

- **Prevention** aims to maximize population health by preventing the occurrence of negative health conditions. This is not easily done in RA because of the uncertain aetiology, but there are some known environmental factors such as cigarette smoking (Klareskog et al, 2007), and more research on risk factors will make it possible to prevent RA by, e.g. vaccination in the future.

- **Cure** aims to ascertain survival by controlling the disease progress. This is partly the case in RA, although the state of full disease-control – remission – is debated (Pincus et al, 2006).

- **Rehabilitation** aims to optimize functioning by strengthening the resources of the individual, which is a relevant intervention provided for many persons after disease onset.

- **Support** aims to raise the quality of life by palliation of symptoms and by providing assistance. This strategy is often hard to separate from the rehabilitation strategy in clinical practice.

Examples of interventions facilitating activity and participation in daily living in long-term RA are assistive devices, surgery and physical exercise. Assistive devices are not to be considered as a treatment of the disease, but as a way to enhance the patients’ functional
ability enabling them to participate in real-life situations. Assistive devices are, e.g. orthopaedic footwear, personal care devices such as sock aid, and mobility devices such as a rolling walker (de Boer et al, 2009). Surgery is performed for instance to replace severely and permanently affected joints. In a cohort of early RA patients recruited 1985-1989 orthopaedic surgical procedures were performed in more than every second patient, and almost every fourth patient had at least one large joint replacement done (Kapetanovic et al, 2008). Long-term moderate or high-intensity exercise is beneficial for RA patients (de Jong & Vliet Vlieland, 2005; Brodin et al, 2008). Thus, it is important to consider the proper context and appropriate support for each patient (Swärdh et al, 2008), and patients with radiologic damage in large joints should not be encouraged to attend moderate to high-intensity weight-bearing exercise unless individualized to protect affected joints (de Jong & Vliet Vlieland, 2005).

**Multidisciplinary team care**
Multidisciplinary team care has been used since the 1950s in arthritis management (Vliet Vlieland et al, 2006b). The teams in RA traditionally consist of a doctor, nurse, physiotherapist, occupational therapist, and sometimes a social worker (Petersson, 2006). The role of the patient in the team-context has switched from a passive patient to an active person in the centre of the process (Petersson, 2006). A multi-disciplinary approach is, however, not available to all patients in all countries, and there are some studies that have shown that similar outcomes can be reached using other approaches (Vliet Vlieland et al, 2006b). Approaches other than multidisciplinary team care might be preferable in situations with limited funding. Three alternative models of care suggested by Vliet Vlieland et al (2006a) are the use of information technology and telemedicine, patient initiated care, and extended roles of health professionals. More studies on the role of team care are warranted (Petersson, 2005).

**The cycle of rehabilitation**
Rehabilitation management can be described as a cycle involving four intermittent steps in a rehabilitation cycle; assessment, assignment, intervention, and evaluation (Stucki, 2005). Assessment includes identification of patient state (problem), assignment is the assignment to health professionals and intervention principles, intervention refers to setting the goal to be achieved and specifying the intervention techniques and measures to be used, and finally evaluation is the evaluation of whether or not the goal set was reached (Stucki, 2005). This intermittent cycle is certainly true for RA management (Figure 2).
In the cycles of rehabilitation, different members of the multi-professional team together with the patient have common goals (‘to enable people with disabilities to lead the life that they desire’), and provide patient education with the aim of giving patients necessary strategies and tools for making daily decisions and for coping with disease (Vliet Vlieland, 2003). Treatment goals and treatment plans are often defined, evaluated and tuned at team conferences, which are important hallmarks in multidisciplinary team care (Vliet Vlieland, 2003). Although common goals are important, different professionals have foci regarding their profession-specific features. Hence, the rheumatologists might focus on controlling disease activity and prescribing effective pharmaceuticals. Physiotherapists might focus on improvement or restoration of body functions or structures (Taal et al, 2006). Occupational therapists might focus on facilitating and restoring patients’ functioning and activity in daily living, e.g. by comprehensive occupational therapy training of motor functions, or the prescription of assistive devices (Steultjens et al, 2002).
Castles in the sand?
The cycles of rehabilitation are much like a sunny day at the beach when you and two friends decide to build the largest sandcastle ever! Unfortunately you only have one bucket and one shovel. When building the sandcastle you and your friends will need to use three different strategies because of your equipment conditions; use the bucket, use the shovel, or just use your hands. Your common goal is to build a sandcastle (compare this with a rehabilitation team with the common goal of helping a patient to a good life). Getting more sand and piling it on the growing sandcastle can be done in three different ways (comparable with different strategies used by different professionals). Each time new sand is piled on the sandcastle (each time an intervention is made by a clinician) you must take into account the actions done by the others before (Maybe they finished the tower you were building while you went to get more sand, and adding more sand now would ruin everything?). Awareness of the strategies of your friends might be considerably useful when deciding where to empty your next bucket of sand.

Treatment goals
The goals in regarding treatment of early RA are not clearly specified and can differ between different clinicians and different patients. Remission is an often suggested aim, but what is meant by remission is not generally agreed upon. Some criteria of remission have been defined (see e.g. Pinals et al, 1981; Aletaha & Smolen, 2005a; Aletaha et al, 2005b), but this matter is still discussed (Pincus, 2006). Three ‘ultimate goals’ have been described by Smolen and Aletaha (2006a):

- relief of pain, stiffness and swelling
- prevention of newly evolving joint erosions and joint-space narrowing
- restoration of functional abilities.

Disease activity as measured by ‘disease activity score’ (DAS) is related to joint damage (Scott et al, 2003) and therefore achieving ‘minimal’ disease activity is often a relevant goal (e.g. Wells et al, 2005). Nevertheless, progression of joint damage might proceed even when disease activity measures are considered to be low (Smolen et al, 2006b).

Referring to Pincus (1997), Smolen and Aletaha (2006a) claim that only ‘no evidence of active disease’ should constitute the ideal situation. Such a state involves no swollen or tender joints and no progress of joint damage. Remission criteria can therefore be separated into clinical and structural remission (Smolen & Aletaha, 2006a). Clinical remission can be
defined as ‘no or minimal evidence of the inflammatory response’. Structural remission requires no further radiographic changes. Expressed slightly differently; the state of remission can include both the absence of activity and the absence of damage. Aletaha et al (2006) address remission from a functional perspective by dividing functional limitations into reversible and irreversible components. Consequently, there can be different opinions on what should be considered as remission in situations where patients are considered to be in clinical but not in structural remission, at least in cases where the absence of structural remission is associated with functional limitations.

Another issue is whether remission can be considered even if a patient is under medication. Smolen and Aletaha (2006a) see no reason for a definition of remission excluding medication. RA can be described as a dysregulation of normal cellular and molecular events. Such dysregulation might be persistent and medical treatment may therefore be required. The combination of such dysregulations and medical treatment might very well be associated with a state of clinical and/or structural remission.

**Treatment strategies**

Treatment strategies are the ‘paths’ that are supposed to lead to treatment goals. In the case of early RA, such ‘paths’ include pharmaceuticals, physical exercise programs, prescriptions of assistive devices.

Until the early 1990s, the main treatment strategy regarding pharmacological treatment in RA was to ‘go slow’, in line with the dictum of Hippocrates; ‘primum non nocere’ (first do no harm). In the early 1990s, there was a shift in medical treatment strategies by advocating early ‘aggressive’ intervention with DMARDs. The aim was to arrest the disease process as early as possible in order to prevent chronic damage. In 2009, early potent DMARD medication is common practice and the question of strategy is rather which pharmaceutical(s) to use. Should DMARDs be used as mono-therapy or as combination-therapy? A recent study by van der Kooij et al (2009) shows that initial combination therapy leads to quicker improvement than initial mono-therapy. Or should biologics be the first choice? The biologics have shown good results, but are very expensive, and at present they cannot be prescribed to all early RA patients. Therefore, there is a need to identify optimal individual treatment strategies as early as possible, regarding overall prognosis as well as individual response-to-therapy and risk of treatment failure/side-effects.
Treatment goals or treating the goals?

We can certainly discuss who is to decide about treatment goals? Are the treatment goals acceptable today or are the goals what should be treated? The general opinion in this thesis is that everybody involved in the disability context of a certain situation (a certain patient) have important contributions to make.

Even though intensive research is done to understand the mechanisms of disease onset and progression, we still await means to prevent and cure RA. In the meantime, rehabilitation (and support) remains the main strategy for persons with RA in clinical practice. The section of Physical and Rehabilitation Medicine in the European Board of Physical and Rehabilitation Medicine (UEMS) in 2007 published a white book on physical and rehabilitation medicine (UEMS, 2007). They clearly state their attribution to the biopsychosocial model of disability, and as a result they re-define ‘physical and rehabilitation medicine in Europe’ by emphasizing the ‘promotion of physical and cognitive functioning, activities, participation and modifying personal and environmental factors’. They also formulate the responsibility of rehabilitation to be ‘prevention, diagnosis, treatment, and rehabilitation management’. The view is holistic and a multi-professional team approach is provided. In line with this, the aim of rehabilitation is to ‘enable people with disabilities to lead the life that they would wish’. Stucki et al (2007) express the aim quite similarly, although slightly differently, as to ‘enable people with health conditions experiencing or likely to experience disability to achieve and maintain optimal functioning in interaction with the environment’.

Thanks to the modern anti-rheumatic treatment strategies, the number of RA patients in need of surgery is expected to decrease and Weiss et al (2006) have already identified decreasing RA-related surgical procedures to the lower limbs in Swedish RA patients between 1987 and 2001. They conclude that these results reflect trends in the modern management and reduced disease severity of RA in Sweden.

There are no major primary prevention strategies, but at the environmental level the best established avoidable risk factor for RA, is cigarette smoking (Klareskog et al, 2007).
Guidelines
In order to give the best possible guidelines concerning care of patients with RA, recommendations regarding particular patterns of practice have been published (Saag et al, 2008). ACR’s guidelines for the management of RA (ACR, 2002) are one set of recommendations for the management of RA with goals to prevent or control joint damage, to prevent loss of function and to decrease pain. These criteria were formulated using a Delphi procedure. In 2008, a panel of experts updated recommendations for the use of non-biological and biological DMARDs (Saag et al, 2008). The European league against rheumatism (EULAR) used a ‘standardised operation procedure’ to provide recommendations for the management of early arthritis, and summarized 12 recommendations including diagnosis, baseline status and pharmacological treatment, patient education, how to monitor disease activity, structural damage and functional assessment, and non-pharmacological interventions (Combe et al, 2007). Other guidelines have been compiled nationally, e.g. by the Swedish Society for Rheumatology.

Guidelines are continually updated according to new knowledge. At present, ACR and EULAR collaborate to establish new guidelines to be used for early diagnosis and treatment decisions (Klareskog et al, 2009).

Prognosis
Prognosis is of special interest with reference to interventions preventing disability in RA. Studies of radiographic progression in early RA have shown that the first two years after diagnosis to a large extent predict the overall development of erosions (Scott, 2002). Aletaha et al (2007) suggested that disease activity at diagnosis and disease activity at three months after diagnosis are significantly related to the level of disease activity one year after diagnosis. Thus, patients undergoing therapy, and who reach moderate disease activity or lower within 3 months, are very likely to achieve remission in 1 year. Establishing prognosis as early as possible from the time of disease onset is therefore a key interest.

Functional capacity in early RA is mainly associated with disease activity, as compared to joint damage in late disease (Welsing et al, 2001), but there are differences in individual patients depending on the individual progression of the disease. Established prognostic factors are currently of limited use in individual patients (van Riel & Fransen, 2007) and there is therefore a need for prognosticators to use when establishing prognosis in individual patients.
Some prognostic factors meaningful for disease susceptibility and/or progression are:

- genetic: e.g. shared epitope (SE) and PTPN22 (Plenge; 2009)
- environmental: e.g. smoking, (Olsson et al, 2004; Klareskog et al, 2007)
- disease activity and disability at onset: e.g. swollen and tender joints, erythrocyte sedimentation rate (ESR), C-reactive protein (CRP) (Morel & Combe, 2005)
- immunological factors: e.g. rheumatoid factor (RF) (Quinn et al, 2005) or anti-citrullinated protein antibodies (ACPA) (Kastbom et al, 2004)
- radiological factors: radiographic score at disease onset (Goronzy et al, 2004).

Overall, the prognosis for individual patients with early RA is considerably better today than it was 20 years ago, thanks to intensive research, and perhaps mainly to the early treatment initiatives beginning in the 1990s (Aletaha & Huizinga, 2009).

‘Early intervention in rheumatoid arthritis’ – the Swedish TIRA project

The Swedish TIRA project started as a multi-centre project in cooperation between ten rheumatology units in southeast Sweden in 1996 (Thyberg et al, 2004). The purpose was to establish rational routines for early diagnosis and multi-professional interventions, and to collect research data in order to improve the knowledge basis of clinical decisions. Clinical examinations were performed by physicians, occupational therapists, and physiotherapists. A database for research purposes was also created. Further, a biobank containing serum samples and whole blood was established. Patients included in the TIRA study were followed-up by visits after 3, 6, 12, 18, 24 months, and then once a year.

To date there are two cohorts; the TIRA1 cohort consisting of patients included during 27 months 1996-1998, and the TIRA2 cohort consisting of >500 patients included from 2006-2009. The studies included in this thesis are mainly based on the TIRA1 cohort, but also on the TIRA2.
Aims
This thesis project had three main aims concerning disease and disability, prognosis in early RA, and decision support:

- Disease and disability: To elucidate how clinical manifestations of early RA contribute to disease and disability outcomes (Papers I & III).
- Prognosis in early RA: To strive for better potential to establish prognosis in early RA (Papers I & II).
- Decision support: To facilitate decision support through analysis of the decision-making environment in chronic care (Papers I & IV).

Specific aims:

The aims of Paper I was twofold. It was primarily to identify prognosticators and their relative explanatory power of disease activity in early stages of RA, and second to identify characteristics of patients where the disease activity is not successfully managed by conventional anti-rheumatic drugs, and ultimately to find predictors of an early need for treatment with biologics.

The aim of Paper II was to examine whether representation of physicians’ expert knowledge in a simple heuristic model could be used to improve data mining methods in prognostic assessments of RA patients.

The aims of Paper III were to clarify whether there are differences between women and men, with regard to the reported level of fatigue, and to explore the strength of the relationships between fatigue and disease activity, pain, sleep disturbance, mental health, and activity limitation in early rheumatoid arthritis, and to explore the consistency of such findings.

The aim of Paper IV was to identify the social and organizational requirements for a decision support system based on data-mining techniques to be implemented in a clinical rheumatology setting.
Methods

The Swedish TIRA project
This study is associated with a Swedish multicenter study ‘Early interventions in RA’ (TIRA) (Hallert et al, 2003). Patients with recent-onset (≤ 1 year) RA who fulfilled ≥ 4/7 RA classification criteria, as defined by the American College of Rheumatology 1987 (Arnett et al, 1988), or at least: morning stiffness ≥ 60 minutes, symmetrical arthritis, and arthritis of small joints were included in the TIRA1 cohort 1996-1998. Inclusion in the TIRA2 cohort started in 2006. The primary aim of the study is early intervention and at all visits the patients meet a physician, an occupational therapist and a physiotherapist. Interventions are offered on an individual schedule depending on clinical assessments during the study period. Data for genetics, disease activity, disability, health economics and medication are registered at inclusion and at 3, 6, 12 months after inclusion and thereafter annually for the 8-year follow-up. The same procedure was performed for both TIRA cohorts with the additional criteria of synovitis in at least one peripheral joint if at the same time the patient tested positive for anti-CCP in the TIRA2 cohort. The ‘new’ TIRA2 cohort offers the potential to compare the results obtained in the new study with the 10-year old TIRA1 data regarding a broad range of aspects of health in relation to different interventions.

Study design
The studies included in this thesis are based on quantitative data in the TIRA1 cohort (Papers I-III), the TIRA2 cohort (Paper I), and on qualitative data according to separate data collection (Papers II & IV). Although prognosis and decision support are overlapping features, a suggestion for an overview of the studies is outlined in Table 3.

Operationalizing of concepts
The main measures used are listed in Table 4 according to their classification in ICF terminology and the aims of the thesis.
<table>
<thead>
<tr>
<th>General aim</th>
<th>Paper(s)</th>
<th>Design</th>
<th>Research questions</th>
<th>Subjects</th>
<th>Data collections</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Disease and disability</strong></td>
<td>III</td>
<td>Quantitative, multiple cross-sectional</td>
<td>Relationships between fatigue and related variables in early RA, comparisons between women and men.</td>
<td>N1=276</td>
<td>TIRA1 M12 M24 M36</td>
</tr>
<tr>
<td></td>
<td>I</td>
<td>Quantitative, cross-sectional and longitudinal</td>
<td>Examine components in baseline status and first 3 months progression data.</td>
<td>N1=320</td>
<td>TIRA1o2 M0 M3</td>
</tr>
<tr>
<td><strong>Prognosis in early RA</strong></td>
<td>I</td>
<td>Quantitative, cross-sectional and longitudinal</td>
<td>Predict disease activity at one year after diagnosis by components in baseline status and first 3 months progression data.</td>
<td>N1=320</td>
<td>TIRA1o2 M0 M3 M6 M12</td>
</tr>
<tr>
<td></td>
<td>II</td>
<td>Quantitative, qualitative, cross-sectional</td>
<td>Model physicians’ expert knowledge to make better decisions about prognosis</td>
<td>N1=279</td>
<td>TIRA1 M0 5 consultants at a RA-unit</td>
</tr>
<tr>
<td><strong>Decision support</strong></td>
<td>I</td>
<td>Quantitative, cross-sectional and longitudinal</td>
<td>Production of a prediction model identifying patients with poor prognosis.</td>
<td>N1=320</td>
<td>TIRA1o2 M0 M3 M12</td>
</tr>
<tr>
<td></td>
<td>IV</td>
<td>Qualitative</td>
<td>Examine important social and organizational requirements at an RA unit for implementation of a decision support system.</td>
<td>-</td>
<td>Consultants, nurses, occupational therapists, physiotherapists, nurses, social workers at an RA unit</td>
</tr>
</tbody>
</table>
Table 4. Variables used in the studies, their classification in ICF terminology, their use in relation to aims, and their use in the different studies (Papers I-IV).

<table>
<thead>
<tr>
<th>Variables</th>
<th>ICF-Component</th>
<th>Follow-up</th>
<th>Aims in the separate studies</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td>Disease and disability</td>
</tr>
<tr>
<td><strong>Serological markers</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Anti-CCP</td>
<td>NA</td>
<td>Any*</td>
<td>I</td>
</tr>
<tr>
<td>RF</td>
<td>NA</td>
<td>Inclusion</td>
<td>I</td>
</tr>
<tr>
<td><strong>Disease</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>CRP (mg/L)</td>
<td>NA</td>
<td>All</td>
<td>I</td>
</tr>
<tr>
<td>ESR (mm/h)</td>
<td>NA</td>
<td>All</td>
<td>I</td>
</tr>
<tr>
<td>DAS-28 (score)</td>
<td>Body function and structure</td>
<td>All</td>
<td>I III</td>
</tr>
<tr>
<td>PGA (0-4)</td>
<td>Body function and structure</td>
<td>All</td>
<td>I</td>
</tr>
<tr>
<td><strong>Disability</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pain (VAS 0-100 mm)</td>
<td>Body function and structure</td>
<td>All</td>
<td>I III</td>
</tr>
<tr>
<td>Sleep disturbance (VAS 0-100 mm)</td>
<td>Body function and structure</td>
<td></td>
<td>III</td>
</tr>
<tr>
<td>Fatigue (VAS 0-100 mm)</td>
<td>Body function and structure</td>
<td></td>
<td>III</td>
</tr>
<tr>
<td>Mental Health (0-100)</td>
<td>Body function and structure</td>
<td></td>
<td>III</td>
</tr>
<tr>
<td>HAQ (0-3)</td>
<td>Activity limitation</td>
<td>Yearly</td>
<td>I III</td>
</tr>
<tr>
<td><strong>Personal factors</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Age (years)</td>
<td>Personal factor</td>
<td>Inclusion</td>
<td>I III</td>
</tr>
<tr>
<td>Gender (woman/man)</td>
<td>Personal factor</td>
<td></td>
<td>I III</td>
</tr>
</tbody>
</table>

CRP=C-reactive protein, mg/l. ESR=erythrocyte sedimentation rate. DAS-28=Disease Activity Score (28 joint count). PGA=physicians global assessment of disease activity, score 0-4. Pain=self-estimated pain. VAS=Visual Analogue Scale. Mental Health as measured by the standard Swedish version of Short Form 36. HAQ=Health Assessment Questionnaire; Age is age at inclusion. NA = not applicable. * Anti-CCP was measured at any of the follow-ups.
Disease activity was measured by C-reactive protein (CRP), the erythrocyte sedimentation rate (ESR), and the 28-joint count disease activity score (DAS-28) (Prevoo et al, 1995), and by the physicians’ global assessment of disease activity (PGA; score 0–4 where 0 corresponds to no activity and 4 represents high activity).

Disability was measured in terms of impairment by measuring pain using visual analogue scales of 0–100 mm, where 0 represents no pain (Huskisson, 1974). Sleep disturbance and fatigue were measured in the same manner. Mental health was reported according to the standard Swedish version of Short Form 36 (SF-36), scored 0-100 where 100 represents the best possible mental health (Sullivan et al, 1994).

Disability was also reported in terms of activity limitations by the Swedish version of the Health Assessment Questionnaire (HAQ) with a score of 0–3, where 0 corresponds to no difficulty and 3 to unable to perform activity (Ekdahl et al, 1988).

Serological markers were the rheumatoid factor test (RF) and the test of anti-CCP. RF was measured at the time of diagnosis, and anti-CCP at one or some of the follow-ups. If at least one test of anti-CCP was positive the patient was treated as anti-CCP-positive.

Other measures were personal factors such as age at inclusion and gender.

Statistical analyses
Univariate as well as multivariate statistical methods were used (Table 5). All analyses were performed using the Statistical Package for the Social Sciences (SPSS) version 15.0 and/or version 17.0. Means, standard deviations and 95% confidence intervals were used for descriptive statistics. In inferential statistics \( p < .05 \) were reported.

Independent \( t \)-test, dependent \( t \)-test, Pearson Correlation and Chi-Square test of homogeneity are standard procedures in inferential statistics often used in epidemiological or disability research settings. Principal component analysis (PCA), multiple linear regression (MLR), univariate logistic regression (ULR), receiver operating characteristics (ROC),
Table 5. Statistical methods used in relation to aims, and use in different studies (Papers I-III).

<table>
<thead>
<tr>
<th>Statistical method</th>
<th>Aims</th>
<th>Disease and disability</th>
<th>Prognosis</th>
<th>Decision support</th>
</tr>
</thead>
<tbody>
<tr>
<td>Independent t-test</td>
<td></td>
<td>III</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Dependent t-test</td>
<td></td>
<td>III</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pearson Correlation</td>
<td></td>
<td>III</td>
<td></td>
<td></td>
</tr>
<tr>
<td>PCA</td>
<td></td>
<td>I</td>
<td>III</td>
<td></td>
</tr>
<tr>
<td>MLR</td>
<td></td>
<td>III</td>
<td>I</td>
<td>I</td>
</tr>
<tr>
<td>K-mean Clustering</td>
<td></td>
<td>III</td>
<td>II</td>
<td>II</td>
</tr>
<tr>
<td>Fisher r to z transformation</td>
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<td></td>
<td></td>
</tr>
<tr>
<td>ULR</td>
<td></td>
<td></td>
<td>I</td>
<td></td>
</tr>
<tr>
<td>ROC</td>
<td></td>
<td></td>
<td>I</td>
<td></td>
</tr>
</tbody>
</table>

PCA = principal component analysis, MLR = multiple linear regression analysis. ULR = univariate logistic regression analysis. ROC = receiver operating characteristics.

K-mean clustering, and Fisher r to z transformation are not as commonly used and are briefly described below.

**Principal Component Analysis – PCA**

PCA is an analysis used to describe underlying structures in data. It is a procedure suitable when there are many measures that correlate with each other. As an illustration, length and weight have a strong correlation. In a diagram illustrating 20 persons with measures of length and weight (Figure 3) the persons are distributed along a line with a certain direction. The pointer illustrating the line and the direction is called a component and would be a simpler way to describe the persons according to both length and weight. The conceptual meaning of the component in this example would be body size.

In PCA numerous components are identified to describe the structures in data. The first component is placed in the direction of the largest variation. Assume that we have a room (a 3-dimensional space), described by three variables X, Y and Z. Assume also that we have a sample of measures whose shape is like an egg when plotted in the room. If we want to describe it by components, the first component would be placed in the direction from the bottom to the top of the egg, since this is the direction of the largest variation of the measures. The second component would be placed in the direction with the largest remaining variation, orthogonal to the first component. This procedure continues with every new component being orthogonal to the established ones. The number of components calculated depends on how well the components are able to describe the underlying structure in data. After components
are described they can be rotated to better fit the data. Rotation can be orthogonal (components are kept orthogonal) or non-orthogonal (allowing the components to correlate). Orthogonal rotation is often recommended since it is easier to interpret, but the choice of rotation method should be based on theory, and if theory suggests that components should correlate then non-orthogonal rotation is preferred.

**Multiple Linear Regression – MLR**

MLR is a procedure that determines what proportion of the variance of a continuous variable is associated with, or explained by, at least two other variables, taking into account the associations between those other variables. Assume that the understanding of multivariate statistical methods (Y) after reading a statistical analyses section in a doctoral thesis could be measured in 30 persons. Assume also that the time spent reading that section (X₁) of the thesis and prior knowledge of multivariate statistics (X₂) were measured. All measures are made on a ratio scale. We can then use an MLR to determine what proportion of the variance in Y that can be explained by variance in X₁ and variance in X₂. Assume that the correlation between Y and X₁ is 0.50 and the correlation between Y and X₂ is 0.50. Then X₁ and X₂ by themselves explain 25% (0.50*0.50=0.25) of the variance in Y as illustrated in Figure 4.
Figure 4. $Y$ is the understanding of multivariate statistical methods. $X_1$ is the time spent reading statistical methods section. $X_2$ is prior knowledge in multivariate statistics. The correlation of $Y$ with $X_1$ and $X_2$ is 0.50 implying an explained variance of 25%. This is indicated by a 25% overlap of $X_1$ with $Y$ and by a 25% overlap of $X_2$ with $Y$. In (a) the correlation between $X_1$ and $X_2$ is 0 indicated by no overlap of $X_1$ and $X_2$. In (b) the correlation between $X_1$ and $X_2$ is 0.71 implying a 50% overlap between $X_1$ and $X_2$.

In Figure 4 a there is no correlation between the predictors which implies that they both contribute to explaining different parts of the variance in $Y$. In Figure 4 b there is a correlation between the predictors (multi-collinearity) which implies that the additional variance explained by $X_2$ to the variance already explained by $X_1$ is small. Such a situation might imply that $X_2$ is not included in the model at the same time as $X_1$. In our example this would mean we ended up with a result showing that the understanding of multivariate statistical methods is explained by the time spent reading the statistical methods section. The fact that prior knowledge in multivariate statistics explains just as much of the variance of understanding of multivariate statistical methods is then not shown by the results. Using PCA prior to MLR might give a richer understanding of results in such situations.

**Univariate Logistic Regression – ULR**
ULR is a procedure similar to MLR, but with a criteria variable that is dichotomous. Instead of predicting the value of the criteria variable (as in MLR) the probability of a certain value of the criteria variable is predicted. When running a ULR each item in the analysis is assigned a certain probability of having a predefined value of the dichotomous criteria variable. The probabilities can be put into an ROC analysis.

**Receiver Operating Characteristics – ROC analysis**
ROC analysis provides help in selecting cut-off values based on demands on sensitivity and specificity when predicting group membership out of a dichotomous variable. If a classification rule tells how to predict, e.g. a positive or negative outcome according to whether a certain variable has values below or above a certain cut-off, the sensitivity is the ratio between the correctly predicted positive-classifications (true positive, TP) and all
positive outcomes. The specificity is the ratio between the correctly predicted negative-classifications (true negative, TN) and all negative outcomes. The relation between the sensitivity and the specificity is often illustrated graphically by the ROC curve. The ROC curve can then be used to choose a suitable cut-off that determines which values should be predicted to what category of the dichotomous variable (or group membership) while balancing sensitivity and specificity.

**K-mean clustering**
K-mean Clustering is a procedure for dividing items into different groups (clusters). Items can be thought of as being part of a multi-dimensional space with one coordinate-axis for every variable used when describing the items. ‘K’ indicates the number of groups and has to be specified before the analysis is run. ‘Mean’ indicates that every cluster generated has a ‘mean’ for every variable describing the items. The ‘mean’ can be thought of as a centre of gravity of the cluster. In K-mean clustering K coordinates, initial cluster centres, in the multi-dimensional space are described and in the next step every item is connected to the cluster centre which is closest according to a certain distance-measure. In the clusters formed, new centres are calculated and the connection procedure is repeated. This procedure is repeated until the cluster centres converge.

**Fisher r to z transformation**
When comparing differences of correlation coefficients a transformation of the correlation coefficients can be made to z-score. Those z-scores can then be tested against the (null-) hypothesis of no difference. In other words, if two correlation coefficients differ the Fisher r to z transformation can tell whether the difference is significant or not.

**Disease and disability**
The first aim of this thesis, to examine clinical manifestations of early RA and their relative contributions to disease and disability, was approached by using two different measures as outcomes; fatigue and disease activity.

**Disability – fatigue**
Levels of fatigue were measured at M12, M24 and at M36 (Paper III) and were compared between women and men using the independent samples $t$-test and between different follow-ups using the paired samples $t$-test. Correlations were calculated with Pearson’s correlation coefficients and the consistencies of correlations were examined with the Fisher $r$ to $z$ transformation. PCA with direct oblimin rotation was performed for each follow-up for
women and men separately to identify underlying components in variables representing disease activity and the studied aspects of disability. The components were chosen upon statistical as well as theoretically reasonable interpretations from a clinical perspective. MLR was used to explain fatigue by using age at inclusion together with the components identified with the PCA.

**Disease – disease activity**
The patients were subdivided by gender, cohort or combinations of gender and cohort (Paper I). The measures were divided into two different groups reflecting two different attributes:

- Baseline status: measures at time of diagnosis (age, CRP, ESR, DAS-28, HAQ, PGA, pain)
- Early progression: the change in baseline status over the first three months (change in CRP, ESR, DAS-28, PGA, pain)

For each combination of patients and measures the underlying structure in data were described using PCA with direct oblimin rotation for baseline status and for early progression data.

A third set of attributes used, however without PCA, were the serological RA markers

- particle agglutinating RF (as tested and reported by the local laboratories affiliated to the participating rheumatology units), and
- the second generation anti-CCP antibody test (Immunoscan RA CCP2, EuroDiagnostica, Arnhem, NL) analyzed centrally at the rheumatology research lab in Linköping (Kastbom et al, 2004).

**Prognosis in early RA**
The second aim of this thesis, to strive for better potential to establish prognosis in early RA, was approached from two approaches. First, the components generated according to baseline status, the components generated according to the early progression, serological markers and their explanatory prognostic power in explaining disease activity at one year after the diagnosis of RA were examined (Paper I). Second, a methodological approach modelling heuristics of experts in chronic care was conducted and evaluated according to prognosis (Paper II).
Prognosis of disease activity at one year after diagnosis
To identify measures constituting significant RA patterns in early RA and their explanatory
prognostic power the components identified in relation to disease (Paper I) and serological
markers (RF and anti-CCP) were used as predictors in an MLR (using forward and backward
methods to choose the best possible model) with DAS-28 at M12 as criterion.

Heuristic modelling
Five consultants in rheumatology were interviewed in a semi-structured manner to investigate
their perspectives on CRP and ESR when making prognostic judgments about patients with
RA. Their heuristics or expertise was modelled in a mathematical model representing ‘the
heuristics of expertise’. The model can be thought of as lenses of expertise, and when used by
a novice with no prior clinical knowledge, such as in a computer application, the lenses help
view data in clinical databases from a perspective of expertise. Two different practices using
the ‘lenses’ were compared to not using the ‘lenses’. In mathematical terminology we used a
mathematical model to transform crude data in two different ways. Each set of transformed
values and the set of crude data were used in K-mean clustering identifying 3 and 4 clusters.
Each set of clusters was then evaluated after how well they separated prognostic subgroups of
patients according to PGA, using 95% confidence intervals.
**Decision support**

The third aim of this thesis, to facilitate decision support, was examined in two ways. First from a medical informatics approach considering two different treatment strategies was used to produce easy to use prediction rules identifying patients with poor prognosis in early RA (Paper I). Second, social and organizational requirements for a decision support system based on data-mining techniques to be implemented in a clinical rheumatology setting were examined at an RA unit using qualitative methods (Paper IV).

**Supporting prediction of poor prognosis**

*Identification of components and their contribution to disease activity*

The patients were subdivided by gender, cohort or combinations of gender and cohort. The components generated from the PCA together with the serological markers were used as predictors in an MLR (using forward and backward methods to reach the best possible model) with DAS-28 at M12 as criterion.

*Prediction of poor prognosis*

A random-number generation algorithm was used to divide the study populations into two equally large groups; the derivation cohort and the validation cohort. The derivation cohort was used to generate a set of decision rules based on clinical data collected within 3 months after diagnosis of RA. The decision rules were optimized to predict the likelihood of disease activity one year after the RA diagnosis. Because the introduction of the decision protocol was not allowed to cause significant extra costs, data not regularly collected were disregarded. In the validation step of the analysis, the validation cohort was used to assess the diagnostic accuracy of the protocol according to Standards for Reporting of Diagnostic Accuracy (STARD) criteria (Bossuyt et al, 2003; Smidt et al, 2005).
Different treatment strategies were assumed to represent the clinical practices at hand in the two cohorts based on the fact that new pharmaceuticals were available in the TIRA2 cohort, along with better knowledge of RA disease, implying that different decisions on the treatment of individual patients were not improbable. Only patients with DMARD prescribed at the time of diagnosis were included. This yielded two different treatment strategies based on clinical practice in real-world settings:

- **Early aggressive 1990 strategy (EAG90 strategy):** In the mid-90’s, a clinical diagnosis of RA was usually based on the 1987 ACR criteria especially in the early arthritis clinics (e.g. TIRA-1). Anti-CCP had not yet been introduced in clinical routine. At this time, the previously used ‘pyramid concept’ (‘go low, go slow’) was rapidly being changed to a more aggressive approach using DMARDs early on after diagnosis (most often sulfasalazine or oral methotrexate 7.5mg/week as the first choice).

- **Early aggressive 2000 strategy (EAG2000 strategy):** In 2005, i.e. when the TIRA-2 project was planned, routine management of RA had undergone a revolution. The ACPA tests had been introduced all over Sweden and used routinely at primary care units for diagnostic purposes. Although the 1987 ACR were still used as a basis for diagnosis and classification into RF-positive/RF-negative, anti-CCP had now been introduced for diagnostic routine at primary care units. For rheumatologists, a positive anti-CCP now also constituted a diagnostic bias, probably contributing to somewhat earlier diagnosis of RA. At this time, institution of DMARDs already at the day of RA diagnosis, had become the normal strategy, starting with oral or subcutaneous methotrexate 20-25mg/week. If the effect is considered insufficient at the 3-months follow-up, combination therapy with other DMARDs is commonplace, and if this is still insufficient, many patients are started on biologics (primarily TNF inhibitors) within a year of diagnosis.

The patients were subdivided by gender, cohort or combinations of gender and cohort. The measures were divided into two different groups reflecting two different attributes:

- **Baseline status** – measures at time of diagnosis (age, CRP, ESR, DAS-28, HAQ, PGA, pain)
- **Early progression** – the change in baseline status over the first three months (change in CRP, ESR, DAS-28, PGA, pain)
For each combination of patients and measures the underlying structure in data was described using PCA with direct oblimin rotation. The components, together with serological markers – RF and anti-CCP test – were used as predictors in an MLR analysis (using forward and backward methods to choose the best possible model) with DAS-28 at M12 as criterion.

Poor prognosis was assumed for patients with high or moderate levels of DAS-28 at M12 and good prognosis was assumed for patients with low or remission levels of DAS-28 at M12. To generate easy applicable prediction-rules identifying patients with a poor prognosis, a three-step procedure was used.

Both TIRA cohorts went through a median-split procedure according to age, pain, DAS-28 and HAQ and thereafter the resulting groups were randomly divided into a derivation and a validation cohort, controlling for gender.

Pearson correlation coefficients were calculated to examine the correlation between DAS-28 at M12 and variables at time of inclusion; age, DAS-28, pain, PGA, HAQ. Variables at M0 that correlated significantly with DAS-28 at M12 were chosen for further analysis. Correlations between DAS-28 at M12 and changes in DAS-28 pain and PGA during first 3 months after M0 were also examined, and selected for further analyses if they correlated significantly with DAS-28 at M12 and if there was also a significant correlation between the variable at M0 and DAS-28 at M12.

ULR for each variable chosen from correlation analysis was performed with DAS-28 at M12 as a criterion (good prognosis=remission or low levels of DAS-28 at M12; poor prognosis=moderate or high levels of DAS-28 at M12), once for patients treated according to the EAG90 strategy and once for patients treated according to the EAG2000 strategy. Produced probabilities from the ULR were analysed using the ROC analysis and limits were chosen that demanded at least 80% specificity. The probabilities from the ULRs were ordered according to size together with the corresponding original variable values. The limits expressed in measures of the original variables were then chosen as the mean of the corresponding variable-values just smaller and just larger than the probability limit.
Each variable generated three different conditions, using limits generated by the limit generation (Step 2) with at least 80% specificity, due to the following rule:

- Condition a: Variable ≥ Limit
- Condition b: Variable < Limit
- Condition c: Either a or b.

Potential prediction rules were then generated by using conditions of the variables gender (woman, man, either woman or man), anti-CCP (positive, negative, either positive or negative), and the variables chosen from correlation analysis with the conditions a-c described above. If all conditions were fulfilled, the potential prediction rules predicted poor prognosis.

The rules were validated first irrespective of gender, and thereafter for women and men separately. Rules fulfilling the criteria of at least 90% specificity, 10% sensitivity, and 60% positive predictive value (PPV) when tested on the derivation cohort were also validated against the validation cohort according to the same criteria, which resulted in a set of prediction rules.

Prediction rules were combined in a decision tree which was evaluated based on the whole validation cohort, but also on the patients treated according to the EAG2000 strategy separately. Validation was based on sensitivity, specificity, PPV and accuracy.

**Social and organizational requirements for decision support**

A non-participating but open observational study was performed at a rheumatology unit (RU). Notes were taken during observation (although not in the presence of the patients and when possible not in the presence of the health professionals), and entered into a word processor as soon as possible after each observation. The documents were ordered using headlines referring to recurrent or unexpected events, and thereafter key factors were identified and introduced as ‘stimuli-questions’ to participants in focus group interviews. Key factors were starting points for discussion, but new topics were also open for discussion. The focus group interviews were recorded and transcribed. Quotations were ordered first according to each participant and labels were developed to categorize the quotations. New documents were ordered according to the labels, which were related to the key factors (similar although not identical) discussed that formed conclusions. For an overview of the procedure see Figure 5.
Figure 5. Flow chart showing the procedure that examines social and organizational requirements for decision support at a rheumatology unit.

**Ethics**

All patients in the TIRA project gave their written informed consent to participate and the project was approved by the Linköping local ethics committee.
Results
The results are presented in the order of the three aims; disease and disability, prognosis in early RA, and decision support.

Disease and disability
Results are presented first according to disability, using fatigue as an outcome, and second according to disease, based on disease activity at one year after diagnosis.

Disability – Fatigue

Differences between women and men
At M12 and M36 women reported more fatigue and lower values for mental health than men. To examine the influence of age, the explained variances in fatigue had been analyzed and found to be 1% for men and <0.01% for women, the correlations between age and fatigue were small. Women reported significantly more activity limitation than men at all follow-ups.

Differences over time
There were no significant differences, neither in women nor in men, when comparing each variable, at M12 with M24, and M24 with M36, respectively. Women showed no significant differences in correlations between M12 and M24 versus correlations between M24 and M36. Men showed a significantly higher correlation for HAQ between M12 and M24 than between M24 and M36, \( z = 2.64, p < .01 \). Men also showed a significantly lower correlation for sleep disturbances between M12 and M24 than between M24 and M36, \( z = 2.49, p < .05 \).
Identification of underlying components
In women, the PCA resulted in two components. Similar components were revealed at all three follow-ups. The first component explained most of the variance and included disease activity, activity limitation, and pain at all follow-ups (Table 6). Sleep disturbance also explained this component, but to a large extent it shared the amount of explained variance with the former variables. The second component, which explained a smaller part of the variance, included mental health and sleep disturbance, i.e. high values for mental health in combination with low values of sleep disturbances or vice versa (Table 6).

Table 6. Principal components (C1 and C2) from PCA at 12 months after inclusion (M12), 24 months after inclusion (M24), and 36 months after inclusion (M36) for women. High indicates high relevance for variable to the component (significant loading in pattern matrix). Partial indicates partial relevance for variable to the component (significant loading in structure matrix but not in pattern matrix). Explained variance is the variance explained for each component and total explained variance is the altogether explained variance. Only significant loadings are presented.

<table>
<thead>
<tr>
<th>Relevance</th>
<th>M12 (N = 151)</th>
<th>M24 (N = 137)</th>
<th>M36 (N = 122)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Var</td>
<td>Pat</td>
<td>Str</td>
</tr>
<tr>
<td>C1</td>
<td></td>
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<td></td>
</tr>
<tr>
<td>High</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>DAS-28</td>
<td>.94</td>
<td>.85</td>
<td>.77</td>
</tr>
<tr>
<td>HAQ</td>
<td>.79</td>
<td>.84</td>
<td>.79</td>
</tr>
<tr>
<td>Pain</td>
<td>.50</td>
<td>.68</td>
<td>.50</td>
</tr>
<tr>
<td>SleepD</td>
<td>.48</td>
<td>.48</td>
<td>.48</td>
</tr>
<tr>
<td>MH</td>
<td>.94</td>
<td>-.44</td>
<td>-.44</td>
</tr>
<tr>
<td>SleepD</td>
<td>-.64</td>
<td>-.64</td>
<td>-.64</td>
</tr>
<tr>
<td>Explained variance (%)</td>
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<td>61</td>
<td>56</td>
</tr>
<tr>
<td>C2</td>
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<td></td>
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<tr>
<td>High</td>
<td></td>
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</tr>
<tr>
<td>MH</td>
<td>.94</td>
<td>.94</td>
<td>.94</td>
</tr>
<tr>
<td>SleepD</td>
<td>-.64</td>
<td>-.64</td>
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<tr>
<td>Explained variance (%)</td>
<td>15</td>
<td>15</td>
<td>15</td>
</tr>
</tbody>
</table>

Var=Variable; Pat=loading from pattern matrix; Str=loading from structure matrix; DAS-28=Disease Activity Score (28 joint count); HAQ=Health Assessment Questionnaire; MH=Mental Health; SleepD = Sleep Disturbance. Note: Pattern matrix indicates each variable’s unique contribution with the component and the structure matrix indicates each variable’s total relation with the component.
In men, the PCA revealed results similar to those in women, i.e. two components at all three follow-ups (Table 7). The first component included disease activity, activity limitation and pain. The second component included mental health and sleep disturbance. However, there were some differences compared to the results in women. Sleep disturbance had no significant contribution to the first component at any follow-up, and activity limitation and pain had no significant contribution to the first component at M36. With respect to the second component, mental health had no significant influence at M24, and pain had some influence at M36.

**Table 7.** Principal components (C1 and C2) at 12 months (M12), 24 months (M24), and 36 months (M36) after inclusion, respectively, for men. High indicates high relevance for variable to the component (significant loading in pattern matrix). Partial indicates partial relevance for variable to the component (significant loading in structure matrix but not in pattern matrix). Explained variance is the variance explained for each component and total explained variance is the altogether explained variance. Only significant loadings are presented.

<table>
<thead>
<tr>
<th>Relevance</th>
<th>M12 (N = 63)</th>
<th>M24 (N = 53)</th>
<th>M36 (N = 48)</th>
</tr>
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<tbody>
<tr>
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<td>Pat</td>
<td>Str</td>
</tr>
<tr>
<td>C1</td>
<td>High</td>
<td>DAS-28</td>
<td>.81</td>
</tr>
<tr>
<td></td>
<td></td>
<td>HAQ</td>
<td>.78</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Pain</td>
<td>.75</td>
</tr>
<tr>
<td></td>
<td>Partial</td>
<td>DAS-28</td>
<td>.91</td>
</tr>
<tr>
<td></td>
<td></td>
<td>HAQ</td>
<td>.79</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Pain</td>
<td>.78</td>
</tr>
<tr>
<td>C2</td>
<td>High</td>
<td>MH</td>
<td>.92</td>
</tr>
<tr>
<td></td>
<td></td>
<td>SleepD</td>
<td>-.63</td>
</tr>
<tr>
<td></td>
<td>Partial</td>
<td>MH</td>
<td>.89</td>
</tr>
<tr>
<td></td>
<td></td>
<td>SleepD</td>
<td>.68</td>
</tr>
<tr>
<td></td>
<td>Explained Variance (%)</td>
<td>45</td>
<td>46</td>
</tr>
<tr>
<td></td>
<td>Explained Variance (%)</td>
<td>26</td>
<td>20</td>
</tr>
<tr>
<td>Total variance explained (%)</td>
<td>70</td>
<td>66</td>
<td>63</td>
</tr>
</tbody>
</table>

Var=Variable; Pat=loading from pattern matrix; Str=loading from structure matrix; DAS-28=Disease Activity Score (28 joint count); HAQ=Health Assessment Questionnaire; MH=Mental Health; SleepD = Sleep Disturbance. Note: Pattern matrix indicates each variable’s unique contribution with the component and the structure matrix indicates each variable’s total relation with the component.

**Explained variance**

In women, the components from the PCA and age at inclusion explained between one third (M12) and half of the variance (M24 and M36) in fatigue, according to the MLR analysis (Table 8). When using the components from the PCA at the follow-up one year earlier as predictors together with age at inclusion, the variance in fatigue at M24 and M36 was explained by approximately one fourth. When using components from the PCA at M12 as
predictors together with age at inclusion, the variance in fatigue at M36 was explained by approximately one sixth.

At M12, the first component had a larger influence on the prediction of fatigue than the second component, but at M24 and M36 the second component had a larger influence than the first. Age at inclusion had a significant influence on the prediction of fatigue only at M36 (and when using data from all three follow-ups simultaneously).

In men, the components from the PCA together with age at inclusion explained almost between one third (M12 and M24) and half of the variance in fatigue (M36) (Table 8). When using the components from the PCA at the follow-up one year earlier as predictors together with age at inclusion, the variance in fatigue at M24 and M36 was explained by approximately one tenth. When using the components from the PCA at the M12 as predictors together with age at inclusion, the variance in fatigue at M36 was explained by approximately one fourth.

Table 8. Multiple Linear Regression Analysis with beta-coefficients at 12 months (M12), 24 months (M24), and 36 months after inclusion (M36), respectively, with fatigue as criterion and components 1 and 2 (C1 and C2) together with age at inclusion as predictors. R2 is explained variance in criterion from predictors.

<table>
<thead>
<tr>
<th>Follow-up</th>
<th>Predictor</th>
<th>Women</th>
<th>Men</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>M12</td>
<td>M24</td>
</tr>
<tr>
<td>M12</td>
<td>C1</td>
<td>.38</td>
<td>.29</td>
</tr>
<tr>
<td></td>
<td>C2</td>
<td>.31</td>
<td>.25</td>
</tr>
<tr>
<td></td>
<td>Age</td>
<td>.34</td>
<td>.22</td>
</tr>
<tr>
<td>M24</td>
<td>C1</td>
<td>.33</td>
<td></td>
</tr>
<tr>
<td></td>
<td>C2</td>
<td>-.48</td>
<td>-.52</td>
</tr>
<tr>
<td></td>
<td>Age</td>
<td>.50</td>
<td>.27</td>
</tr>
<tr>
<td>M36</td>
<td>C1</td>
<td>.34</td>
<td></td>
</tr>
<tr>
<td></td>
<td>C2</td>
<td>-.45</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Age</td>
<td>-.17</td>
<td></td>
</tr>
<tr>
<td></td>
<td>R²</td>
<td>.46</td>
<td></td>
</tr>
</tbody>
</table>

At M12, the second component had a larger influence on the prediction of fatigue than the first component, but at M24, the first component had a larger influence on the prediction of fatigue than the second component. At M36, the first component still had the largest influence on prediction of fatigue, and age at inclusion was a significant predictor.
Disease – disease activity

Disease activity at M12 was used as outcome data in Paper I (Table 9, Table 10). ESR, DAS-28, HAQ and pain at M0 correlated significantly with DAS-28 at M12, while age, CRP and PGA at M0 did not. PGA-progression, however, had the largest correlation with DAS-28 at M12 among progression measures the first 3 months. The progression of DAS-28 and pain also correlated significantly with DAS-28 at M12, whereas the progression of CRP and ESR did not.

Table 9. Descriptives for the TIRA1 and the TIRA2 cohorts divided by gender (data from Paper I).

<table>
<thead>
<tr>
<th>Variable</th>
<th>TIRA1 women</th>
<th>TIRA1 men</th>
<th>TIRA2 women</th>
<th>TIRA2 men</th>
</tr>
</thead>
<tbody>
<tr>
<td>Baseline status</td>
<td>N</td>
<td>Mean</td>
<td>SD</td>
<td>N</td>
</tr>
<tr>
<td>Age, years</td>
<td>215</td>
<td>54.57</td>
<td>15.60</td>
<td>105</td>
</tr>
<tr>
<td>CRP, mg/l</td>
<td>213</td>
<td>27.85</td>
<td>26.79</td>
<td>99</td>
</tr>
<tr>
<td>ESR, mm/hour</td>
<td>211</td>
<td>35.37</td>
<td>23.92</td>
<td>98</td>
</tr>
<tr>
<td>DAS-28</td>
<td>205</td>
<td>5.24</td>
<td>1.23</td>
<td>94</td>
</tr>
<tr>
<td>HAQ, score 0-3</td>
<td>212</td>
<td>0.91</td>
<td>0.60</td>
<td>103</td>
</tr>
<tr>
<td>PGA, score 0-4</td>
<td>193</td>
<td>1.95</td>
<td>0.82</td>
<td>96</td>
</tr>
<tr>
<td>Pain, VAS 0-100 mm</td>
<td>211</td>
<td>47.85</td>
<td>23.35</td>
<td>99</td>
</tr>
<tr>
<td>Early progression</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>CRP, mg/l</td>
<td>199</td>
<td>-12.48</td>
<td>26.53</td>
<td>95</td>
</tr>
<tr>
<td>ESR, mm/hour</td>
<td>195</td>
<td>-11.83</td>
<td>21.32</td>
<td>94</td>
</tr>
<tr>
<td>DAS-28</td>
<td>190</td>
<td>-1.22</td>
<td>1.58</td>
<td>89</td>
</tr>
<tr>
<td>PGA, score 0-4</td>
<td>167</td>
<td>-0.61</td>
<td>0.97</td>
<td>89</td>
</tr>
<tr>
<td>Pain, VAS 0-100 mm</td>
<td>202</td>
<td>-10.60</td>
<td>29.90</td>
<td>95</td>
</tr>
<tr>
<td>1 year after diagnosis</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>DAS-28</td>
<td>189</td>
<td>3.83</td>
<td>1.45</td>
<td>84</td>
</tr>
<tr>
<td>Serological markers</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>RF</td>
<td></td>
<td>N+</td>
<td>N−</td>
<td>N+</td>
</tr>
<tr>
<td>N</td>
<td>215</td>
<td>132</td>
<td>83</td>
<td>105</td>
</tr>
<tr>
<td>anti-CCP</td>
<td>150</td>
<td>93</td>
<td>57</td>
<td>66</td>
</tr>
<tr>
<td>TOTAL</td>
<td>215</td>
<td>105</td>
<td>285</td>
<td>123</td>
</tr>
</tbody>
</table>

Age is age at inclusion, CRP=C-reactive protein; ESR=erythrocyte sedimentation rate; DAS-28=disease activity score, 28-joint count; HAQ=Swedish version of health assessment questionnaire; PGA=physicians global assessment of disease activity; VAS=visual analogue scale; N+=number of positive tests; N−=number of negative tests; RF=positive test of rheumatoid factor; anti-CCP=positive test of antibodies to citrullinated peptides.
Table 10. Pearson correlation coefficients for variables at baseline status and early progression (data from Paper I).

<table>
<thead>
<tr>
<th>Baseline status</th>
<th>DAS-28 (M12) Score</th>
<th>Age years</th>
<th>CRP mg/l</th>
<th>ESR mm/hour</th>
<th>DAS-28 (M1)</th>
<th>HAQ score 0-3</th>
<th>PGA score 0-4</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age Years</td>
<td>.02</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>CRP mg/l</td>
<td>.06</td>
<td>.21***</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>ESR mm/hour</td>
<td>.29***</td>
<td>.25***</td>
<td>.60***</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>DAS-28 (M1) Score</td>
<td>.25***</td>
<td>.15***</td>
<td>.41***</td>
<td>.57***</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>HAQ score 0-3</td>
<td>.15**</td>
<td>.12**</td>
<td>.28***</td>
<td>.21***</td>
<td>.43**</td>
<td></td>
<td></td>
</tr>
<tr>
<td>PGA score 0-4</td>
<td>.02</td>
<td>.10*</td>
<td>.36***</td>
<td>.25***</td>
<td>.53***</td>
<td>.37***</td>
<td></td>
</tr>
<tr>
<td>Pain VAS 0-100 mm</td>
<td>.12*</td>
<td>.01</td>
<td>.14***</td>
<td>.08*</td>
<td>.35***</td>
<td>.49***</td>
<td>.27***</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Early progression</th>
<th>DAS-28 (M12) Score</th>
<th>ΔCRP</th>
<th>ΔESR</th>
<th>ΔDAS-28</th>
<th>ΔPGA</th>
<th>ΔPain</th>
</tr>
</thead>
<tbody>
<tr>
<td>ΔCRP</td>
<td>.07</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>ΔESR</td>
<td>.11</td>
<td>.47***</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>ΔDAS-28</td>
<td>.19*</td>
<td>.34***</td>
<td>.54***</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>ΔPGA</td>
<td>.32***</td>
<td>.28***</td>
<td>.20*</td>
<td>.54***</td>
<td></td>
<td></td>
</tr>
<tr>
<td>ΔPain</td>
<td>.15*</td>
<td>.21**</td>
<td>.22**</td>
<td>.55***</td>
<td>.37***</td>
<td></td>
</tr>
<tr>
<td>RC-DAS-28</td>
<td>.20**</td>
<td>.29***</td>
<td>.47*</td>
<td>.94***</td>
<td>.52***</td>
<td>.48***</td>
</tr>
</tbody>
</table>

Age is age at inclusion, CRP=C-reactive protein; ESR=erythrocyte sedimentation rate; DAS-28=disease activity score, 28-joint count, M1 means at inclusion and M12 means at 1-year follow up; HAQ=Swedish version of health assessment questionnaire; PGA=physicians global assessment of disease activity; VAS=visual analogue scale. Δ means ‘difference’ in the corresponding variable. *** p < .001, ** p < .01, * p < .05.

The PCA for baseline status and early progression, for each of the nine possible combinations of TIRA cohorts and gender, resulted in two components (Table 11). The underlying patterns in the components are described below:

- baseline status, component Base1: Level of disease and disability (DAS-28, HAQ, PGA, pain)
- baseline status, component Base2: Inflammatory indicator level (age, CRP, ESR)
- early progression, component Prog1: Disease and disability progression (change in DAS-28, PGA, and pain)
- early progression, component Prog2: Inflammatory indicator progression (change in CRP and ESR).
**Prognosis in early RA**
Results for prognosis in early RA are presented according to prognostic factors on a group level and followed by results from a knowledge engineering approach of modelling the heuristics of experts.

**Prognosis of disease activity at one year after diagnosis**
The results of the MLR (Figure 6) revealed that approximately one fourth of the variance in DAS-28 at M12 could be explained by the predictors. Early progression explained a considerable part of the variance. Anti-CCP was notably a significant predictor in men but not in women. More variance in DAS-28 could be explained in men when serological markers were used. Without the use of serological markers there was a small tendency that more variance could be explained in women.

Smaller amounts of variance in DAS-28 at M12 in the TIRA2 cohort could be explained than in the TIRA1 cohort. Serological markers were not significant predictors in any model and the only significant models when separating women and men were for women when baseline status and first early progression were predictors.
Table 11. Principal component analysis (PCA) for combinations of gender and cohorts. Each PCA generated two components described by loadings from pattern matrices (P1 and P2) and structure matrices (S1 and S2) (data from Paper I).

<table>
<thead>
<tr>
<th>TIRA1 and 2 cohorts</th>
<th>Women and Men</th>
<th>Women</th>
<th>Men</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>P1</td>
<td>S1</td>
<td>P2</td>
</tr>
<tr>
<td>Baseline status</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Age</td>
<td>0.63</td>
<td>0.59</td>
<td>0.55</td>
</tr>
<tr>
<td>CRP</td>
<td>0.72</td>
<td>0.76</td>
<td>0.74</td>
</tr>
<tr>
<td>ESR</td>
<td>0.83</td>
<td>0.85</td>
<td>0.88</td>
</tr>
<tr>
<td>DAS-28</td>
<td>0.56</td>
<td>0.67</td>
<td>0.49</td>
</tr>
<tr>
<td>HAQ</td>
<td>0.79</td>
<td>0.80</td>
<td></td>
</tr>
<tr>
<td>PGA</td>
<td>0.62</td>
<td>0.67</td>
<td>0.65</td>
</tr>
<tr>
<td>Pain</td>
<td>0.84</td>
<td>0.79</td>
<td>0.87</td>
</tr>
<tr>
<td>Early progression</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>ΔCRP</td>
<td>0.86</td>
<td>0.86</td>
<td>0.91</td>
</tr>
<tr>
<td>ΔESR</td>
<td>0.88</td>
<td>0.88</td>
<td>0.42</td>
</tr>
<tr>
<td>ΔDAS-28</td>
<td>0.77</td>
<td>0.86</td>
<td>0.53</td>
</tr>
<tr>
<td>ΔPGA</td>
<td>0.83</td>
<td>0.81</td>
<td>0.8</td>
</tr>
<tr>
<td>ΔPain</td>
<td>0.79</td>
<td>0.77</td>
<td>0.81</td>
</tr>
</tbody>
</table>

| TIRA 1 cohort       |     |     |     |     |     |     |     |     |     |     |
|---------------------|---------------|-------|-----|-----|-----|-----|-----|-----|-----|
| Baseline Status     |     |     |     |     |     |     |     |     |     |     |
| Age                 | 0.41| 0.87| 0.86| 0.74| 0.63| 0.72| -0.52| 0.64| 0.70| 0.46|
| CRP                 | 0.84| 0.74| 0.46| 0.63| 0.72|     |     |     |     |     |
| ESR                 | 0.85|     | -0.88| -0.92| 0.52| 0.64| 0.70| 0.46|     |     |
| DAS-28              | 0.37| 0.12| 0.77| 0.77| 0.42| 0.87| 0.9 | -0.88| -0.9 | 0.46|
| HAQ                 | 0.65| 0.68| 0.61| 0.67| 0.67| 0.67| 0.68|     |     |     |
| PGA                 | 0.78| 0.73| 0.84| 0.77|     |     |     |     |     |     |
| Pain                | 0.94| 0.92| 0.95| 0.93|     |     |     |     |     |     |
| Early progression   |     |     |     |     |     |     |     |     |     |     |
| ΔCRP                | 0.87| 0.91| 0.42| 0.87| 0.91| 0.43| 0.82| 0.89| -0.47| 0.89|
| ΔESR                | 0.87|     | 0.42| 0.87| 0.91|     |     |     |     |     |
| ΔDAS-28             | 0.83| 0.89| 0.44| 0.84| 0.89| 0.43| 0.82| 0.89| -0.47| 0.89|
| ΔPGA                | 0.82| 0.81| 0.81| 0.81| 0.87| 0.83|     |     |     |     |
| ΔPain               | 0.76| 0.75| 0.8 | 0.78| 0.65| 0.66|     |     |     |     |

| TIRA 2 cohort       |     |     |     |     |     |     |     |     |     |     |
|---------------------|---------------|-------|-----|-----|-----|-----|-----|-----|
| Baseline Status     |     |     |     |     |     |     |     |     |     |     |
| Age                 | 0.46| 0.63| 0.71| 0.53| 0.54| 0.64| 0.43| 0.72| 0.63| 0.73|
| CRP                 | 0.46| 0.63| 0.71| 0.53| 0.54| 0.64| 0.43| 0.72| 0.63| 0.73|
| ESR                 | 0.81| 0.84| 0.79| 0.83|     |     |     |     |     |     |
| DAS-28              | 0.51| 0.65| 0.57| 0.69| 0.55| 0.67| 0.51| 0.65| -0.42| -0.57|
| HAQ                 | 0.76| 0.81| 0.8 | 0.79| 0.83| 0.68| 0.77|     |     |     |
| PGA                 | 0.60| 0.68| 0.48| 0.67| 0.72|     |     |     |     |     |
| Pain                | 0.87| 0.82| 0.8 | 0.78|     |     |     |     |     |     |
| Early progression   |     |     |     |     |     |     |     |     |     |     |
| ΔCRP                | 0.83| 0.89| 0.44| 0.84| 0.89| 0.43| 0.82| 0.89| -0.47| 0.89|
| ΔESR                | 0.87|     | 0.42| 0.87| 0.91|     |     |     |     |     |
| ΔDAS-28             | 0.56| 0.74| 0.45| 0.68| 0.67| 0.79| -0.56| 0.69| 0.82| 0.43|
| ΔPGA                | 0.76| 0.76| 0.79| 0.77| 0.65| 0.66| 0.51| 0.62|     |     |
| ΔPain               | 0.89| 0.85| 0.83| 0.80| 0.85| 0.83|     |     |     |     |

Age is age at inclusion, years; CRP=C-reactive protein, mg/l; ESR=erythrocyte sedimentation rate, ml/hour; DAS-28=disease activity score, 28-joint count; HAQ=Swedish version of health assessment questionnaire, score 0-3; PGA=physicians global assessment of disease activity, score 0-4; Pain=self-estimated pain by visual analogue scale, 0-100; Δ means ‘difference’ in the corresponding variable. Only coefficients > .40 are reported.
Figure 6. Multiple Linear Regression Analysis (MLR) for combinations of gender and TIRA cohorts. Predictors are the components from PCA representing baseline status, early progression, and serological markers. Criterion is 28-joint count disease activity score (DAS-28) at 1 year after diagnosis. Explained variances in DAS-28 by the predictors are indicated in bold in the circles and numbers of patients included in regression models are indicated in parenthesis. Numbers next to the predictors are beta-values in the regression models. Only significant predictors are included. The arrows show the additional variance explained when early progression and/or serological markers are added to baseline status as predictors in the MLR.
Heuristic modelling

The consultants’ perspectives on what are considered as low values were almost identical (ESR ≤ 12 mm for men and ESR ≤ 20 mm for women, CRP ≤ 10 mg/L for both men and women), with the exception of some minor differences regarding low values for ESR. Opinions of what are to be considered as elevated or definitely high values differed only slightly (an elevated value is roughly ESR = 60 mm and CRP = 70 mg/L, while ESR = 100 mm and CRP = 100 mg/L are definitely high values).

To give ESR and CRP equal influence, ESR and CRP values were transformed to the interval [0, 1]. 90% of the values were estimated to be represented by values spanning from low to elevated (0, .9) by a linear transformation. Values ranging from elevated to definitely high were transformed to the interval [.9, 1) in a decreasing manner using Eq. (1). Values considered as low were transformed to 0 and values considered as definitely high were transformed to 1

\[
f(x) = p + (1 - p) \cdot \left[ 1 - \left( 1 - \frac{x - x_1}{x_2 - x_1} \right) \frac{p}{x_1 - x_0} \frac{(x_2 - x_1)}{1 - p} \right]
\]

In Eq. (1), \(x\) is the variable for which the consultants’ experience is being modelled (ESR or CRP), \(f\) is the modelled value, \(x_0\) is the ‘lower limit value’ for which all lower values are considered as low, \(x_1\) is the ‘first upper limit value’, the point at which higher values are considered as elevated, \(x_2\) is the ‘final upper limit value’ above which all higher values are considered definitely high, \(p\) is the width of the interval which \([x_0, x_1)\) is transformed to. The ‘limit values’ used in Eq. (1) for ESR and CRP in the knowledge engineering step are shown in table 12.

Table 12. Values for model limits \(x_0, x_1, x_2,\) and \(p\) determined in the knowledge engineering step when modelling consultants’ views of erythrocyte sedimentation rate (ESR) and C-reactive protein (CRP).

<table>
<thead>
<tr>
<th>Variable</th>
<th>(x_0)</th>
<th>(x_1)</th>
<th>(x_2)</th>
<th>(p)</th>
</tr>
</thead>
<tbody>
<tr>
<td>ESR (men)</td>
<td>12</td>
<td>60</td>
<td>100</td>
<td>.90</td>
</tr>
<tr>
<td>ESR (women)</td>
<td>20</td>
<td>60</td>
<td>100</td>
<td>.90</td>
</tr>
<tr>
<td>CRP (men and women)</td>
<td>10</td>
<td>70</td>
<td>100</td>
<td>.90</td>
</tr>
</tbody>
</table>
279 patients had values for ESR, CRP and PGA, and were selected for analysis. Running K-mean-clustering using three clusters resulted in a ‘low value group’ (low values for both ESR and CRP), a ‘medium value group’ (medium values for both ESR and CRP), and a ‘high value group’ (high values for both ESR and CRP). This could have been expected since there is a positive correlation (.66) between ESR and CRP. The same is true for the transformed values where the correlation between the modelled values for ESR and CRP are positive, varying between .66 and .68.

Running K-mean-clustering using four clusters made the situation more complex. A ‘low value group’ and a ‘high value group’ appeared as when three cluster were used. There were also two ‘medium value groups’. Despite minor differences in size and mean values for the clusters in the different model(s), the results were quite similar in this respect.

In the case of three clusters, the three patient subgroups identified using Model B on the basis of ESR and CRP differed significantly from each other with regard to PGA scores (Table 13). Model A identified one significant difference (‘low’ vs. ‘high’). In comparison, the analyses based on crude data identified no significant differences between any groups. In the case of four clusters, no significant differences were found in the crude data model with regard to PGA. Model A and Model B, however, both allowed the identification of significantly different groups based on ESR and CRP (Model A: ‘low’ vs. ‘high’; Model B: ‘low’ vs. any of the other tree clusters).

Table 13. Validation of derived models A and B against crude data using physicians’ global assessment scores (PGA) as proxy for patient outcome. Mean values (95% confidence interval) are displayed for each cluster (three and four clusters, respectively).

<table>
<thead>
<tr>
<th></th>
<th>Crude data</th>
<th>Model A</th>
<th>Model B</th>
</tr>
</thead>
<tbody>
<tr>
<td>3 Clusters</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1 (low)</td>
<td>N: 188</td>
<td>PGA: 1.89 (1.78-2.01)</td>
<td>N: 154</td>
</tr>
<tr>
<td>2 (medium)</td>
<td>N: 70</td>
<td>PGA: 2.10 (1.93-2.27)</td>
<td>N: 72</td>
</tr>
<tr>
<td>4 Clusters</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1 (low)</td>
<td>N: 171</td>
<td>PGA: 1.88 (1.76-2.00)</td>
<td>N: 146</td>
</tr>
<tr>
<td>2 (medium)</td>
<td>N: 36</td>
<td>PGA: 2.19 (1.98-2.41)</td>
<td>N: 31</td>
</tr>
<tr>
<td>3 (medium)</td>
<td>N: 51</td>
<td>PGA: 2.00 (1.77-2.23)</td>
<td>N: 62</td>
</tr>
<tr>
<td>4 (high)</td>
<td>N: 21</td>
<td>PGA: 2.33 (1.89-2.77)</td>
<td>N: 40</td>
</tr>
</tbody>
</table>
**Decision support**

Results facilitating decision support, the third aim of this thesis, are presented first as a method for predicting poor prognosis in individual patients, and second in terms of social and organizational requirements for decision support.

**Supporting prediction of poor prognosis in individual patients**

**Patients**

ESR, DAS-28, HAQ and pain at M0 correlated significantly with DAS-28 at M12, while age, CRP and PGA at M0 did not. PGA progression, however, had the largest correlation with DAS-28 at M12 among progression measures the first 3 months. The progression of DAS-28 and pain also correlated significantly with DAS-28 at M12, whereas the progression of CRP and ESR did not (Table 10).

**Prediction of poor prognosis**

Derivation and validation cohorts are presented in Table 14.

| Table 14. Descriptive statistics for derivation and validation cohorts. |
|------------------------------|------------------------------|------------------------------|------------------------------|
| **Derivation cohort** | **Validation cohort** |
| | EAG90-strategy | EAG2000-strategy | EAG90-strategy | EAG2000-strategy |
| | N | M | SD | N | M | SD | N | M | SD | N | M | SD |
| Women | 85 | - | - | 55 | - | - | 82 | - | - | 58 | - | - |
| Men | 35 | - | - | 18 | - | - | 37 | - | - | 22 | - | - |
| CCP+ | 54 | - | - | 42 | - | - | 59 | - | - | 40 | - | - |
| CCP− | 27 | - | - | 20 | - | - | 29 | - | - | 9 | - | - |
| HAQ | 119 | 0.87 | 0.59 | 68 | 0.96 | 0.63 | 118 | 0.91 | 0.57 | 71 | 0.87 | 0.61 |
| DAS-28 | 112 | 5.38 | 1.16 | 69 | 4.66 | 1.56 | 116 | 5.40 | 1.15 | 72 | 4.70 | 1.39 |
| RC-DAS-28 | 110 | -18% | 34% | 56 | -24% | 40% | 110 | -22% | 31% | 64 | -37% | 30% |
| TOTAL | 120 | - | - | 73 | - | - | 119 | - | - | 80 | - | - |

CCP+ and CCP− are results from tests of anti-CCP; HAQ=Health Assessment Questionnaire; DAS-28=Disease activity score, 28-joint count; RC-DAS-28=relative change in DAS-28 during first 3 months.
Table 15. Rules predicting poor prognosis according to treatment strategy. Poor prognosis is predicted when all conditions for a certain rule are fulfilled. Woman/Man indicates gender-specific rules. Positive indicates positive test for anti-CCP. HAQ, DAS-28 and RC-DAS-28 indicate that value has exceeded predefined limit. Good means that value has not reached the predefined limit. ‘-’ means that the value doesn’t matter.

<table>
<thead>
<tr>
<th>Gender</th>
<th>CCP</th>
<th>HAQ</th>
<th>DAS-28</th>
<th>RC-DAS-28</th>
<th>Sens. (%)</th>
<th>Spec. (%)</th>
<th>PPV (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>EAG90-strategy</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Rule 1</td>
<td>Man</td>
<td>Positive</td>
<td>≥ 1.3</td>
<td>-</td>
<td>-</td>
<td>33</td>
<td>100</td>
</tr>
<tr>
<td>Rule 2</td>
<td>Man</td>
<td>Positive</td>
<td>-</td>
<td>DAS-28 &lt; 6.16</td>
<td>-</td>
<td>11</td>
<td>93</td>
</tr>
<tr>
<td>Rule 3</td>
<td>Man</td>
<td>Positive</td>
<td>-</td>
<td>-</td>
<td>≥ 12% Decrease</td>
<td>33</td>
<td>100</td>
</tr>
<tr>
<td>Rule 4</td>
<td>Man</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>&lt; 12% Decrease</td>
<td>42</td>
<td>91</td>
</tr>
<tr>
<td>Rule 5</td>
<td>-</td>
<td>Positive</td>
<td>-</td>
<td>DAS-28 ≥ 6.16</td>
<td>-</td>
<td>22</td>
<td>100</td>
</tr>
<tr>
<td>Rule 6</td>
<td>-</td>
<td>-</td>
<td>≥ 1.3</td>
<td>DAS-28 &lt; 6.16</td>
<td>≥ 12% Decrease</td>
<td>14</td>
<td>93</td>
</tr>
<tr>
<td>EAG2000-strategy</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Rule 7</td>
<td>Woman</td>
<td>Positive</td>
<td>&lt; 1.3</td>
<td>DAS-28 ≥ 6.16</td>
<td>-</td>
<td>13</td>
<td>93</td>
</tr>
<tr>
<td>Rule 8</td>
<td>Man</td>
<td>Positive</td>
<td>-</td>
<td>-</td>
<td>≥ 2% Increase</td>
<td>33</td>
<td>100</td>
</tr>
<tr>
<td>Rule 9</td>
<td>Woman</td>
<td>Positive</td>
<td>-</td>
<td>DAS-28 ≥ 6.16</td>
<td>-</td>
<td>16</td>
<td>100</td>
</tr>
</tbody>
</table>


The limits identified using ULR and ROC analysis were 1.2 for HAQ, 6.16 for DAS-28, and 12% reduction of DAS-28 during the first 3 months when using the EAG90 strategy, and 1.315 for HAQ, 5.9 for DAS-28, and 2% increase in DAS-28 during the first 3 months when using the EAG2000 strategy. Six non-redundant rules that fulfil the derivation criteria were generated for the EAG90 strategy and 3 non-redundant rules were generated for the EAG2000 strategy (Table 15). Combining the rules resulted in one decision tree for women (Figure 7) and one decision tree for men (Figure 8).

Validation of the decision tree yielded the results in Table 16. In the total validation cohort, more than every fourth patient with a poor prognosis could be identified (sensitivity 25%), only 1 out of 10 patients were erroneously predicted a poor prognosis (specificity 90%). The PPV was 76% and the accuracy was 53%. Overall, 55% had moderate or high levels of DAS-28 at M12. The patients treated according to the EAG2000 strategy in the validation cohort showed similar results with a sensitivity of 26% and a specificity of 87%. The PPV was 56% and the accuracy was 63%. Overall, 39% had moderate or high levels of DAS-28 at M12.

Table 16. Performance of the decision tree according to sensitivity (sens), specificity (spec), positive predictive value (PPV), and accuracy (acc).

<table>
<thead>
<tr>
<th></th>
<th>Full validation cohort</th>
<th>EAG2000 treated patients in validation cohort</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Sens (%)</td>
<td>Spec (%)</td>
</tr>
<tr>
<td>All</td>
<td>25</td>
<td>90</td>
</tr>
<tr>
<td>Women</td>
<td>27</td>
<td>86</td>
</tr>
<tr>
<td>Men</td>
<td>21</td>
<td>100</td>
</tr>
</tbody>
</table>

* Based on 12 men with good prognosis and 2 men with poor prognosis.
Figure 7. Prognostic decision tree for women based on the prediction rules generated. DAS-28 is disease activity score, 28-joint count. HAQ is Health Assessment Questionnaire. DAS-28 reduction or increase is the relative change in DAS-28 first 3 months. Correctly prognosticized patients/all patients prognosticized.

Figure 8. Prognostic decision tree for men based on the prediction rules generated. DAS-28 is disease activity score, 28-joint count. HAQ is Health Assessment Questionnaire. DAS-28 reduction or increase is the relative change in DAS-28 first 3 months. Correctly prognosticized patients/all patients prognosticized.
Social and organizational requirements for decision support

The observation points that guide the observations, the key factors identified and used as stimuli-questions in the focus group interviews, and the labels identified after the focus group interviews are outlined in Table 17. They were ‘milestones’ in the interpretations, and led to the final results.

Table 17. Observation points defined prior to the observation studies, key factors revealed from observation studies and used as stimuli questions prior to the focus group interviews, and labels indentified leading to final results.

<table>
<thead>
<tr>
<th>Observation points</th>
<th>Key factors</th>
<th>Labels</th>
</tr>
</thead>
<tbody>
<tr>
<td>Information processes</td>
<td>Information</td>
<td>Information gathering/exchange</td>
</tr>
<tr>
<td>Decision-making</td>
<td>Decision-making</td>
<td>Decision-making</td>
</tr>
<tr>
<td>Events in care</td>
<td>Computers</td>
<td>Attitudes</td>
</tr>
<tr>
<td>Others</td>
<td>Wishes</td>
<td>Good/bad things</td>
</tr>
<tr>
<td></td>
<td>Others</td>
<td>Advises, Requests, Important quotations.</td>
</tr>
</tbody>
</table>

Decision-making was found to be situated, patient-focused and long-term in nature. Decision-making practices always had specific patients in focus and one senior physician had medical responsibility for each patient. The nurses involved with the patient often discussed the clinical management with the ‘responsible’ physician, and other involved practitioners often asked questions about the patient (either directly verbally or using notes) at the offices of their colleagues. Every week there were formal conferences where all professions took part. During these meetings, all patients were discussed from these ‘different points of view’ in order to decide on diagnosis and treatment. In this context, the health professional categories had different areas of responsibility, e.g. physicians were in charge of diagnosis and medication, and occupational therapists were in charge of hand function.

Day-to-day decision-making was based on a physical closeness between the staff at the RU. There was not much free space, especially in the rooms of the receptionists and the nurses, and neither was there much free space in the rooms of the physiotherapists or the occupational therapists. Contrary to the physical closeness of the health professionals, the clinical information provided at the unit was spread over many locations. The different practitioners communicated in order to uphold a shared awareness and an up-to-date management plan for each patient, and each patient was also invited to become actively involved in the decision-making process.
Paper-based patient records were involved in almost every decision and they were the central information source. However, the records were also associated with several problems. It was hard to get an overview of the total care situation for a patient, and it was also difficult to follow the chronological order of events in different healthcare services. To uphold shared awareness, the health professionals read across disciplines what other health professionals had concluded, or which actions had been undertaken.

The main part of peer-to-peer communication was informal, e.g. performed during coffee breaks in the break room. These discussions could range from specific issues in clinical management routines, second opinions or administrative solutions concerning phone consultations to what to do with papers that belonged to a colleague on sick leave. The coffee break was described as an excellent opportunity to put questions to colleagues who were otherwise hard to get in touch with. In fact, ‘things that you hear during coffee break’, was included as an important basis for decision-making. The corridor was also a place where a considerable part of the informal exchange of information took place. Other ways of exchanging information between health professionals were via reports and sometimes via e-mail.
Discussion
The discussion begins with results and methods, and thereafter the prognosis in early RA is followed by guidelines, treatment strategies and interventions. Disability is discussed together with inter-disciplinary team care and the discussion ends up with some comments on medical informatics and an example of a decision support application.

Results
Discussion of the results will follow the three aims of the thesis; disease and disability, prognosis in early RA, and decision support.

Disease and disability

Disability – fatigue
Compared to men, women reported somewhat more fatigue, activity limitation, and lower mental health values throughout the three follow-ups, although the difference was not statistically significant regarding fatigue and mental health values at the second follow-up. The finding that the differences with respect to fatigue were not consistently significant through the consecutive measurements may reflect a questionable clinical significance, and is in accordance with the variation of conclusions in the literature about differences between women and men (Belza et al, 1993; Wolfe, 2004; Pollard et al, 2006, Huyser et al, 1998). Although the women were somewhat younger than the men, the correlations between age and fatigue were small (Table 2) and therefore age was not a likely explanation for the difference in fatigue.

The results concerning more activity limitation in women tally with other studies, and may partly be due to the lower grip force in women as a group (Thyberg et al, 2004). The reported levels of mental health values in the groups were similar to the levels of mental health values reported by patients with a longer duration of RA, and a larger proportion of women in a recent Norwegian study by Odegård et al (2005), and were similar to the levels of a Swedish reference population (Thyberg et al, 2005). In American patients with early RA, as well as in American general population norms, considerably lower levels of mental health values have been reported compared to healthy referents (Riemsma et al, 1998). In comparison with these differences, the difference in mental health values between women and men in our study was very small, and the clinical significance is questionable.
Regarding all disease and disability variables, there were no significant differences between the three follow-ups, in women or men. The absence of any signs of disease progress with respect to these variables, in the group as a whole, may be due to the early clinical intervention program. However, the interventions were individually based, complex, and modified according to repeated clinical assessments, and it is beyond the aim of this study to evaluate the effect of these interventions.

According to the results of the PCA in women, the first component included disease activity, activity limitation and pain. Although sleep disturbance had some influence on this component, a large part of the explained variance was shared with the former variables when describing the component. This component explained most of the variance in the MLR, and is in this discussion tentatively called physical disability. The second component included mental health values and sleep disturbance, representing high values for mental health in combination with low values for sleep disturbance, and vice versa. This component explained a smaller part of the variance, and in this discussion it is tentatively called mental aspects. The results of the PCA in men were similar to the results in women, although there were some differences. Paying attention to similarities, the components may tentatively be interpreted in the same terms as in women, i.e. physical disability and mental aspects. These interpretations of the PCA make sense in relation to the notion that RA is a pathologically well-defined somatic disease with a typical pattern of physical manifestations of varying magnitudes (Conaghan et al, 1999), and that the mental aspects of this may vary partly depending on psychosocial mechanisms which are not specific for the disease process, but more dependent on contextual factors (WHO, 2001).

According to the results of MLR in women as well as in men, the components physical disability and mental aspects together explained a substantial part of the variance in fatigue through the three follow-ups. The findings tally partly with the results of Pollard et al (2006), but their conclusion that the association between fatigue and disease activity is only secondary is not supported by the analysis. This is probably because a PCA was performed prior to the MLR instead of entering the set of inter-related variables directly into the MLR, to avoid the artefacts that have been discussed by Huyser et al (1998). Thus, it is suggested that disease activity is among those factors closely related to fatigue, and this conclusion is in accordance with the results of the intervention part of the study reported by Pollard et al (2006); that treatment with anti-TNF agents results in improvements in disease activity and fatigue.
Findings support the notion that fatigue is closely related to physical aspects of disability, such as pain and activity limitation. According to qualitative interviews by Tack (1990), patients with RA reported that constant pain along with different activities contribute to fatigue, and that fatigue is an important cause of activity limitation. According to a review by Fishbain et al (2003), chronic pain is fatiguing in a number of different diagnoses and sleep problems are commonly found in patients with chronic pain.

Findings also support the notion that fatigue is closely related to mental aspects, which may be a mental reaction to physical disability. In addition to conceptions of physical causes, the patients interviewed by Tack (1990) also felt that variations in fatigue were related to emotional stress. Huyser et al (1998) also concluded that fatigue is related to psychosocial variables, apart from pain and the disease activity per se. In addition to the possible influence from a prior affective disorder (Jump et al, 2004), it is possible that RA patients acquire mental health problems as a result of a complex interaction of pain (Dickens et al, 2002), activity limitations and participation restrictions, personal factors such as low self-efficacy and inadequate coping strategies, and environmental factors such as lack of social support (Huyser et al, 1998).

To a fairly great extent, the patterns of co-variation between fatigue and the studied variables seem to be consistent, because similar combinations of components explain similar percentages, i.e. 30-50%, of variation according to the MLR at the one-, two-, and three-year follow-ups. In addition to methodological explanations for the differences in the patterns of co-variation between the years in the group of men with regard to different measures assumed to explain fatigue, it is difficult to exclude the possibility of shifts in the conditions for different disabling mechanisms (Bickenbach et al, 1999). As shown by the variation in the beta-coefficients in Table 8, the component physical disability in women explained more than the component mental aspects at M12 (0.38 compared to 0.31), but less at M24 and M36, while the opposite was seen in men. A shift in disabling mechanisms may be influenced by contextual factors, such as assistive technology, social support, attitudes and financial assets (WHO, 2001; Bickenbach et al, 1999; Riemsma et al, 1998). In analogy with this, the different patterns of co-variation between women and men could partly be due to different disabling mechanisms, which may contribute to the greater diversity found in the group of men, as expressed by the standard deviations. These differences may also be partly due to methodological factors, such as differences in the sample size.
Disease – disease activity
Four similar components were generated independent of combinations of gender and/or cohort. The two baseline components, base1 and base2, were closely related to the two progression components, prog1 and prog2. Base1 and prog1 represented the level of (at inclusion) or change in levels (first 3 months) of disease and disability, while base2 and prog2 represented the level of (at inclusion) or change in (first 3 months) the inflammation indicator. The component base 1 had similarities to the ‘physical disability’ component in Paper III.

We found that the aggregate components ‘baseline status’ and ‘early progression’ together with serological markers RF and anti-CCP explained 26% of the variation in disease activity at M12 as measured by DAS-28 in the total clinical population. In line with previous reports, the component ‘early progression’ contributed most to the explained variance (Aletaha et al. 2007). As also has been found in attempts to predict outcomes in unspecified arthritis cohorts (van der Helm-van Mil 2007; 2008), such a component is not to be interpreted as disease-progression per se, but as disease progression confounded by diagnostic and therapeutic interventions The explained variance would probably have increased if the clinical intervention strategies used at clinics and by individual clinicians had also been modelled. The differentiation of RA into different phenotypes according to anti-CCP, as suggested by Klareskog et al (2009), is supported by our results which indicate that anti-CCP is a major contributor to the explanation of DAS-28 at M12 for men, thus indicating that anti-CCP to a major extent is related to a more aggressive disease.

Prognosis in early RA
The second aim, to strive for better potential to make a prognosis in early RA, can be considered twofold. The first part, using PCA and MLR to predict DAS-28 at M12, strived to understand more of the underlying components for good or poor prognosis in early RA. The second part, knowledge engineering to mathematically model expertise, strived to develop a methodology that makes use of heuristics in data mining methods to use in clinical databases.

Prognosis and underlying components
Aggregate components from ‘baseline status’, ‘early progression’, and from serological markers explained 26% of the variation in disease activity at M12 as measured by DAS-28 in the total clinical population. Two similar components (‘disease and disability’ and ‘inflammatory indicator level’) were found in both ‘baseline status’ and ‘early progression’, which in turn can be interpreted as support for the consistency of the components.
The components constituting ‘early progression’ contributed most to the explained variance, which is in line with previous reports (Aletaha et al. 2007). This component is not to be interpreted as a progression of RA per se, but as a progression of RA confounded by therapeutic interventions. These results are therefore hard to interpret in relation to the ‘pure’ progress of RA, because the clinical intervention strategies may have varied between clinicians. Nevertheless, the results can be interpreted in relation to ‘clinical practice’ which provided the best possible treatment at the time of this study. In general, DMARD was initiated both early and late in the TIRA1 cohort but almost without exception at M0 in the TIRA2 cohort. Some different DMARDs are also available in the TIRA2 cohort and the difference between the interventions is most probably the reason for the more rapid decrease in, e.g. DAS-28, PGA, and pain in the TIRA2 cohort (Table 9). Another contributory factor may be the additional inclusion criterion in the TIRA2 cohort; synovitis in at least one peripheral joint and a positive anti-CCP test.

Modelling heuristics – creating lenses of expertise
A knowledge engineering approach was used to transform data by means of a simple procedure using heuristic expert knowledge. The approach was shown to be more efficient when identifying prognostic subgroups than K-mean clustering of crude data. When mining clinical data for patterns, the results from such procedures must pass two ‘gateways’ to be clinically applicable:

- The ‘objective gateway’ – This means that the results fulfil some predefined criteria that can be statistically or mathematically evaluated, e.g. subgroups of patients differ significantly according to a defined outcome measure.
- The ‘subjective gateway’ – This means that the results are beneficial when applied in a clinical context, e.g. if results identify patients with poor prognosis, then they definitely have a clinical relevance in an RA context.

Results obtained using CRP and ESR in heuristic modelling, that identified different subgroups that were evaluated using PGA as outcome measure, clearly passed the first ‘objective gateway’, but are of minor clinical interest. This means the results did not pass the ‘subjective gateway’. The aim of this thesis was, however, not to use this approach to find clinically applicable results in the first place, but to develop a method for
modelling heuristics in an RA context and to evaluate its potential. Since the approach proved to be promising, the methodology will be used in further studies to address clinically applicable research questions.

The approach to identifying prognostic subgroups differs from most other approaches in subgroup discovery (Lavrač et al, 2004). Other approaches mainly address the problem of large search spaces using constraint knowledge (restricting the search space), pattern knowledge (focusing the search) or ontological knowledge (applying weights to attributes) (Atzmueller et al, 2005). In other words, such methods are relevant mainly for larger datasets.

Engineering knowledge in such settings usually aims to exclude uninteresting parts of the database. However, our main interest was not to mine data in large datasets, but to examine heuristic modelling of expert knowledge in a form usable in standard data mining methods. A cluster analysis of a medium-sized dataset (n = 279) was employed, but the approach can also be used in other statistical methods and on larger datasets. For instance, knowledge engineering modelling of expert knowledge can be integrated into other subgroup discovery approaches (Atzmueller et al, 2005; Silberschatz & Tuzhilin, 1996), and into other general approaches to knowledge engineering in databases (Fayyad et al, 1996).

To make results from advanced engineering methods or results from multivariate statistical methods available to the clinical arena, clinically interesting results are not only necessary, but the approaches must show how the results are generated. It must be possible to view and understand the generation of results without being a mathematical expert. Use of K-mean clustering can easily be viewed graphically, and that is the reason for choosing it in this study.

Design your own lens(es) of expertise?

Just a brief comment. Anyone, a professional clinician or a novice person, with an interest in prognosis can specify their own view of different measures available. For instance, there might be different opinions of when different ages are to be considered old or young. When I was a teenager my opinion was that persons over 30 years old were really old. Now my opinion at 36 years of age (yes, that’s my age) is that 30 is not old at all! (But I nevertheless often tell people that I’m ‘closer to 30 than to 25’ when they ask for my age.)

Similarities among and differences between such opinions (different lenses of expertise) could be very interesting to examine! (When I was a kid it was really fun to borrow my grandparents’ glasses because things looked, well, maybe not so interesting, but rather funny. And I certainly felt like an expert!)
One limitation of the model in its present form is that it is only applicable to variables on the interval-/ratio scale. In the next step the model will be developed to include categorical data. Different weights to different variables and different individually-based models will also be compared. Further research involving prospective outcome variables is warranted.

**Decision support**
The third aim of this thesis was to facilitate decision support. First a data-driven approach was used, followed by an environmental examination of decision-making.

*Data-based decision support when establishing prognosis*
In order to provide guidelines for the prescription of biologics, a set of simple decision rules were set based on data collected within three months after diagnosis. The rules can be used to predict disease activity one year after diagnosis. The performance of the prediction rules (sensitivity 25%, specificity 90%, PPV 76%) can be considered to justify further clinical studies in early RA settings. The results from this study are not to be applied without taking the individual patients into consideration, but rather as a powerful indication of which patients are at certain risk of aggressive disease. The prediction rules are nevertheless sufficiently easy to be useful in clinical practice. The results of our study can be helpful both in the process of identifying factors that can explain variations in outcomes on a group level and, most importantly, in predicting outcomes in individual patients (van Riel & Fransen, 2007).

The decision tree suggested for predicting poor prognosis performs great in relation to its simplicity. A major advantage is that the decision tree, in contrast to many other models that predict prognosis, is validated against a validation-cohort. To our knowledge its performance is the best prognostic model that has been validated so far. Its sensitivity, specificity and PPV are considered extremely high given the explained variance of 26% when predicting DAS-28 out of the predictors used in the MLR. Using the same methodology but with even more powerful individual predictors will probably reveal very high sensitivity levels with a retained high level of specificity.

The limits were generated from a data-driven approach – logistic regression analysis combined with an ROC analysis. Another approach would have been a theory-driven approach to specify limits. In further studies such approaches could be combined with data-driven approaches, e.g. by predefined limits on DAS-28 where the legal system allows biologics to be prescribed. and by letting the data set the limits on other variables. In further
studies the outcome variable may also be changed from DAS-28 to, e.g. radiological damage, pain, fatigue. The outcome may also be varied by the time measured, by prioritizing disease activity as an outcome for the first two years and by prioritizing joint damage as an outcome in late disease (Welsing et al, 2001).

The decision tree provided should be considered as a first attempt to identify which individual patients are candidates for even more aggressive pharmaceuticals such as biologics. Notably 12 out of 25 (48%) men in the validation-cohort who tested positive for anti-CCP and with a relative increase in DAS-28 the first 3 months not worse than 2%, in fact had a poor prognosis but were predicted a good prognosis. This is also compatible with the results from the MLR where anti-CCP was a major contributor to the explanation of variance in DAS-28 at M12 for men. The demand for high specificity in this study however ruled out the pure condition of positive anti-CCP in men as an indicator of poor prognosis. A similar argument could be made for women who tested positive for anti-CCP but with a DAS-28<6.16 and with a HAQ<1.3 who were predicted a good prognosis, but in the validation-cohort 26 out of 43 (60%) had in fact a poor prognosis. This indicates that testing positive for anti-CCP alone should be an indication of poor prognosis also for women.

In general, DMARD therapy was initiated both early and late in the TIRA1 cohort, but almost without exception early in the TIRA2 cohort. The difference between the intervention strategies is the most probable reason for the more rapid decrease in DAS-28, PGA, and pain in TIRA2 cohort (Table 9). The different treatment strategies were, however, controlled in the derivation phase of the prognostic decision tree, which showed good performance when validated regardless of treatment strategy.

Decision support in context – environmental issues
Identification of social and organizational requirements on a DSS utilizing data-mining techniques revealed that the clinical decisions at the RA-unit were based on interdisciplinary work and on a considerable amount of informal communication.

Decision-making in the inter-disciplinary setting was an ongoing process with the patient in focus. The patients were invited to be actively involved in the process. This can be described ‘as an integrated activity focused on the patient’ (Andersson et al, 2002). This view, emphasizing patient focus in the workflow, was found to be relevant for the RU in this study,
and needs to be incorporated into the process of designing a DSS for the rheumatology setting. Berg and Goorman (1999) have pointed out that healthcare is bound to the context of its production and therefore different practitioners in the same unit are not separated in practical work. Our study illustrates that this conclusion is particularly valid in the case of rheumatology, as expressed by this RU, in that many different health professionals work together and make decisions in cooperation with each other.

A considerable part of the decision support practices among the practitioners at the RU was informal, e.g. discussions in the break room during coffee breaks. Other occasions were when they met each other in the corridors (although careful considerations to integrity of the patients were taken, and confidential information was not discussed in the corridors), or by knocking on each others’ doors for short questions. The physical closeness, although sometimes expressed as frustrating, facilitated such interaction. These findings can be seen in light of a review of rheumatologist opinion by Kirwan (2004). He reported that continuous adaptation of the care system that includes non-physicians in the care pathways are, today, central components of rheumatology care. Understanding patients’ educational and decision support preferences will require more research.

Three key principles for successful system design suggested by Pratt et al (2004) are incentive structures, understanding workflow, and incorporating awareness. A DSS can achieve a significant position in the incentive structure at the RU only when the unit perceives that its gains exceed its costs. The DSS must provide a gain not only to the RU as a whole, but to every profession and every professional. Finding the optimal position of the DSS in the incentive structure requires further analysis involving all different levels at the RU, in order to avoid some groups or individuals paying all the costs while others gain all the benefits. Even though the incentive structure must be further examined, basic implications are that every professional should be able to access the DSS, and the DSS should provide relevant information exactly at the point in time when requested.

Integration of a DSS into the workflow must be based on patients’ passage through the unit, the formal cooperative structures such as the weekly conferences, and each professional group’s specific routines. This issue is especially complex since it will have an effect on the informal information practices that are highly dependent on the physical environment. Informal communication contributes to care in a positive way. Careful consideration must be
taken to avoid making the DSS disrupt these central structures and at the same time make the DSS a distinguishable expert system resource (Sim et al, 2001). To successfully integrate a DSS into the workflow, clinical as well as administrative routines have to be considered.

Awareness is facilitated by physical closeness at the RU (contributing to formal and informal cooperation), by the paper-based patient records (and the process of searching for the records when they are missing) and the weekly conferences. These facilitators were all considered ‘surfaces of communication and collaboration’. Such practices might in one sense be considered frustrating and time consuming, but in another sense they can all facilitate awareness, and contribute to a feeling of teamwork, which is of certain value in a context aiming for inter-disciplinarity.

Although integration into the practices of the RA unit was the primary purpose, some suggestions for clinical decision support can be expressed in a general manner. Three situations of support are outlined.

Between patient visits details from earlier patient consultations can be examined and related both to general tendencies of RA patients or to other patients showing similar patterns of RA. Earlier treatments and generation of new hypothesis in terms of underlying causes or effects of different treatment strategies can be evaluated. The use of automatic data mining (computer applications searching for patterns in data without the participation of humans except for the initiation of the process) can be introduced as a hypothesis generator (and/or hypothesis evaluator). Another use for the DSS between patient visits may be to present links to other sources of information, e.g. scientific papers, textbooks or links on the Internet.

Before particular patient visits the clinician needs information in order to be updated on the present status of the patient. The patient may have filled in a predefined computerized survey as a preparation for the visit. The information needed is an overview of the patient’s present disease status, the clinicians’ notes from earlier visits, and information that the DSS may provide when relating the patient to other patients in the database.

During the patient visit, the focus should be on clinician–patient interaction. In this situation the DSS must provide brief and relevant information useful for the clinician as well as the patient.
Methods
In this section different aspects of the methods used will be discussed.

Establishing prognosis for individual patients
Using a derivation cohort for derivation and a validation cohort for validation is common
practice in medical informatics. In the arena of RA research, however, there seems to be
numerous studies of prediction with only a derivation cohort, e.g. (de Vries-Bouwstra, 2006;
Courvoisier et al, 2008). Such results are lacking in validation, but could nevertheless be of
great value in clinical practice if validated against another cohort of early RA patients. The
validated rules pointing out patients with poor prognosis in this thesis should be applicable to
comparable populations exposed to similar treatment strategies. Validation against other
cohorts would nevertheless increase external validity, and validation against future patients in
the Swedish TIRA project would also increase internal validity.

The prognostic decision tree is constructed to identify patients with a poor prognosis. The
performance of the prognostic decision tree is not preserved if it is used to identify patients
with a good prognosis, because the validation is based on the prediction of poor – as opposed
to good – prognosis.

The limits used in the rules in this study were constructed from a data-driven approach. In
fact, there are several data-driven approaches that could possibly produce prediction rules that
perform equally as well. Additional studies using similar approaches may refine the prognosis
tree even further. An alternative is to use a theory-driven approach which determines certain
limits as a variant of heuristic modelling. In further research, different sets of limits defined
by different combinations of pharmaceuticals can be hypothesised and validated in a
procedure similar to the approach used in this study.

An issue of discussion is what should be considered as a poor prognosis. Defining a poor
prognosis as having moderate or high levels of DAS-28 at M12, as in this study, can be
considered both too conservative and too liberal at the same time. As powerful
pharmaceuticals are developed, and hopefully are less expensive, the results of medical
treatment are supposed to yield increasingly better prognoses for RA patients which implies
that remission levels of DAS-28 will probably be a better definition of a good prognosis in
years to come. In the context of this study, however, the most expensive and powerful
biologics could not be provided to every patient at risk of not reaching remission at M12, and we therefore chose to be more conservative in our definition of a poor prognosis.

**Components in early RA**

Interpretation of components in PCA is of course somewhat subjective, which may be regarded as a methodological disadvantage. If components are reported it is however possible for readers to make their own evaluations of whether or not the interpretations seem reasonable.

Nevertheless, it is possible to compare such interpretations if the components are reported. Like most interpretations, the interpretation of results from a PCA is not easy and not totally objective.

If the theoretical situation in disability research (WHO, 2001; Bickenbach et al, 1999; Bhaskar & Danermark, 2006) is taken into consideration, the interpretive part of the analysis may also be regarded as an important advantage because it may contribute to reflections on, e.g. conceptual issues. It is not reasonable to exclude any such reflections from the interpretation of the co-variation of studied variables.

One drawback of using PCA is that results are not as easily interpreted as when using more ‘pure’ measures. In contrast, if the variables in the component together represent a theoretically reasonable concept, the interpretation is more fruitful than when using many individual measures. The components in this thesis were interpreted as disease and disability, mental aspects (Paper III), levels of disease and disability, inflammatory indicator level, and changes in the latter two components over the first 3 months (Paper I). They were considered reasonable on a theoretical level, and were therefore not treated as too complex to use in further analyses.

When describing underlying patterns in the data, factor analysis is another method quite similar to PCA. In fact, many researchers treat PCA as a kind of factor analysis, but most statistical experts would consider PCA and factor analysis to be quite different methods due to their different mathematical approaches. PCA is however easier to interpret and describe, and from the point of departure that results should be as clinically applicable as possible, PCA was chosen because of this benefit.
Non-orthogonal rotation was chosen in the PCA because components were probably related. This was also indicated by ESR which was included in two components in Paper I. ESR was included in the component ‘inflammatory indicator level’, and DAS-28, which in turn includes ESR, was included in the component ‘level of disease and disability’.

**MLR and components**

Using components in MLR has benefits and losses. One loss might be the cases where a component predicts an outcome variable and where the component consists of numerous variables. It might in that context be difficult to determine the individual relationships between the variables in the component and the outcome variable. Such individual relationships can, however be examined by using each variable as a lone predictor to predict the outcome variable. Using components as predictors is one strategy to deal with co-linearity (correlations between potential predictor variables). In this thesis (Paper III) such an approach revealed the assumed, but in the literature debatable, relationship between disease activity and fatigue. Disease activity, as measured by DAS-28, was in fact among the factors that were part of the disease and disability component which in turn predicted fatigue in cross-sectional analyses.

One possible implication of co-linearity in this study is that RF and anti-CCP were not simultaneously significant predictors of disease activity (Paper I). Comparing women and men, RF was a significant predictor for disease activity for women, but anti-CCP was a significant predictor for men. Using PCA with RF and anti-CCP as variables would result in a component that could be called the ‘serological marker’. In fact, such an analysis was performed (data not included in the thesis), resulting in two components, and when the components were used as predictors in the MLR, the result was similar to when using RF and the test for anti-CCP as predictors.

One limitation of MLR is that it assumes linear relationships between the predictors and the criterion. Linear models are however often used in epidemiological studies and non-linear approaches require much larger datasets. Another limitation of MLR is in cases where data is sampled from two populations. In such a context, the results reflect the relationships in the compound dataset and a better model would be obtained by the use of two hyper-planes (two different MLRs, one for each population). Such a control was conducted according to Tengstrand et al (2004) by separating the women and men in both Papers I and III. Another
The suggested division would have been to make another separation based on test for anti-CCP. The results also support this division since anti-CCP is a predictor in the model that establishes the prognosis for individual patients. Even though most studies in early RA have not had such a separation of possible RA phenotypes in the study design, such separations are suggested to be implemented in future research designs.

Using the MLR model to predict DAS-28 at M12 is not to be applied to individual patients, although similar approaches have been used in such a manner (e.g. de Vries-Bouwstra et al, 2006). The results are not individual-based, but rather based on a group level. Such an analysis can, however, be interpreted as revealing possible explanatory factors, i.e. significant predictors can be considered to be contributors to the criterion if such a causal relation can be assumed in theory. If not, the underlying causal relationships to these predictors might be one step closer to the causal mechanism of the criterion. To be concrete, approximately one fourth of the variance in DAS-28 at M12 can be explained by baseline status measures, serological markers and early progression. Disease progression the first 3 months after diagnosis explains a major part of the variance. Consequently, we can conclude that the direction the RA disease may take is of considerable concern. From a medical informatics perspective it is therefore suggested that further studies to understand prognosticators of DAS-28 at M12 should focus on mechanisms constituting the progression of the disease.

From another perspective, however, another 3/4 of the variance in DAS-28 at M12 is not explained by components and serological markers. This might seem bad, but can also be positive since one of the most probable explanatory factors is interventions during the first year after diagnosis. If this is the case, it is a sign of successful medical interventions. Controlling for medical interventions is a complex task since different pharmaceuticals affect different components of the immunological response system, and which pharmaceutical that is preferable for each patient is therefore highly dependent on mechanisms that are yet not clearly described in the literature. Again, control for probable phenotypes of RA have the potential of explaining even more outcome variables and if so, support such hypotheses. Only disease activity and disability in combination with two serological markers were included as potential prognosticators. Genetic, environmental, and radiological factors are other prognostic factors not included.
When fatigue was used as criterion, the study design was a repeated cross-sectional design and not longitudinal. Therefore the prediction of fatigue is not really predictive. In strictly statistical terminology, however, ‘predictive’ means whether or not a set of values can predict another set of values, and what the data represents is not an issue. ‘Predictive’ is used in this sense when considering the practical meaning of the results. It is however true that the underlying components are not ‘predictive’ in a temporal sense, since predictors and criterion are measured simultaneously and causal conclusions have to be based on both empirical patterns and theory.

Another approach would have been to use the changes in different fatigue-related measures to predict fatigue at coming follow-ups. Although highly interesting, this would also be a very complex task since this is a cohort-study and not a randomized controlled trial. There are many factors such as different interventions, e.g. the newer biologics have shown to have positive effects on fatigue that need to be controlled for. Since the very nature and mechanisms of fatigue (causal relations) in early RA have not been well examined, the aim of this first step was to examine fatigue and to fatigue-related factors. Instead of using one set of cross-sectional data, three cross-sectional sets of data were used. Thereby insights were obtained into consistencies of relationships between the measures used. A study of disability with fatigue as an outcome aimed to give a first descriptive view of fatigue and to fatigue-related variables in early RA, a relatively unknown area of research.

**Heuristics modelling**

In heuristic modelling a number of questions may be raised. Is the modelling ‘the best’ modelling alternative? Is the modelling ‘representative’ of consultants in rheumatology? Is PGA a reasonable outcome variable of prognosis?

The answer to the first question is easy: No! Or, most likely not! There are most probably other better modelling alternatives that would produce other clusters of patients with more significant differences, according to PGA. The aim here, however, was not to find a ‘best model’, but to find ‘a model’ and evaluate its potential in comparison with the use of crude data. We can ask if in clinical practice there will ever be such ‘best models”? Most probably we can say that some day, at least in theory, there will be an even better model than the golden standard (‘best model’) at present.
To answer the second question above, i.e. if the modelling is ‘representative’ of consultants in rheumatology, the answer is simply: ‘Go ask them’! The model is a compound of these five interviews and should not be considered as an exact modelling of each particular individual in the study. What is interesting is that there are such heuristics that at least remind us of the model, and that the model, in its present state, does separate different prognostic groups better than crude data.

To answer the third question above, if PGA is a reasonable outcome variable for prognostic studies, the answer is that this could be debated. Results from Paper I revealed that PGA hardly has any correlation with DAS-28 at M12. Therefore, the prognostic performance of the heuristic modelling could be questioned. This is, in contrast, true also for CRP, whereas ESR correlated significantly with DAS-28 at M12. The clinical application of results, however, is beyond the scope of this study. The aim was instead to examine the potential of the methodology. Although the validity of PGA as a prognostic outcome variable could be questioned, the methodology of the heuristic modelling could be considered as a promising approach useful in subgroup data mining.

**Observation and focus group interviews**

Using observations followed by focus groups in this thesis was from a quite practical action oriented approach. The main aim was to reveal some knowledge of societal and organisational requirements when introducing a DSS. Observations were aimed to identify information practices, decision practices and events central to daily care. Interest was primarily on actual practice rather than on its underlying reasons. Starting with the predefined areas of interest, no formal presumptions were made. The observations made generated, in an inductive manner, theoretically interesting concepts – key factors – to be further examined in focus groups. This approach was partly influenced by grounded theory (Glaser & Strauss, 1967). In the focus groups things not observed, but nevertheless present in the opinion of clinicians, were examined. This approach has commonalities with institutional ethnography approaches, which are primarily used to reveal power relationships and other characteristics of the institutions.
within which they operate (Babbie, 2008) by starting with the experiences of individuals. A third ‘methodological cousin’ to this approach is participatory action research, which is an approach in which the people studied are given control over the purpose and procedures of the research (Babbie, 2008). Even though the method focus group interviews was predefined, the clinicians contributing to the study were nevertheless able to adjust the discussion during the interviews, deciding what was important to talk about.

**Prognosis**

Prognosis in the study was limited to prognosis in the earliest stages of RA. For individual patients, the major concerns probably concerns long-term prognosis. The prognosis at M12 could, however, be considered as an early indicator of the long-term progression of the disease. If the first two years are predictive of the overall development of RA (Scott, 2002), it is reasonable to assume that preventing RA progression this early will improve the overall outcome of the disease, and thereby prevent disability.

The finding that progression during the in the first 3 months contributes considerably to disease activity at M12 supports the findings by Aletaha et al. (2007). The components ‘levels of disease and disability’ and ‘inflammatory indicator level’, however, indicate that measures in addition to disease activity can be used as prognosticators of disease activity at M12. Using early arthritis initiatives databases, such as the one in the current Swedish TIRA cohort, will enable investigations of such interactions and point out the direction for further investigation, e.g. mining databases for patterns (tendencies) indicating underlying interactions in possible mechanisms of RA progression. Such findings must be validated; preferably using prospective data in normal populations. Another approach could be to use a validation cohort as in this thesis (Paper I).

Besides pointing in the direction of prognosticators and their power to predict disease activity at M12, the study also provided prognostic rules for use with individual patients. The prognostic rules were constructed and validated according to two different treatment paradigms in early RA. The methodology used when constructing the prognostic rules will nevertheless be useful when constructing other prognostic rules, e.g. for outcome at two years after disease onset, for radiologic progression.
**Guidelines treatment strategies and interventions**

**Medical treatment and guidelines**
The present collaboration between ACR and EULAR (Klareskog et al, 2009) will most probably contribute to even further positive changes in clinical practice. Both ACR and EULAR guidelines address medication, although EULAR also more explicitly focuses on patient education and non-pharmacological interventions. Even though it is seven years since the last update of the ACR guidelines, the introduction of new pharmaceuticals and new combination regimens have continued to evolve. In this thesis, patients with a poor prognosis are pointed out as candidates of still more aggressive therapy, perhaps combination therapy as suggested by van der Kooij et al (2009). Since the patients with signs of disease activity progression the first 3 months (as indicated in Paper I) most often have a poor prognosis, a suggestions for treatment strategy can be made: Consider starting with even more aggressive treatment at the time of diagnosis, e.g. combination of traditional DMARDs, or a biologic.

**Rehabilitation**
Patients with RA benefit from medical and rehabilitation strategies. In the following the findings in this thesis are discussed in relation to those strategies.

**Prevention**
Preventions of the causes of RA were not investigated in this thesis. Such preventions would involve studies at the *aetiological* level, and such studies are better suited for clinical research designs such as Kastbom et al (2007). Studies of environmental factors that possibly affect aetiology might also give clues to prevention, e.g. smoking or eating habits.

Preventions of the progress of RA are however a main concern in this thesis, first by indicating prognosticators in the earliest phases of RA, and second by construction and validation of a prognostic model of poor outcome (moderate or high levels of DAS-28 at M12).

**Cure**
‘Cure’ is not yet fully achievable in RA, although there are persons with undifferentiated arthritis that goes into spontaneous remission (van der Helm-van Mil et al, 2007), and it has also been debated as to when disease control is achieved (Pincus et al, 2006). This thesis has mainly addressed disease activity, but primarily concentrating on patients not even close to remission. Minimal disease activity is a relevant goal (as in Wells et al, 2005), but not
necessarily a sufficient (Smolen et al, 2006b). What is more important is whether the RA disease contributes to disability or not, both in the short- and the long-term. Therefore, there is no reason for a definition of remission (‘cure’) that excludes medication or other interventions (Smolen & Aletaha, 2006a). ‘Cure’ in this sense, mainly concerns control of the mechanisms constituting the disease. This is mainly achieved by medical interventions such as conventional DMARDs in single or combination therapy, or biologics.

*Rehabilitation and support*

Living with the *symptoms* of RA disease might be disabling, but rehabilitation and support aim to help the patient overcome disability even in the presence of symptoms. The effects of interventions such as exercise programs or coping strategies are not examined in this thesis, but are nevertheless important issues when dealing with disability in relation to RA.

**Different goals in RA-rehabilitation**

The perspective in this thesis can mainly be seen as clinical, because remission, disease activity and progressive joint damage are described as major concerns of clinicians (Scott et al, 2005). The patients’ worries (pain, psychological impacts and fatigue) are nevertheless included in the study of fatigue in Paper III. This is one step in the direction of the primary goals of the patients. Different patients might of course express different factors as their major concerns, as do different clinicians.

In the following, a case will be made for inter-disciplinary team care. In the next section multi-disciplinary team care will be discussed, and later it will be extended to inter-disciplinary team care.

**Multidisciplinary team care**

The cycle of rehabilitation (Stucki, 2005) (Figure 2) illustrates the different focuses of different clinicians. But at the same time, the clinicians are part of the very same process with a specific patient at the centre. Patients are described as active participants in the care process (Petersson, 2006). In fact, the patient could be involved as a participant in the cycle of rehabilitation as an expert along with clinicians. Clinicians are experts on body functions and body structures in general and in RA in particular. Patients are also experts in RA, but on how RA is constituted in their own lives.
Multi-disciplinary care is, although common, not the only approach suggested. Other equally successful approaches have been observed (Vliet Vlieland et al, 2006a) and other approaches might also be better suited in situations where multi-disciplinary approaches are impossible. The purpose of this thesis is not to evaluate team care, but to examine questions of disability in RA settings in which multi-disciplinary team care is common practice. Nevertheless three comments will be made. First, in situations or countries where multi-disciplinary team care is impossible, another approach must be used, especially in cities or villages far from the nearest RU. Evaluating other approaches in comparison with team care approaches is a complex task. Second, different professionals have different areas of expertise depending on their education or prior experience. Other differences may be whether the focus is on individual patients, certain RUs, or society as a whole? This task also includes ethical considerations, such as if it is ethically valid not to treat some patients, e.g. who live far away from an RU, to the benefit of other patients, e.g. patients who live close to an RU? Third, multi-disciplinary team care is, regardless of efficacy, the most common practice in RA settings in Western countries.

From a perspective of disability research, which is the discipline this thesis is based on, multi-disciplinary approaches have advantages, especially when extending them to inter-disciplinary approaches. This will be discussed in the next section.

Use your own lens(es) of expertise and cooperate!

In this thesis the potential of different individuals is seen from an optimistic perspective. Everyone has some unique and potentially useful knowledge or experience to offer. This uniqueness could be considered as a lens of expertise. And when many experts gather together there is, at least in theory, a larger ‘mass of knowledge’ available. Here a recommendation is made for cooperation in such situations.
Disability and inter-disciplinary team care

Addressing RA disease within the theoretical framework used in this thesis necessitates analyses at different levels and different strata of reality, e.g. by focusing on RA patients’ experience of fatigue. Such reasoning could be done at the psychological level of reality, since experiencing fatigue is clearly psychological. Can fatigue then not be explained by manifestations at other levels of reality than the psychological level? The answer is yes and no. No, since the psychological experience of fatigue is determined by psychological mechanisms. Yes, since actual and empirical happenings are affected by mechanisms at other levels of reality, and include mechanisms at other levels of reality, e.g. fatigue can be explained by the mechanism of pain affecting cognition and thereby causing fatigue, but pain in RA is affected by inflammatory processes in the joints. Fatigue could also more directly be treated as affected by hormones which are present at the biological level of reality. But the mechanism that steers the experience of fatigue nevertheless works at the psychological level.

The discussion of levels of reality is certainly valid in a context of disability research that accepts as valid the biopsychosocial model of disability. The different levels of reality motivate focussing on different phenomena, such as RA-related disability, at different levels. This in turn motivates people with different expertise to join together around a common phenomenon to gain a common understanding. In the case of RA, physicians are experts on pathophysiology and medical interventions to modify such processes, occupational therapists are experts on activities in daily life and how to facilitate these activities by training and assistive devices, health economists are experts on calculating the gains of expensive treatment strategies on personal and societal levels. These are all examples of expertise in the same phenomenon, RA, which are of importance for both individual patients and for society.

There would be a certain risk of reducing the complexity of different phenomena to one level of reality if this division into different levels of reality was not made. This is the case in the bio-medical model of disability (Smart & Smart, 2006; Bickenbach et al, 1999). In such cases studies of hand-function and assistive technology for support would be of no interest. Another such reduction is the social model of disability (Masala & Petretto, 2008) which uses only
mechanisms at the social level to describe disabilities. In such cases medical interventions would be of limited interest since what is considered important would be to organise the society so people with RA would be able to participate in the same way as people without RA.

The definition of disability in this thesis is a phenomenon including persons in relation to biological, psychological, and social levels of reality. In the life of RA patients, as well as in the lives of all other people, there are mechanisms present at all levels of reality. What is considered most important might be very different between different persons and on different occasions. What should be treated as a treatment goal could therefore be related to this discussion. Clinical remission (no or minimal evidence of the inflammatory response) or structural remission (no further radiographic changes) are of course important to achieve (Smolen & Aletaha, 2006a), but they both clearly focus on the physiological level of reality, including body functions. Even the ‘functional remission’ concept tends to focus likewise. In real life minimal disease activity or minimal radiographic changes are positive, but from the theoretical perspective of this thesis they are not decisive (although contributative) mechanisms in real life situations as far as participation in real life situations.

Attributing the biopsychosocial model of disability to the collaboration of experts at different levels of reality contributes to expanding the sphere of discussion. The multi-disciplinary care approach used in most RA settings (Petersson, 2006) in Western countries is thereby preferable from a theoretical perspective even if there can be situations where other approaches are required. In the best of worlds, such conditions of multi-disciplinary ‘modus operandi’ are a basis for inter-disciplinary approaches. Awareness of each other’s goals, activities, and expertise might facilitate the move from multi-disciplinary care to inter-disciplinary care. One reason for findings reported by Vliet-Vlieland et al (2006b) that similar results can be achieved with other approaches, although with lower levels of patient satisfaction, might be that the collaboration of multiple professions were in fact ‘multi’- and not ‘inter’-disciplinary. Research into outcome related to the process of ‘team care’, preferably using ICF, is warranted (Petersson, 2005).
The cycle of rehabilitation can be productive as well as contra-productive when aiming for inter-disciplinary care. Awareness is a key feature! To work physically close might be one such awareness feature as along with weekly conferences (Paper IV). Research following the cycles of rehabilitation is an interesting approach with potential to reveal interactions between interventions at different levels of reality intervened by different professionals.

When using ICF in an RA setting, the focus from a disability perspective might be questioned. ICF is aimed at describing health conditions. To be practically manageable core-sets for RA were produced using a Delphi procedure including 7 physicians and 7 rheumatologists, but only one nurse, one occupational therapist and one physical therapist (Stucki et al, 2004). The concepts included in the RA core sets might be affected by this ‘un-balanced’ group composition. Assuming that physicians’ primarily focus is on body functions (a reasonable assumption since disease activity is a body function concept) one would expect most studies to include such concepts, if studies adopted the ICF terminology. A review of concepts used as outcome measures in RA studies between 2000 and 2004 showed, however, that activity and participation concepts were used in amounts similar to concepts of body functions (Zochling et al, 2006). Concepts linked to environmental concepts represented only 3% of the concepts, but this is however reasonable since the review concerned outcome measures. The study by Stamm et al (2005) reveals that there are additional concepts not included in the RA core set. One such concept used in this thesis is fatigue (fatigability).

ICF is however a useful tool that facilitates discussion about disability by providing concepts related to different aspects of disability, and thereby to different levels of reality. Even if ICF is criticised for not considering the will of individuals, (Nordenfeldt, 2003) ICF can nevertheless be a useful framework for preventing the reduction of reasoning around disability which would yield only for one level of reality.

**Medical informatics**

One of the major aims of medical informatics, early recognition and prevention (Haux, 1997), has been an underlying focus throughout this thesis, conceptualized by the effort to early identify RA patients with a poor prognosis to prevent future disability. Knowledge, or expertise, has been examined by analyzing existing heuristics and representing these in a simple model for use in data mining. Knowledge is also represented as a validated decision tree to indicate which patients have a poor prognosis given a certain treatment strategy.
The decision tree can be considered as a knowledge-based decision support scheme. Thereby is also a second aim of medical informatics, according to Haux (1997), included in this thesis; knowledge-based decision support. It would, in theory, be an easy task to apply the decision tree in a clinical information system to highlight when to be observant of poor prognosis. In practice, however, the adaption of such computer systems is a much more complex task requiring consideration to features mentioned in this thesis, e.g. awareness, incentive structures, and informal communication patterns.

From a disability research perspective, medical informatics might be considered too focused on disease by focusing on body functions, body structures and interventions affecting the disease, and overlooking that disability is also concerned with activity and participation matters. Two potential reasons for this are the history of medical informatics and the levels of reality where most measures available for medical informatics are present. First, since medical informatics was developed with the aim of establishing diagnoses, the methods were naturally developed in relation to disease-related measures constituting mainly body functions, body measures and interventions affecting the disease. Influences from the disability research area might positively change this by contributing to methods that also include measures constituting activity and participation, as well as contextual factors. Second, when measuring different aspects of reality, e.g. aspects related to disability, it is easier to apply quantitative measures when examining features at the lower levels of reality. The higher the levels of reality, the more social constructions are built into the concepts, and constructions are per default not as easily quantified. Since measures in medical informatics need to be quantified to be practically manageable, the focus on the lower levels of reality is naturally most easily attained.

A concrete example in relation to the discussion about inter-disciplinary care, gold standards and models of disability will be outlined. A possible direction for further research based on the results and discussion so far in this thesis will also be outlined.
Decision support suggestions with implications for clinical practice

Today there are large amounts of clinical information available. With the introduction of electronic patient records, clinical information can more easily be transformed to formal registries that can be used in research, even though such transformations are prohibited by the lack of clinically accepted standards. One promising initiative is SNOMED-CT (Cimino & Zhu, 2006), but using ICF can, from a perspective of disability research, prove to be fruitful.

Assuming that large clinical databases are becoming easily available, new generations of decision support application can be based on these. The term ‘decision support system’ could be used as well, but ‘decision support application’ is used here since it is a more general description better suited to describing the idea of an approach rather than the implementations of the approach. The idea of the suggested decision support application is primarily related to the time between patient visits, where patterns in clinical manifestations from different or similar patients might be of interest. The new generation of decision support applications, with particular applicability in rheumatology, is one of automatic data mining. It is described below followed by some concluding remarks.

Different focus – and the role of ICF

First, different professionals, e.g. physicians and occupational therapists, have different focuses on the same clinical phenomenon and therefore they might be interested in different outcomes. The physician might focus on disease activity while the occupational therapist might focus on fatigue. The application will therefore permit different outcomes of interest to be permitted.

ICF might play a role in this case since the division into body functions/body structures, activities and participation, and contextual factors might help by widening the awareness of the phenomenon of interest, in this thesis RA. This is a recommendation affirming the biopsychosocial model of disability. From another perspective, using ICF terminology can also be considered an awareness factor.

Put in relation to remission, the application will allow different opinions of remission, e.g. whether or not remission should include medication.
Different perspectives – inter-disciplinary care and awareness

Second, different professionals might have different ideas of the causal mechanisms of a disease and their relative power. For instance, a physician may consider the test for anti-CCP as being of the uttermost importance when establishing the prognosis in relation to disease activity, while an occupational therapist might consider environmental factors as just as important when dealing with fatigue in the same patients. The application will therefore enable users to assign different weight to different measures related to assumed causal mechanisms.

The application will allow clinicians to examine relations to and differences between different measures of interest for the outcome focused on. In this sense it will fit into a multi-professional care context. If there are organisational prerequisites for collaboration and discussions between clinicians with different professions, the application will have the potential to act as an awareness factor while it can encourage discussions of the different results generated. Put in relation to the findings in this thesis such an application might at least partly have a function similar to the paper-based medical record in Paper IV.

Different knowledge – implications for gold standards

Third, different clinicians within the same profession have different experiences. Even though there are sometimes gold standards or clinically approved guidelines telling them how to make decisions in certain situations, real-life situations are rarely (ever?) perfectly matched by such recommendations. There is always an area of allowed variation where the clinicians have to use their own experience and common sense. This permitted scope might be exemplified by different opinions of what should be considered as high measures of ESR. Maybe there is a variation in opinions of what should be considered high given some other circumstances? Enabling clinicians to specify their own views, based on their personal experiences, on different measures in an easy to use graphical computer application, e.g. like in Paper II, would yield interesting potential to find interesting patterns in data using data mining methods.
Using medical informatics in this manner might seem challenging to the view of gold standards. Gold standards can be considered as being methods of the best available and agreed on expertise, given certain circumstances. Such gold standards in RA are stated in the guidelines provided by ACR and EULAR. There may, however, be an incongruity between the gold standards and developments in clinical care. New treatment strategies, interventions or explanations of causal mechanisms are first discovered, validated, and thereafter, if proven more successful than the best possible method or explanation given, ascribed the status of a gold standard. The application might in this case be considered a magnet with the potential to pull the golden standards in a developing direction.

Due to the fact that some interventions are discovered by mistake or pure chance (e.g. the finding of penicillin by Alexander Fleming in 1928), even invented perspectives can be allowed to use in the application. E.g. a novice clinician might have a clinically considered poor hypothesis of measures of disease at the time of diagnosis in RA, but sometimes the true reason for being afflicted with RA might be such an odd reason that an experienced clinician would never come up with the idea. Allowing such odd ideas might reveal unexpectedly relevant and interesting findings. Another, at least in theory, possible alternative would be to allow patients to put their own views into the application and thereafter mine the data. Such possibilities would be interesting in a variety of ways. Patients have knowledge from experiences of living with RA which most clinicians do not. Such knowledge is not often implemented into research aimed at examining epidemiological mechanisms. Even more interesting is the potential that such an application would provide for finding out what patients in fact do know. Such potential would enable the application to reveal insights into perspectives based on experience that could be evaluated both qualitatively and quantitatively. This is also a way to ‘enable people with disabilities to lead the life that they would desire’ (UEMS, 2007), and patients would in this manner become even more central to the practice of health care.
**Automatic data mining**

*Fourth*, a comment on automatic data mining (computer applications searching for patterns in data without the participation of humans except for initiation of the process). One often applicable strategy in health care is to let computers do what they do best and let humans do what humans do best. In relation to the application computers are suggested to mine for patterns in data, but humans have to initiate such a process specifying what to search for, what perspective to search from, or what can be considered as already known. The time suitable for such initiations is between patient visits. There are numerous ways in which data mining can be performed, and one such approach is taken in this thesis by the use of K-mean clustering to identify different subgroups (Paper II). Automatic data mining delivers results that have to be evaluated.

**Gateways on the way to golden standards or clinical practice**

*Fifth*, results generated from automatic data mining procedures need validation. Such validation procedures can be described in terms of the ‘gateways’ described earlier (objective and subjective gateways). Results passing through the objective gateway (statistically validated results) and through the subjective gateway (clinically interesting results) can be used in three ways:

- First, they can be used to describe the cohort that the results were based upon. Such descriptions might be of considerable value and might have implications for clinical practice in the clinical settings that provide the data.
- Second, results can indicate causal mechanisms causing destructive disease progression. They can thereby be considered as hypothesis generators.
- Third, results can be validated against another validation-cohort and thereby in the next step be usable as evidence in clinical practice. This was the case in Paper I.

**Example**

*Sixth*, an example is provided of how such an application could work when implemented in a clinical setting. For some time Dr Dasco Re has thought about the role of sex hormones in relation to RA. Since analysis of anti-CCP has shown high diagnostic specificity for RA, he wants to examine the relation of anti-CCP, gender and disease activity at one year after diagnosis. He is of the opinion that patients with moderate or high disease activity one year after diagnosis suffer more from the disease than patients with low or remission levels. He also wonders if age has something to do with disease activity at one year after diagnosis.
Based on the fact that in younger age groups considerably more women are afflicted with RA than men, than at higher ages, Dr Dasco Re wants to divide patients according to age and compare these groups, but he is not sure how to divide patients into age groups.

It is Friday afternoon and he will be leaving for a free weekend in about ten minutes. Before he leaves he starts the new application at the RA unit and specifies the outcome variable with the specified limits of interest and also the variables he wants to relate to the outcome. After that he leaves.

The application however does what computers do best and mines the underlying database of clinical data from a cohort of early RA patients. During the weekend the application runs and saves all results that pass through the objective gateway.

On Monday morning physician Dasco Re opens his mailbox and has received an e-mail from the application. It contains a top-ten list of hyperlinks to the potentially most interesting results. Checking the short summaries of the results, two results pass through the subjective gateway, and at the next meeting with other clinicians Dasco Re summarizes the results for discussion among his colleagues.

Concluding remarks
The example above is one in which research is brought close to the reality of everyday clinical practice. In this way knowledge gained from experience has greater potential to affect the research mainly through the production and pilot testing of hypotheses. This is in line with participatory design initiatives (Pilemalm & Timpka, 2008). Of course, the underlying mechanisms of the RA disease have to be examined in clinically controlled studies, but the approach suggested here can be indicative of what to examine in clinical studies.

Limitations
One limitation of the analyses reported in the thesis is that comparisons between the TIRA cohorts are hampered by the differences in inclusion criteria, and by the progressively increasing knowledge about treatment strategies available for the treatment of TIRA2 patients. There was also a larger set of DMARDs available for the treatment of TIRA2 patients. It is, however, reasonable to assume that the same underlying causative
mechanisms were present in both cohorts. Some controls for the different treatment strategies were made in Paper I. Controls for more specific treatment alternatives, e.g. controls for different DMARDs or different combinations of DMARDs, are promising future research alternatives but they will demand larger sets of data than are available for the analyses in this thesis.

Another limitation is that the discussion and recommendations about using biologics are based on the assumption that they are successful alternatives for most patients. In this thesis, there is no evidence to support that biologics are more effective treatment alternatives. Rather, such an assumption is made based on literature on RA treatment (Nurmohamed & Dijkmans, 2008). Furthermore, no investigation was done concerning possible side-effects from any pharmaceutical, used or suggested to be used, throughout this thesis. Therefore all clinical implications based on the results have to take side effects into consideration.

The patients included in the study were also given other interventions, such as glucocorticoids, physical exercise interventions and assistive devices. However, since the outcome variables in the thesis were disease activity and fatigue, such interventions were omitted with the assumption that no major influence on the outcome variables could be ascribed to the omitted interventions as compared to the measures in fact included.
Summary and suggestions for further research

Summary
In this thesis the biopsychosocial model of disability was advocated as opposed to, e.g. the bio-medical model which might be considered too focused on body functions and body structures. Nevertheless, the focus was on chronic disease with measures primarily of body functions and structures. Even though most measures were of body functions and body structures, the aim was to prevent disability.

Methods from medical informatics were used to identify early RA patients with a poor prognosis. Disease progression the first three months after diagnosis was found to be a major prognosticator of disease activity at one year after diagnosis. A positive test for anti-CCP seems to predict a poor prognosis, especially in men.

The focus on expertise has also been modelled in a simple mathematical model. The model was evaluated according to prognosis, and managed to better identify significantly different prognostic groups of patients when using K-mean Clustering, than when using K-mean Clustering on crude data. The focus on expertise, modelling it mathematically, and using it in data mining procedures needs to be further examined.

Disability, examined as fatigue, is related to disease activity, pain and activity limitation, as well as to mental health and sleep disturbances. Women report more fatigue than men in early RA.
Suggestions for further research
Numerous implications for further research can be derived from this thesis. However, only a few suggestions are proposed.

Disease and disability
- Different theories about the presence of causal relations could also be tested by using Structural Equation Modelling methods. Some relationships between fatigue and fatigue-related variables are discussed in this thesis. It would be interesting to examine alternative causal models against empirical data.
- Using a longitudinal design examining progression of RA disease to predict fatigue prospectively would be a suitable next step based on Paper III here. It would possibly give a more comprehensive understanding of fatigue related factors and also better understanding of the similarities and differences between women and men in relation to disease progression and fatigue.
- It would also be interesting to clarify how fatigue and other variables such as pain and contextual factors contribute to work disability, which is an important issue in early RA.

Prognosis in early RA
- Identification of more prognosticators (factors recorded in early disease that can explain variation in central disease outcome) would give even more sensitive prediction rules with retained specificity.
- The development of modelling procedures to include expertise perspectives on categorical measures.
- Comparison of different fields of expertise by comparisons of the performance of different mathematical models representing different heuristic knowledge, to gain new knowledge of gains and losses depending on prior experiences.
Decision support

- Other approaches to identify limits to use in prediction rules could include theory-driven approaches, e.g. by the use of predefined limits of DAS-28 where the health system provider allows the prescription of biologics, and data-driven approaches for other variables.
- Use different criteria for poor or good prognosis.
- Use the same approach for prediction as in this thesis, but with another outcome measure, e.g. DAS-28 at two years after diagnosis, or radiological change at two, three or eight years after diagnosis.
- Involve more control in the analyses for different treatment strategies.

Summary

In general, three different suggestions have been made about different lenses of expertise:

- Use different lenses of expertise to get a better view of whatever is in focus (inter-disciplinary team care).
- Try to design the lenses of expertise and loan them to non-experts making them ‘wiser’ (heuristic modelling).
- Try to design the ‘best’ possible lenses that will make experts even ‘wiser’ experts (mine large amounts of data and try to come up with something clever).

In the end, I don’t know if you normally wear glasses or contact lenses, but one thing is certain: You do wear some kind of lens(es) of expertise! If you do your best to contribute from your expertise-perspective, together with other experts, to gain a common understanding about something then there is greater potential that all of you together will come up with something really useful!

Such an approach is suggested throughout this thesis, and ideally such practices will provide new knowledge of how to prevent disability in rheumatoid arthritis as well as in other chronic diseases.
Conclusions
The conclusions in accordance with the aims are given below.

**Disease and disability**
- Women report more fatigue than men in early RA, although the difference is not consistently significant.
  
  *Concluding remark*: Further studies are warranted to clarify the causal mechanisms related to fatigue, in order to learn more about differences in fatigue and fatigue-related mechanisms between women and men.

- Fatigue in early RA is closely and rather consistently related to disease activity, pain and activity limitation, as well as to mental health and sleep disturbance.
  
  *Concluding remark*: Considering the related concepts measured when treating patients with RA, fatigue can possibly be prevented or limited.

**Prognosis in early RA**
- Using different types of knowledge – different fields of expertise – prior to standardized data mining methods is a promising method when mining (clinical) data for new patterns eliciting new knowledge.
  
  *Concluding remark*: In future studies the application of the methodology used in heuristic modelling to more clinically relevant data is warranted as well as development of the model to include ordinal or nominal measures.

- A considerable part of the variance in disease activity at one year after diagnosis can be explained by disease progression during the first three months after diagnosis.
  
  *Concluding remark*: Disease progression during the first 3 months after diagnosis is an important prognosticator of disease activity at one year after diagnosis.
**Decision support**

- A prognostic tree that predicts patients with a poor prognosis (moderate or high levels of DAS-28) at one year after diagnosis yielded 25% sensitivity, 90% specificity and had a PPV of 76%. The prognostic tree was comparable to other prediction initiatives in the literature, but as opposed to most such initiatives, it was also validated against a validation-cohort. The prognostic tree can also be considered easier to apply clinically than present methods.

  **Concluding remark:** The decision tree can be used to identify patients at certain risk of poor prognosis at one year after diagnosis of RA, but the potential side-effects of pharmaceuticals when deciding about pharmaceutical interventions should be taken into consideration.

- Incorporating decision support by a decision support application at an RU should include incentive structures, workflow and awareness. Informational communication structures can have a large impact on clinical practice.

  **Concluding remark:** Decision support applications could have the function of awareness factors that support informal (and formal) communication patterns. All potential users should be included in gains as well as costs of using decision support applications.
Sammanfattning på svenska

Introduktion: Reumatoid artrit (RA) är en kronisk inflammatorisk sjukdom. Dagens behandlingsstrategi bygger på tidiga multiprofessionella insatser för att reducera sjukdomsaktivitet och minska risken för framtida funktionshinder. Idag finns stora datamängder tillgängliga gällande medicinering och utfall vid RA. Dessa data erbjuder möjligheter att generera ny kunskap som kan användas för att forma beslutsstöd.


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