Diffusion, implementation and consequences of new health technology

**The cases of biological drugs for rheumatoid
arthritis and the Swedish national guidelines**

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Jesper Waldersten

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ABSTRACT

Improvements in health technology raise hopes for better patient outcomes and a more efficient delivery of health care. However, the processes of diffusion and implementation of new health technology have turned out to be complicated and to pose a number of challenges for the healthcare sector. Many attempts have been made to influence and manage the introduction and diffusion of health technology. A prominent example is the Swedish national guidelines that aim at influencing both clinical and political decision-making in the health sector.

The overall aim of this thesis is to describe and analyze the factors influencing the diffusion and economic consequences of the introduction of a new health technology with large variations in use, and to explore the process of implementation of nationally produced guidelines as an instrument for improving effectiveness and equity. The empirical focus is kept on the new effective but very expensive biological disease-modifying antirheumatic drugs (bDMARDs) for rheumatoid arthritis (RA), since they implied a substantial treatment change when they were introduced; and on the national guidelines for cardiac care, since they were the first national guidelines produced, hence allowing a long-term perspective in the exploration of their implementation.

Paper I presents a register study with data from national and regional registries on healthcare use and work participation in patients with RA and shows that there was a 32 percent increase in the total fixed cost of RA during 1990-2010, mainly after the introduction of bDMARDs. Paper II shows that the prescription of bDMARDs varied substantially among 26 rheumatologists who were presented with hypothetical patient cases, and that there were also disparities between rheumatologists practicing in the same clinic. Paper III presents data from the Swedish Rheumatology Quality Register covering 4010 RA-patients, and shows that physician preference was an important predictor for prescription of bDMARDs, when using multivariate logistic regression to adjust for patient characteristics, disease activity and the physician's local context. Paper IV is a

qualitative study about prescription decisions, showing that a constellation of various factors and their interaction influenced the prescription decisions of 26 interviewed rheumatologists. The factors included the individual rheumatologist's experiences and perceptions of evidence, the structure of the department including responsibility for costs, peer pressure, political and administrative influences, and participation in clinical trials. The patient as an actor emerged as an important factor. Paper V is a longitudinal qualitative study exploring the responses among four Swedish county councils to the national guidelines for cardiac care through 155 interviews with politicians, administrators and clinical managers. The results show that unilateral responses to the national guidelines within the county councils have been rare, but there have been attempts to compromise and to attain a balance between multiple constituents. There are examples of local information meetings, the use of the national guidelines in local healthcare programs, and performing audits with the national guidelines as a base. But performing explicit prioritization, as advised in the national guidelines, is rarely found. Over time, however, a more systematic use of the national guidelines has been noted.

In conclusion, the diffusion of new health technology is influenced by a wide array of factors, both at individual and organizational levels, as well as by their interaction. The diffusion resulted in large economic consequences and unequal access due to variations, also at clinical level. Moreover, given that healthcare decision-making is influenced by many different factors, the simple influx of evidence-based guidelines will unlikely result in automatic implementation. Attempts to influence healthcare decisions need to have a system perspective and to account for the interaction of factors between different actors.

LIST OF PAPERS

- I. Kalkan A, Hallert E, Bernfort L, Husberg M, Carlsson P. Costs of rheumatoid arthritis during the period 1990-2010: a register-based cost-of-illness study in Sweden. *Rheumatology* 2014, 53(1):153-60.
- II. Kalkan A, Hallert E, Carlsson P, Roback K, Sjöwall C. Individual variations in treatment decisions by Swedish rheumatologists regarding biological drugs for rheumatoid arthritis. *Scandinavian Journal of Rheumatology* (forthcoming).
- III. Kalkan A, Husberg M, Hallert E, Roback K, Skoog T, Thyberg I, Carlsson P. Physician preferences and variations in prescription of biological drugs for rheumatoid arthritis– a registry-based study of 4010 patients in Sweden. (submitted).
- IV. Kalkan A, Roback K, Hallert E, Carlsson P. Factors influencing rheumatologists' prescription of biological treatment in rheumatoid arthritis: an interview study. *Implementation Science* 2014, 9:153.
- V. Kalkan A, Sandberg J, Garpenby P. Management by knowledge in practice– implementation of national healthcare guidelines in Sweden. *Social Policy and Administration* Oct 2014, online first.

ABBREVIATIONS

bDMARDs	Biological disease-modifying antirheumatic drugs
CFIR	Consolidated Framework for Implementation Research
CPI	Consumer price index
DAS28	28-joint Disease Activity Score
DMARDs	Disease-modifying antirheumatic drugs
DP	Disability pension
EBM	Evidence-based medicine
EULAR	European League against Rheumatism
HCQ	Hydroxychloroquine
HPI	Healthcare price index
HTA	Health technology assessment
MTX	Methotrexate
NBHW	National Board of Health and Welfare
NG	National guidelines
NGCC	National guidelines for cardiac care
NICE	National institute for Health and Care Excellence
NSAIDs	Non-steroidal anti-inflammatory drugs
RA	Rheumatoid arthritis
RCT	Randomized controlled trial
SBU	Swedish Council on Health Technology Assessment
sDMARDs	Synthetic disease-modifying antirheumatic drugs
SRF	Swedish Society for Rheumatology
SRQ	Swedish Rheumatology Quality Register
SSZ	Sulphasalazine
TLV	Dental and Pharmaceutical Benefits Agency
TNF	Tumor necrosis factor
QALY	Quality adjusted life year

INTRODUCTION

Improvements in health technology, i.e. pharmaceuticals, devices, procedures and organizational systems, raise hopes for better patient outcomes and a more efficient delivery of health care. In a simplistic model, proven effectiveness, safety and cost-effectiveness of new health technology result in the diffusion and implementation of the health technology into routine practice. However, the processes of diffusion and implementation have been shown to be complicated and to pose a number of challenges for the healthcare sector (1-4).

First of all, the knowledge base for new health technology is not always as clear-cut as would be desirable. Knowledge about effectiveness, safety and cost-effectiveness is rarely unambiguous or applicable in all settings (5-6). At the time point of introduction, certain knowledge about the health technology might be missing or difficult to interpret. New health technology is often a 'moving target' that can be difficult to assess and its' diffusion may be difficult to manage, but decisions about its' use are nonetheless made (7). Secondly, apart from knowledge about the new health technology, diffusion and implementation are influenced by a number of other factors (8-11). Some of these include characteristics of the users, the setting, and external influences. This process is hence far more complex than might be foreseen at the time point of introduction. Thirdly, all the consequences of new health technologies are in many cases difficult to predict. While improving patient outcomes, at the same time their use might compromise other ambitions of the healthcare sector such as equity, fairness and cost-control. New health technologies are often more expensive than the existing technologies they replace, and they have been pointed out as the major driver of healthcare spending (12-13). In addition, health technology is often diffused at a different pace in different settings, thereby contributing to the large variations seen in healthcare practice (14-15).

Due to the multitude of challenges for health care posed by new health technologies, many attempts have been made to influence and manage the introduction and diffusion of pharmaceutical innovations in particular. These attempts are a function of the healthcare system within which they take place.

In Sweden, health care is publicly funded and offers universal access. The responsibility for delivering and financing healthcare services is decentralized to 21 independent regional entities called county councils. In the county councils, directly elected politicians make decisions concerning the overall financing and organization, while cost responsibility for individual departments is often delegated to the medical management, and the latter also direct everyday clinical activities (16). Attempts to influence the use of health technology include reimbursement decisions by the Dental and Pharmaceutical Benefits Agency (TLV) that stipulate which drugs are subsidized, and the growing number of health technology assessments (HTAs) that are intended as input in decision-making (17). One example is the systematic reviews of the scientific base for technologies issued by the Swedish Council on Health Technology Assessment (SBU) (18). Another important example is the national guidelines issued by the National Board of Health and Welfare regarding treatment and health technology use in large disease areas where the state of knowledge is uncertain, where there are large variations in treatment, and/or where treatments are particularly costly (19).

In view of the many challenges posed by the diffusion and implementation of health technologies, more knowledge in this area is warranted. To obtain increased understanding about health technology diffusion, this thesis will explore one specific case in depth, the biological drugs used in the treatment of rheumatoid arthritis (RA). Since their introduction into the market around 2000, biological drugs have had widespread diffusion both in Sweden as well as in other countries (20). It would have been possible to select a different type of health technology for a case study, such as a medical device or a procedure, but there are three factors that make the study of biological drugs particularly interesting. First, the perceived innovative value of these drugs was high when they were introduced in that they caused a technology shift in the treatment of

RA (21). Second, Sweden has generally had among the highest prescription levels of biologics per capita in Europe, which has had a significant economic impact on local healthcare budgets (20). And third, prescription levels have varied greatly between different county councils (22). Hence, exploring the diffusion of biological drugs is interesting from patient-, healthcare system- and societal perspectives. When exploring these topics, it is appropriate to consult the widespread research on diffusion of innovations (23), implementation (1-3, 24), and small-area variations (14, 15, 25, 26).

To obtain increased knowledge about not only the diffusion of new health technology, but also about the attempts to influence it, this thesis will additionally explore implementation of the Swedish national guidelines. When they were introduced, the national guidelines were considered an innovation since they represent a unique ambition to influence the use of both medical treatments and healthcare resources by means of collected scientific knowledge. In contrast to international healthcare guidelines that mainly concern clinical decisions, the Swedish national guidelines aim at being used in both clinical and political-administrative decision-making concerning priority setting (27). In 2012, national guidelines covering the treatment of RA were formulated in Sweden, and this was the 10th disease group with formulated guidelines (28). It is still too early to fully evaluate how these guidelines have been implemented locally, especially since previous research has highlighted the importance of a long-term perspective in such evaluations. The first national guidelines were published in 2004 and covered cardiac care (29). These guidelines have been revised three times and are the guidelines with which actors in Swedish health care have the most experience. Evaluations of the implementation of the national guidelines for cardiac care were performed in 2004, 2007 and 2011, providing a unique opportunity to analyze the implementation process over a long period of time and to explore trends that have developed over time among the different decision-makers in the county councils (30, 31). This will be presented and analyzed in this thesis by drawing on policy implementation theory and institutional theory (32, 33).

Aims

The overall aim of this thesis is to describe and analyze the factors influencing the diffusion and economic consequences of the introduction of a new health technology with large variations in use, and to explore the process of implementation of nationally produced guidelines as an instrument for improving effectiveness and equity.

More specifically, the aims of the included papers are:

Paper I: To examine changes in the total costs for RA during 1990–2010, 10 years prior to the introduction of biologic drugs and 10 years after, and to discuss potential reasons for changes in costs.

Paper II: To determine whether there are individual differences among rheumatologists regarding prescription of biologics for patients with RA, and to elucidate reasons for possible variations.

Paper III: To test the hypothesis that physician preferences are an important determinant for the prescription of biological drugs in Sweden.

Paper IV: To identify and explore factors influencing the individual rheumatologist's decision about prescribing biologicals.

Paper V: To explore the response by four Swedish county councils to the national guidelines for cardiac care, launched in 2004 as the first document of its kind aimed at influencing both clinical and political decision-making in the health sector.

Overview of the thesis

This thesis deals with diffusion of new health technology and implementation of a knowledge-based health policy document. First, the background will outline a theoretical and an empirical section representing the ingredients necessary for contextualizing the work undertaken in this thesis. We will consider theories about health technology and how it is spread through exploration of the literature on diffusion and implementation. The wider policy approach of the Swedish national guidelines motivates us to look into the theories on policy implementation and institutional theory. The empirical aspects of the health technology studied, i.e. the biological drugs, are then described, as are the Swedish national guidelines. Thereafter, the methods and results of the five underlying studies are presented. Based on the results of the thesis, this is followed by a discussion about the diffusion of biological drugs and the ensuing consequences, factors influencing the prescription of biological drugs, and implementation of the national guidelines. Finally, the conclusions are presented.

BACKGROUND

As an introduction, the theoretical and empirical context of this thesis will be presented. The aim of this background material is to supply the tools needed for navigating in the analyses of Papers I-V, but also to clarify the multi-disciplinary nature of this thesis.

Theoretical context

Health technology

The term 'health technology' is usually broadly defined as "different methods for prevention, diagnosis and treatment in health care", involving drugs, procedures and programs (34). Health technology is systematically evaluated in health technology assessment (HTA) that evaluate the costs and effects of a health technology from several perspectives, including the ethical, social, and economic perspective (18). HTA is a form of policy research that systematically examines short- and long-term consequences of the application of health technology and presents this in reviews and clinical guidelines, intending to support decision making. It is closely connected to the area of evidence based medicine (EBM) that aims to increase the use of the best available evidence in healthcare (35). The use of HTA has increased with time in Sweden, as well as in other countries (18, 36).

Processes by which health technology is taken into practice

Accounts of the history of research on the spread of health technology innovations usually start with the innovation research documented by Everett

Rogers in 1962 in his *Diffusion of Innovations*. In that work, terminology and theories about diffusion and adoption were presented, and many of them are still in use in much of today's implementation science research. The most common of these concepts include adoption, diffusion, dissemination and implementation (23).

In Rogers (1962) research on innovations, a linear sequence was initially presented that started with knowledge about a new idea, followed by persuasion, adoption, implementation and confirmation. This linear sequence has been questioned, and the different parts of an innovation process are no longer seen as separate. However, adoption is considered as a crucial step and is defined by Rogers as "a decision of making full use of a new idea as the best course of action available" (23).

Innovations are spread with or without a systematic and active process. Diffusion stands for a relatively passive process, where new ideas and concepts are spread in a social system (1). Most of the research on the diffusion of innovations has focused on simple, product-based innovations, for which the unit of adoption is the individual, and diffusion occurs by means of simple imitation (23). It has been emphasized that it is important not to use diffusion theories to overgeneralize to complex, process-based innovations in service organizations, for which the unit of adoption or assimilation is the team, department, or organization in which various changes in structures or ways of working will be required (1). In such circumstances there is almost always a formal decision-making process, an evaluation phase or phases, and planned and sustained efforts at implementation.

If diffusion can be considered as 'let it happen', dissemination stands for a planned and active process aiming at reaching adoption. Dissemination is an active approach using planned strategies to distribute information material about the health technology to the target audience via determined channels. Examples of dissemination strategies are conferences and educational efforts, as well as reports, literature reviews and marketing. In innovation research the process of implementation is understood as efforts that occur after an adoption

decision has been made. It is the integration of an innovation into the routine practice of the adopter (37). Implementation has been described as:

“A planned process and systematic introduction of innovations and/or changes of proven value; the aim being that these are given a structural place in professional practice, in the functioning of organizations or in the health care structure.” (8).

Two contrasting approaches to implementation have been distinguished: the ‘rational model’ and the ‘participation model’ (38). In the so-called rational model, a health technology cycle is central, where after the primary research and synthesis of the research findings have taken place, dissemination and implementation follow. The point of departure is clear: the availability of new methods that are considered to be worth applying. Steering takes place externally and mainly “from above” (8). The participation model, on the other hand, uses the needs and experiences from practice as its departure point. The change happens incrementally, with no exact starting point, and is steered by people in everyday practice. The phases of development, testing, dissemination and introduction of an innovation are intertwined. Both approaches have been criticized; the rational model for paying too little attention to the knowledge, experience and diversity of needs in the target group, and the participation model for not always introducing the best available care and for neglecting the structural factors (8). Elements of both schools of thought have been used in the research aimed at understanding what influences implementation.

Factors influencing diffusion and implementation

Much research has been conducted with the aim of understanding factors impacting the process of diffusion and implementation of health technology (1-3, 8-11, 37, 39, 40). This research has particularly evolved in the field of ‘implementation science’, which has developed in the area of health care since the 1990s (10, 41, 42). Implementation science is “the study of methods to promote the systematic uptake of research findings and other evidence-based

practices into routine practice, and hence to improve the quality (effectiveness, safety, appropriateness, equity, efficiency) of health care” (43). It includes the study of influences on healthcare professional and organizational behavior.

Policy-makers have increasingly recognized the critical role of implementation science in reducing the gap between what research has shown to be effective and what is actually practiced in health care (2). Several overviews that condense this research have been published. Those regularly referred to in implementation science include Greenhalgh et al. 2004, Grol et al. 2005, Estabrooks et al. 2006, Nutley et al. 2007 and Grimshaw et al. 2012 (1, 8-11). The following is an overview of Greenhalgh's review, as well as a further development of that review (24) that has been applied in this thesis.

The work by Greenhalgh et al. (2004) has been described as a landmark systematic review in this area (1, 44). It was performed for the United Kingdom National Health Service and it integrated 13 distinct disciplinary research traditions in order to provide a detailed picture of the factors affecting dissemination and implementation in health services organizations. They suggest six broad categories within which influences and activities in organizational diffusion may be sorted: (1) the innovation itself; (2) the adoption/assimilation process; (3) communication and influence (diffusion and dissemination, including social networks, opinion leadership, champions, and change agents); (4) the inner (organizational) context, including both antecedents for innovation in general and readiness for particular innovations; (5) the outer (interorganizational) context, including the impact of environmental variables, policy incentives and mandates, and interorganizational norms and networking; and (6) the implementation process.

Using the review by Greenhalgh et al. (2004) as the starting point, the Consolidated Framework for Implementation Research (CFIR) was developed (24). According to this framework, the implementation theories often differ in their definitions and terminologies, while also exhibiting extensive overlap. The CFIR was established in order to comprise common constructs found in

published implementation theories. It is a pragmatic 'meta-theoretical' framework, including constructs from a synthesis of 19 theories about dissemination, innovation, organizational change, implementation, knowledge translation and research uptake. This framework reflects a 'professional consensus' in that it specifies a consistent list of constructs that are believed to influence implementation, but it does not specify in what way (positively or negatively) these constructs influence implementation. The CFIR constructs are organized into five major domains: 1) the characteristics of the innovation (e.g. evidence strength); 2) the outer setting (e.g. peer pressure); 3) the inner setting (e.g. culture); 4) the characteristics of the individuals involved (e.g. knowledge); and 5) the process used to implement the innovation (e.g. engaging opinion leaders) (24).

The processes by which health technologies are diffused and implemented occur in a specific setting and are largely influenced by this setting (1, 24). In decisions about health innovations in Sweden, several groups of actors are involved: political, administrative and medical decision-makers. Due to the largely decentralized system, medical specialists play a pivotal role in decisions about drug prescribing. Their influence derives not only from their expertise, but also from their social status and the power of their professional organizations (16), why studying their preferences and behavior is especially important in the exploration of diffusion and implementation of health technology in Sweden.

Small-area variations

Since diffusion and implementation of health technologies occur at a different pace in different settings, this can contribute to the practice variations seen in health care between countries, regions as well as departments. Extensive small-area variations, i.e. large differences in the rates of use of medical services between geographic regions, were brought forward on the agenda in the 1980s and have since then been documented in the delivery of health care in Europe as well as in the United States (14, 25, 26, 45-49). Variations have also been documented between practitioners within the same region and

hospital (26). Some of these can be explained by variation in patient illness, which is why the term ‘unwarranted practice variation’ has been introduced. The most widely accepted definition of unwarranted practice variation is that coined by Jack Wennberg: “Variation in the utilization of health care services that cannot be explained by variation in patient illness or patient preferences” (50). When evaluating practice variations, clinical care can be grouped into three categories that will have different implications for patients, clinicians, and policy-makers, respectively:

- Effective care is viewed as interventions with benefits that far outweigh the risks; in this case the “right” rate of treatment is 100 percent of patients defined by evidence based guidelines to be in need, and unwarranted variation is generally a matter of underuse.
- Preference sensitive care is when more than one generally accepted treatment option is available, in which case the right rate should depend on informed patient choice. Patient choice is often delegated to physicians, which is why treatment rates for this kind of care can vary extensively because of differences in professional opinion.
- Supply sensitive care comprises clinical activities such as diagnostic tests, hospital admissions and physician visits, for which the frequency of use relates to the capacity of the local healthcare system. Most of these services are used in caring for chronic illness. However, the question has been raised as to whether more supply sensitive care is better. Studies in the United States show that regions with high rates of use of supply sensitive care do not have better overall outcomes, as measured by mortality and indicators of the quality of care (50). This research concludes that more resources should be put into turning supply sensitive care into evidence based care that is effective or preference sensitive.

The causes of population-based unwarranted variation include variation in the supply of resources, such as fewer physicians in one area than in another.

They also include different definitions of appropriateness of intervention and referral, either between individual clinicians, sometimes even within the one institution, or between different groups of clinicians working in the different populations. There are also variations that may be due to attitudes, both individual and population-based. Interventions for dealing with variation in clinical practice include the use of information technology, care decision support systems, explicit care pathways and clinical guidelines (51).

Implementation of policy instruments

Various policy instruments are used to influence the use of health technology in order to make that use more evidence-based and equal. As was mentioned in the introduction, the national guidelines produced by the National Board of Health and Welfare is one of the ways to influence decisions about use of health technology in Sweden. Similar guidelines exist in other countries (52, 53). Since they encompass both clinical and political-administrative decision-making, the use of the Swedish national guidelines throughout the healthcare organization is preferably explored using policy implementation theories. In contrast to the 'implementation science' field, which is fairly new, research on policy implementation in the public sector in general has a long tradition, with the first studies emerging in the 1950s (54). This area developed rapidly in the 1970s during a period of growing concern about the effectiveness of public policy (55-57).

Many first-generation policy implementation studies were explorative, primarily seeking to position implementation within a policy cycle divided into a series of stages such as agenda setting, policy formulation, legitimation, implementation and evaluation (58). As the research evolved, two schools of thought emerged for studying implementation: top-down and bottom-up. Top-down theorists viewed the design of policy as central and identified factors to explain an implementation gap from the perspective of central government, e.g. unclear or flawed policy, insufficient compliance by the implementers, a lack of resources, opposition within the policy community and unfavorable socioeconomic conditions (57). This research was criticized

for focusing too much on implementation failures, and starting in the early 1980s a second generation of studies aimed at taking the next step in theory development by moving beyond a success or failure perspective and focusing more on variables that could explain the impact of the implementation process (57, 59).

The various bottom-up theorists criticized the top-down theorists for seeing the implementation as a purely administrative process and failing to account for the role of the frontline staff who put policy into action (57). Bottom-up theorists instead emphasized the role of local-level context and service deliverers (54, 60, 61). In addition, bottom-up theorists focused more on the nature of the problem that the policy was targeting, for example youth unemployment, rather than the goals of the policy itself. Bottom-up theorists in turn were criticized for tending to overemphasize the autonomy of the frontline staff and for lacking an explicit theory explaining what influenced the process and how change occurred (57).

The top-down versus bottom-up debate had many facets, intertwining normative, theoretical and methodological issues (62). Matland (1995) is said to be an example of a more elaborated insight into the circumstances associated with both schools (54). According to Matland, implementation depends on the characteristics (the degree of conflict and ambiguity) of the individual program/policy in terms of both the goals for the policy and the means to implement it (32). Writing in the aftermath of the top-down/bottom-up debate, Matland's contribution was to pin down the complexity of implementation, as he stressed that intrinsic features of policy will force this process in different directions, none of them deemed to be more or less "successful". Matland viewed the implementation process as influenced by local conditions such as resources, coalitions, activities, and distribution of power. Although underscoring the "context" of implementation, Matland never had the ambition to explore the inner life of organizations that had to respond to external policy initiatives. He attempted to present a simplified model to reconcile the split between two schools of thought. The different implementation processes that emerge are not the result of a self-propelled

process. Accordingly, we should not expect the implementation of any program, i.e. guidelines, to follow a uniform and optimal shape that is context-free. Implementation occurs as the result of strategic responses in organizations with particular traits.

Institutional ability to respond to policy instruments

The setting for the implementation of policy has been highlighted previously in this section. Following March (1994) concerning the complexity of organizations, we should not assume that the response to external pressures, materialized, for example, as national guidelines, is clear-cut or the result of unified lines of action (63). On the contrary, the county councils are in Sweden an example of organizations staffed with multiple actors who have conflicting agendas and interests. Professions are important institutional actors that provide “technical expertise” and also serve as agents in crafting governance structures and in working out policies (64). Furthermore, the county councils are political organizations, and their response to external pressures will reflect political institutional behavior (65).

Organizations can react to institutional pressures in a number of ways, and Oliver (1991) has outlined a broad range of potential responses that are available for organizations and how these become part of their strategic actions. Oliver (1991) maintains that “organizations confront incompatible and competing demands that make unilateral conformity to the environment difficult because the satisfaction of one constituent often requires the organization to ignore or defy the demands of another” (33). Organizational responses to institutional pressures toward conformity will depend on why these pressures are being exerted, who is exerting them, what these pressures are, how and by what means they are exerted, and where they occur. Five institutional factors- cause, constituents, content, control, and context, correspond, respectively, to these five basic questions (33).

Depending on these five aspects, five general strategies are predicted as responses by organizations experiencing institutional pressure. These

strategies range from following taken-for-granted norms, to strategies aimed at reaching a compromise between conflicting expectations, to avoiding regulatory initiatives by e.g. changing goals or applying symbolic activities, to defying or manipulating by changing the content of the reform, e.g. by using power (33).

Empirical context

Before we move on to the specific studies, let us first have a closer look at the empirical context of this thesis, that of biological drugs for RA and of the Swedish national guidelines.

Rheumatoid arthritis

Rheumatoid arthritis (RA) is a chronic systemic inflammatory disease associated with joint destruction, disability and pain (66, 67). The course of the disease is progressive, and given that the average onset of RA occurs between the ages of 40 and 60, the disease imposes a considerable economic burden both for patients and society (68-70). The prevalence of RA in Scandinavia is 0.5-0.8 percent, with women more often affected than men (71).

Technology shift in the treatment of rheumatoid arthritis

The main goals of RA-treatment are a reduction in joint inflammation, slowing or halting the progression of erosive joint damage, and improving or maintaining joint function (67). In order to influence the disease course of RA, a number of disease-modifying anti-rheumatic drugs, DMARDs, have been introduced. DMARDs are a heterogeneous collection of agents grouped together according to use and convention. The term is used in contrast to non-

steroidal anti-inflammatory drugs, NSAIDs, which are agents that treat the inflammation but not the underlying cause, and glucocorticoids (corticosteroids), which blunt the immune response but are insufficient to slow down progression of the disease (72).

The use of DMARDs can be traced back to the 1930s when injectable gold was first used to treat RA (67). Since then, several novel agents have been introduced, particularly in recent years. The time sequence of drug development is summarized in Figure 1. Between the 1950s and 1980s, the DMARDs that were introduced for RA treatment included antimalarials (hydroxychloroquine, HCQ), pencillamine (D-Pen), sulphasalazine (SSZ) and methotrexate (MTX). As a group, they have been shown to reduce joint swelling and pain, decrease acute-phase markers, limit progressive joint damage, and improve function, but the degree to which all this is accomplished is variable. Adverse effects of these DMARDs include both minor adverse effects such as nausea, and serious adverse effects such as liver damage, blood dyscrasias, and interstitial lung disease (72).

Figure 1. Historical development of drugs introduced for RA.

HCQ: Hydroxychloroquine, D-Pen: D-pencillamine, SSZ: Sulfasalazine, MTX: Methotrexate, AZA: Azathioprine, CsA: Cyclosporine-A

During the 1990s, important changes evolved in the treatment of RA. Treatment strategies shifted from being ‘careful’ to early-instituted, potent DMARDs. MTX emerged as the first-line DMARD for most patients, comprising a combination of generally satisfactory efficacy, acceptable

toxicity, and patient convenience. Furthermore, a combined use of MTX with other DMARDs proved to be very efficient and became accepted as a valid treatment option with additional benefit. Hence, MTX was used in combination with one or even two other DMARDs, for instance MTX, SSZ, and HCQ, i.e. triple therapy (73).

At the end of the 1990s, approximately 70 years after the introduction of the first DMARD, the first biological DMARDs, the tumor necrosis factor (TNF) inhibitors etanercept and infliximab, were introduced. This was seen as a major breakthrough in the treatment of RA. During the whole time span of seven decades prior to the biological DMARDs, fewer than 10 new DMARDs entered the market, as compared to the total of nine biologic DMARDs that have emerged since 1998. The term 'biological drugs' refers to drugs that are manufactured in or extracted from biological sources, in contrast to chemically synthesized pharmaceutical products such as conventional DMARDs. Other examples of biological drugs include vaccines, hormones and blood factors. Biological DMARDs target molecules that have been shown to play important roles in the pathology of RA. More specifically, they are targeted toward suppressing key inflammatory pathways involved in joint inflammation and destruction. TNF inhibitors, i.e. etanercept, infliximab, adalimumab, certolizumab pegol and golimumab, were the first licensed biological DMARDs, followed by abatacept, rituximab, and tocilizumab. For simplicity, biological DMARDs in this thesis will be termed bDMARDs, as opposed to nonbiological, synthetic DMARDs, hereafter called sDMARDs (74).

Several randomized controlled trials have shown that bDMARDs reduce disease activity and improve quality of life (75, 76). The different bDMARDs are essentially considered to have similar efficacy and safety (77). The randomized controlled trials that were the basis for regulatory approval of the first bDMARDs showed that a combination of bDMARDs and MTX resulted in better control of symptoms over a period of 1-2 years compared to only MTX treatment among patients with established RA (78). And in early RA, bDMARDs have shown improved clinical effect when compared with only MTX (78). Only a few randomized trials have compared bDMARDs with a

combination of sDMARDs in patients with an insufficient response to MTX monotherapy, which is a common clinical decision situation (79-81). A study of patients with early RA, where 258 participants were randomly allocated to treatment with SSZ, HCQ and MTX or to treatment with infliximab plus MTX, showed improved clinical outcomes after 12 months and better radiographic results after 24 months for the group with infliximab plus MTX. However, a convincing clinical difference between the groups was lacking after 24 months of treatment (79). In a 48-week, double-blind trial with 353 participants with RA, who had active disease despite MTX therapy, it was concluded that triple therapy, with SSZ and HCQ added to MTX, was noninferior to etanercept plus MTX with respect to clinical benefit measured with DAS28 (80). Further, longitudinal observational studies have indicated that a similar effect as that found with bDMARDs might be achieved with sDMARDs, at a 30-40 times reduced cost (82, 83).

The bDMARDs are not without side effects or long-term risks and can cause a variety of adverse effects, including allergic, immunological and other reactions. There is an increased risk of tuberculosis with TNF inhibitors, as well as hepatitis B and C infection. Because RA patients have an increased risk of lymphoma secondary to the disease itself, the extent of the increased risk of developing a cancer such as lymphoma while taking immunosuppressive medications remains debatable (72, 84).

The use of bDMARDs has increased rapidly over the last decade, and prescription of these drugs has subsequently been extended to patients with less severe disease than previously (85, 86). Sweden has had among the highest prescription levels per capita in Europe (20). At present, there are nine different bDMARDs on the Swedish market and this pharmaceutical group accounts for the largest sales in the country, approximately 5 percent of the value of pharmaceutical sales in Sweden (81). The prescription of bDMARDs has varied considerably among county councils (22). Twice as many RA-patients per capita receive biologicals in county councils that prescribe the most as compared to county councils that prescribe the least (87). This variation has occurred despite the existence of guidelines from the Swedish

Society for Rheumatology (SRF) (2004), the National Board of Health and Welfare (2012), as well as from international guidelines (28, 77, 88, 89).

Policy instruments to influence the use of health technology

At present, in Sweden, there are national guidelines for 12 disease areas, as well as two disease areas with preliminary guidelines (19). They originally were formulated at a time when transparency in health care led to regional variations appearing on the agenda (90). In addition, economic constraints increased awareness of the need for explicit prioritization (91). The National Board of Health and Welfare formulates guidelines for the treatment of serious diseases that involve many patients, hence being costly to society. The objective of producing guidelines is part of the wider responsibility to ensure that all individuals living in Sweden and suffering from a disease receive the treatment that yields the best health results in relation to the cost of the treatment (27).

The national guidelines focus on disease areas where there is a great need for guidance for professionals and decision-makers in the healthcare sector (29). The National Board of Health and Welfare traditionally works in a network with various organizations of the medical profession (92). In the elaboration of national guidelines, multi-professional expert groups are appointed to produce factual backgrounds and recommendations for priorities within the specific disease area. The expert groups aim at gathering the scientific basis for a large number of typical cases of conditions-measures that cover the entire chain of care. The purpose is to present a priority grading for each treatment alternative for specific medical conditions. The priority grading is based on balancing the patient's medical needs and the treatment's effects against its costs, which is expressed as the cost per quality adjusted life year (QALY) gained, when such data is available. Starting from the scientific basis, priority grading takes place during a discussion process involving all professional categories mentioned above. In addition, patient organizations, political decision-makers, and all the relevant specialist associations are consulted (27).

The objective of the national guidelines is to be a tool for resource allocation decisions in health care that are made by health care professionals and managers as well as administrative and political leaders. The national guidelines are intended to provide input to local healthcare programs, i.e. locally produced or adapted guidelines for delivery of care in the county council. Additionally, they are intended to support explicit- and needs-based prioritization and to increase the dialogue between decision-makers. The national guidelines are supplemented with quality indicators that are regularly measured either through electronic medical records or via the national quality registers. In addition, comparisons of these indicators among the Swedish county councils are published each year in the Open Comparisons report issued by the National Board of Health and Welfare and the Swedish Association of Local Authorities and Regions (27).

The national guidelines are recommendations, and it is up to each county council to implement them locally, on a voluntary basis. In this way the national guidelines comprise part of the Swedish tradition of soft-law governance where various forms of informal social pressures such as shaming, peer pressure and moral responsibility play an important role in achieving conformity (93). The Swedish guidelines are similar to the National Service Framework in the United Kingdom, since both use the concept of EBM in their assessment of available facts, where the evidence in available studies is graded according to special criteria (94). They are also similar to the guidelines produced by the National Institute for Health and Care Excellence (NICE), which incorporate health economics (95). However, the national guidelines in Sweden have been given specific features of priority rankings to encourage and support explicit prioritization (96-98). This distinguishes them from a number of professionally produced European guidelines (99). Previous studies have evaluated the implementation of guidelines from a clinical perspective (100, 101) but few have taken into account the specific aim of the Swedish national guidelines of being used in wider policy decisions at the county councils.

The first national guidelines including priority setting were those for cardiac care that were released in 2004 and updated in 2008 and 2011. They consist of recommendations for the types of prevention, diagnosis, treatment and rehabilitation that are most effective for five disease categories within the cardiac care field. The relevant interventions are ranked one to ten in degree of

priority, and the organizational and economic effects that the interventions can be expected to have are described. Furthermore, the guidelines include recommendations regarding methods that should not be utilized at all or not on a routine basis (Do Not Do) as well as recommendations regarding methods where sufficient evidence is still lacking so that they are only intended to be used as part of clinical research and development (R&D) (29).

METHODS AND MATERIALS

Methods are described in papers I-V, and are briefly summarized below and in Table 1.

Table 1. Overview of the design and methods of each study.

Paper	Aim	Data collection and participants	Design
I	To examine changes in the total costs for RA during 1990–2010, 10 years prior to the introduction of biologic drugs and 10 years after, and to discuss potential reasons for changes in costs.	National and regional registries on inpatient and outpatient care, drugs, sick leave and disability pensions.	Quantitative
II	To determine whether there are individual differences among rheumatologists regarding prescription of biologics for patients with RA, and to elucidate reasons for possible variations.	Interviews and patient cases presented to 26 rheumatologists.	Quantitative & qualitative
III	To test the hypothesis that physician preferences are an important determinant for the prescription of biological drugs in Sweden.	Data from the Swedish Rheumatology Quality Register including 4010 patients during 2008–2012.	Quantitative
IV	To identify and explore factors influencing the individual rheumatologist's decision about prescribing bDMARDs.	Interviews with 26 rheumatologists.	Qualitative
V	To explore the response by four Swedish county councils to the national guidelines for cardiac care, launched in 2004 as the first document of its kind aimed at influencing both clinical and political decision-making in the health sector.	Interviews with 155 politicians, administrators and clinical managers.	Qualitative

Paper I. Register-based cost-of-illness study

This study aimed to retrospectively examine changes in the total costs for RA during 1990–2010, comprising a period of 10 years prior to the introduction of bDMARDs and 10 years afterwards, and to discuss potential reasons for changes in costs. Sweden has extensive national registries that provide a unique opportunity to examine longitudinal healthcare consumption as well as work participation for a specific patient group (102, 103). Patients with RA as the primary cause of treatment or work absence and with data on healthcare consumption and work participation, were identified in national and regional registries.

Costs were calculated using a societal perspective, as recommended for health economic analyses in Sweden (104). Data on inpatient care and surgical interventions were available from the inpatient care register for the whole study period. For outpatient care, data were derived from regional databases in the Östergötland County Council, the Västra Götaland Region and the Region of Skåne, since data in the national outpatient care register were not complete before 2005. These three regions, with a prevalence of RA similar to the national prevalence, cover approximately one-third of the Swedish population, suggesting that these data are an appropriate estimate for total outpatient use. Data on drugs prescribed to patients with RA (excluding bDMARDs), were available for 1991, 1997 and 2001 from Apoteket AB (Swedish pharmacies). The total sales of bDMARDs in Sweden were available from 2000 onwards from Apotekens Service.

For indirect costs, the human capital method was applied, assuming that all sickness absence of people aged <65 years is associated with loss of productivity. Data on sick leave days due to RA for men and women were obtained for 1991, 2001 and 2005–2010 from the Swedish Social Insurance Agency (Försäkringskassan). Data on the number of men and women with ongoing RA-related disability pensions were obtained for 1991, 1996, 2002 and 2003–2010.

Both current and fixed prices were calculated (105). For current prices, healthcare consumption and days with sick leave or disability pension (DP) for each specific year were multiplied by average healthcare prices and the average annual cost of labor for that year. For fixed prices, the sum was inflation-adjusted to equal the price level for 2010.

Papers II and IV. Interview-based study of prescription decisions

In order to identify and explore factors that influence the individual rheumatologist's decision about prescribing bDMARDs, we conducted interviews with 26 senior rheumatologists in rheumatology departments at five university hospitals in Sweden (106). The hospitals were chosen in order to cover different parts of Sweden including both southern and northern areas with diverging population densities. The chosen hospitals also represented areas with disparate proportions (both high and low numbers) of RA patients being treated with bDMARDs, ranging from 144 to 245 per 100 000 inhabitants in the included county councils, to get a representation of different levels of regional prescriptions. In Sweden approximately 50 percent of RA-patient visits to rheumatologists occur at university hospitals (107). Although there might be limitations in the transferability to other hospital settings, university hospitals were chosen in order to guarantee a similar setting for the physicians in terms of research exposure and RA-patient workload. We deliberately chose senior rheumatologists and excluded physicians who were not specialists in rheumatology or lacked experience with patients with RA (108, 109).

The rheumatologists who agreed to participate were interviewed either by telephone (n=20) or face-to-face (n=6). We utilized a semi-structured interview guide with closed- and open-ended questions to allow for increased flexibility. The rheumatologists were asked to freely elaborate on factors that influence prescription decisions and what they saw as barriers and facilitators in using bDMARDs. To guide data collection and analysis, we also used a comprehensive implementation framework, the CFIR, that supports the

exploration of essential factors that may be encountered during implementation (24). After responding to the open-ended questions, the informants were asked to rate predefined factors, derived from the CFIR model and previous research (24, 110), that could influence prescription. The physicians were asked to what extent they believed that the various factors influenced prescription decisions (not at all, to some extent, quite a lot, to a large extent). By combining qualitative and quantitative data, an overall interpretation of factors influencing prescription could be formed (111).

The transcripts of the interviews were organized using the Nvivo software and analyzed using qualitative content analysis in accordance with Hsieh and Shannon (112). Qualitative content analysis is a method for explorative and descriptive analysis of transcripts based on empirical data (113). The interviews were analyzed by the first author (AK), who consulted the rest of the project group for alternative interpretations of the data (114). The coding scheme was developed gradually, clustering the themes that emerged in the data, all while looking for disconfirming data. The clustered themes corresponded to the categories in the CFIR model, which was thereby confirmed as a helpful tool in analysis (24). The quantitative findings were analyzed using standard descriptive statistics (mean, min-max and standard deviation) in order to summarize and illustrate the features of the data. Integration of the qualitative and quantitative findings was done during the final interpretation and analysis of the data by comparing the themes in the qualitative part with the quantitative ratings.

Additionally, the 26 interviewed rheumatologists were asked to describe how they would treat presented patient cases. This was done in order to determine whether there were individual differences among rheumatologists regarding prescription of bDMARDs for patients with RA, and, if so, to elucidate the reasons for such variations. Ten written hypothetical patient cases were sent to the rheumatologists one week before the interview. All cases described patients who were diagnosed with RA according to the 2010 ACR/EULAR classification criteria but differed with regard to age, work status, smoking behaviour, disease progression, laboratory and clinical values, comorbidities,

and previous treatments. The ten cases were thoroughly elaborated by a senior rheumatologist and described RA patients who potentially could be prescribed biologics or other treatments, and in no case was the choice of treatment too obvious. The cases were tested in a pilot study with three senior rheumatologists, and minor changes were made in the patient descriptions according to their suggestions. The study participants were asked how they would treat the hypothetical patients; whether they would prescribe a bDMARD (YES/NO), and why they would or would not prescribe bDMARDs.

Paper III. Register-based study of prescription choices

As a complement to Papers II and IV, in Paper III we further examined prescriptions for RA patients in the Swedish Rheumatology Quality Register (SRQ). This register covers all departments offering anti-rheumatic treatment in Sweden, public as well as private. The percentage of prevalent RA patients included in the register was 84 percent in 2012, estimated by linking the SRQ to the Patient and Pharmaceutical registries of the National Board of Health and Welfare (115).

Patients agreeing to participate are entered into the register with information on clinical and demographic characteristics: sex, age at visit, age at onset of RA and smoking behavior; and laboratory markers: rheumatoid factor (RF) and anti-citrullinated protein antibody (ACPA) status. The subsequent visits are registered with information on erosion and disease activity assessed by the 28-joint Disease Activity Score (DAS28), i.e. tender and swollen joint counts, erythrocyte sedimentation rate and physician's and global assessment of disease activity. In addition, disability measured with a modified Health Assessment Questionnaire (HAQ) and a VAS-scale, and health related quality of life (HRQL) measured with the EQ-5D are registered as well as patient's global assessment of health.

For the present study we chose patients prevalent in the register between January 2008 and December 2012 ($n=30\,127$) who, on at least one occasion, had one sDMARD and changed treatment for the first time to either bDMARD or sDMARD during the period. Among eligible patients, we first performed a descriptive analysis of factors characterizing patients who changed from one sDMARD to another sDMARD, and patients who changed to a bDMARD. We then evaluated factors that affected prescription decisions to change to bDMARDs, compared to changing to a new sDMARD, using multivariable logistic regression. In our first model, we used data on patient characteristics (sex, age, duration of RA), disease activity (DAS28, HAQ, patient's global assessment of disease activity, pain, swollen and tender joint count, and the occurrence of RF and/or ACPA) and previous anti-rheumatic treatments (accumulated sDMARDs prescribed during the period). In the second model, we added the physician's global assessment of disease activity: 0-4. We subsequently quantified physician preference for the use of bDMARDs among the 314 physicians with at least 50 unique patients during the current period. We then assessed whether there was a significant influence of physician preference, independent of patient-related and clinical factors. Finally, in the fourth model, we adjusted for whether the physician worked in a county council with a high or low prescription rate of bDMARDs, and tested if the physician's preference still had a significant impact with regard to the average prescription rate at each county council.

Paper V. Interview-based study of the implementation of the Swedish National Guidelines

Upon release of the first national guidelines, the national guidelines for cardiac care (NGCC), the National Board of Health and Welfare commissioned Linköping University to follow the implementation of the guidelines. During 2004, a total of 74 interviews were performed in four Swedish county councils: Sörmland, Västra Götaland, Skåne, and Västernorrland (30). These county councils were chosen by the National Board of Health and Welfare to ensure

diversity in preconditions such as size, location and access to a university hospital. The selection of informants was done strategically through the help of a contact person in each county council who mapped out the organization. The interviewed politicians, administrators and medical managers were strategically chosen, based on their having a role in the county council, that gave them specific insight and knowledge about the implementation of the NGCC in their county council. All of them had been encouraged by the National Board of Health and Welfare to use the NGCC as a decision support, and their respective roles, responsibilities and views on the NGCC played a large part in the implementation process. This sort of expert interviewing is especially appropriate when exploring processes that involve people who have valuable insight into the issue at hand (109).

The need for a long timeframe in order to judge an implementation process has been pointed out by previous policy implementation research (116). The second interview round was performed in 2007, and comprised 45 interviews with the same categories of informants (31). In 2011 we performed 36 interviews, following the inclusion criteria in the previous studies. The interviews were performed by two of the authors (AK, JS). This extensive empirical material presents a rare opportunity to analyze an implementation process over a long period of time and explore trends that developed over time within the different levels of the county councils. This large number of interviews were carried out with the aim of covering the various perspectives of the different professional groups: politicians, administrators and medical managers. Additionally, the first interview round was based on “snowball sampling” increasing the number of interviews, while the following rounds included key people from the different groups of actors.

Semi-structured interview guides utilizing closed and open-ended questions were developed for each category. The purpose was to gain information on the perceptions of the NGCC, on the means that had been used to implement the guidelines, and how this process had evolved in the different settings. The interviewed experts were encouraged to talk openly throughout the interviews about the implementation of the NGCC. The empirical material

was analyzed using thematic analysis (117). The ambiguity-conflict model and the typology of strategic responses to external pressures were used to explore the response to the NGCC among the different actor groups in the county councils (32, 33). In the social sciences it is often difficult to have a clear deductive approach without inductive traits (118). That was also the case in this study where, in parallel to using the model by Matland (1995) and Oliver (1991), we maintained an open and explorative stance throughout the study, thereby using a hybrid approach including inductive and deductive analysis (119). The thematic analysis of the empirical material was performed separately by two authors (AK, JS), who then compared their coding of the interview transcripts and through discussion decided on the final themes.

RESULTS

The main findings of the five papers included in this thesis will be discussed in this section. First, the trajectory of changes in the total costs for RA during 1990–2010 will be presented. Second, the results of the constructed patient cases, as well as reasoning in prescription decisions, will be described. Thereafter, the register analysis will be presented. In the fourth part, factors influencing the individual rheumatologist's decision about prescribing bDMARDs will be explored in depth. Finally, the results concerning how national guidelines are implemented locally at the county councils will be described.

Costs of RA 1990-2010 (Paper I)

Inpatient care

Utilization of inpatient care due to RA decreased substantially in terms of numbers of patients, admissions and hospital days throughout the study period. The annual decline in the number of admissions and hospital days was more pronounced between 1994 and 2000 than after 2000. The proportions of RA inpatient care decreased, with RA accounting for 1 percent of all inpatient days in the early 1990s and 0.3 percent in 2009.

Outpatient care

Outpatient care due to RA remained rather unchanged with approximately 90 000 visits and 45 000 patients each year throughout the 2000s.

Drugs

The costs of drugs for RA remained relatively constant at €10 million per year during the 1990s, but gradually increased each year after 2000. The total drug costs equaled approximately €210 million in 2010, adjusted based on the CPI.

Sick leave

The number of sick leave days due to RA was halved over the period. The annual percentage change fluctuated, but there was a downturn by the end of the period. Similar fluctuations and a decline in sick leave days were simultaneously seen in the general population covering all diagnoses, but they were slightly more pronounced for RA.

Disability pension

The total prevalence of individuals with DPs due to RA declined after the mid 1990s, from approximately 10 000 to 7000. In total, the proportions of RA-related DPs decreased, as RA made up 3 percent of all DPs in the early 1990s and 1.5 percent in 2010.

Costs

When total fixed costs were calculated at the price level of 2010 using the CPI, there was a 32 percent increase in total fixed costs for RA (Fig. 2 A and B). Hence, the decreases in healthcare consumption, DPs and sick leave due to RA are largely outweighed by price increases.

Figure 2. Total annual cost for RA, € million, 1990–2010. Costs A) in current prices, B) adjusted to 2010 prices using the CPI.

The proportion of indirect costs decreased over the years but still constituted the major part of total costs, with DPs as the major cost driver. Simultaneously, there was a sharp increase in the amount of direct costs, mainly after the introduction of bDMARDs. In later years the costs for bDMARDs accounted for an increasing share of total costs. However, a leveling off of total costs was observed at the end of the period.

Fig. 3 shows the proportion of total costs for RA represented by each cost type during the two decades. Drug costs increased from 3 percent to 33 percent of total costs between 1990 and 2010, while indirect costs decreased from 75 percent to 57 percent of total costs. Simultaneously, inpatient care decreased from 15 percent to 3 percent of total costs.

Figure 3. The proportion of total costs for RA in 2010 prices represented by each cost type.

Treatment decisions for patient cases (Paper II)

Table 2 presents the prescription choices of the 26 rheumatologists for the 10 patient cases. The choices varied substantially between the respondents, some selecting bDMARDs for 9/10 patients and others for 2/10 patients. In five of the 10 hypothetical cases, approximately half (46–62 percent) of the respondents declared that they would prescribe bDMARDs. In specific patient cases the number of rheumatologists indicating that they would prescribe bDMARDs ranged between 2 and 26 out of the total of 26 rheumatologists.

Table 2. The rheumatologists' choices of drug treatment for the different patient cases.

Rheumatologist number	Patient case number										Number of cases that would be prescribed bDMARDs	Region
	3	1	4	6	10	8	5	2	9	7		
1	x	x	x	x	x	x	x	x	x		9	D
2	x	x	x	x	x	x	x	x		x	9	C
3	x	x	x	x	x	x	x	x	x		9	B
4	x	x	x	x	x	x	x	x			8	C
5	x	x	x	x	x	x	x	x			8	C
6	x	x	x	x	x	x		x		x	8	C
7	x	x	x	x	x	x		x			7	C
8	x	x	x	x	x	x	x				7	E
9	x	x	x	x	x	x	x				7	B
10	x	x	x	x		x			x		6	A
11	x	x	x	x	x	x					6	E
12	x	x	x	x	x			x			6	C
13	x	x	x	x		x		x			6	B
14	x	x	x		x	x		x			6	B
15	x	x		x	x	x		x			6	B
16	x	x		x	x	x		x			6	A
17	x	x	x		x		x				5	E
18	x	x	x				x		x		5	A
19	x		x		x		x				4	D
20	x	x	x				x				4	E
21	x	x	x				x				4	E
22	x	x	x				x				4	D
23	x	x		x							3	A
24	x	x	x								3	A
25	x	x	x								3	D
26	x						x				2	D
Percent that would prescribe bDMARDs	100	92	85	62	62	58	54	46	15	8		

X = yes, would prescribe bDMARDs.

Some clustering of rheumatologists recommending prescription of high or low levels of bDMARDs in each included region was noted, although respondents from all regions appeared throughout the prescription spectrum. For example,

the ten respondents with highest level of prescription were represented in all five regions.

Reasoning behind treatment decisions

Both the decision to prescribe bDMARDs and the choice to prescribe some other treatment were primarily motivated by medical aspects described in the patient cases. For patients who had not previously received triple therapy, most respondents who refrained from prescribing bDMARDs explained that they first wanted to try additional treatment with traditional DMARDs (patient cases 2, 5, 6, 7, 8, and 10). A good response to ongoing treatment was also used as motivation for not introducing bDMARDs (patients 7 and 9).

There was contradictory reasoning regarding the patient who had had squamous cell carcinoma (patient 5), with half of the rheumatologists recommending restriction of bDMARDs due to the previous cancer diagnosis, and the other half pointing out that considerable time had passed since the surgery for that condition. The only case where all physicians would prescribe bDMARDs was patient 3, who had been on triple therapy for quite some time and still exhibited moderate disease activity, adverse prognostic factors, and several swollen and tender joints.

Some rheumatologists also referred to lifestyle-related factors or social function of the patient. Several respondents said that they would ask patients who were smokers to quit smoking before initiating bDMARDs, since smoking can reduce the effect of these drugs. The social function most often mentioned was the patient's occupation. For example, several respondents indicated that they would prescribe bDMARDs for a dentist (patient 2) in order to prevent joint destructions, taking into consideration the current condition of the patient and the fact that she required the use of her hands in her occupation. The age of the patient was another factor that was mentioned by several respondents.

Register analysis of factors influencing the prescription (Paper III)

In the register analysis there were several significant differences between the patients who were not prescribed bDMARDs during the period 2008-2012, but who, on at least one occasion, had an sDMARD prescription and changed treatment for the first time to either a new sDMARD or a bDMARD. As the descriptive analysis shows in Table 3, patients changing to bDMARDs were slightly younger at the visit as well as at the onset of RA. The disease duration was also longer among patients changing to another sDMARD. Patients who were started on bDMARDs were on average included in the register at an earlier time point (2007 vs. 2008) and were also younger at inclusion (54 vs. 55.7 years). The number of patients who were anti-CCP positive and who had erosion during the period was higher among those who were prescribed bDMARDs. They also had a larger number of tender and swollen joints, higher levels of DAS28, HAQ, physician's global assessment of disease activity and patient's global assessment of disease activity. They also suffered more from fatigue and had lower EQ-5D-scores.

Table 3. Descriptive analysis of factors associated with patients changing treatment from one synthetic DMARD (sDMARDS) to either a biological DMARD (bDMARD) or another sDMARD.

Factor	Change to bDMARD	N	Change to another sDMARD	N	Sign
Patient characteristics					
Sex (% women)	74	3 510	75	2 378	0.393
Age at visit (years)	56.9	3 182	58.0	2 179	0.000
*Age at onset of RA (years)	47.3	3 476	51.3	2 349	0.000
*Current smoker (%)	16	2 570	17	1 538	0.359
Duration of RA at visit (years)	9.6	3 476	6.8	2 349	0.000
Laboratory markers					
RA seropositive (%)	80	3 453	72	2 329	0.000
*anti CCP-positive (%)	82	677	72	582	0.000
Disease activity					
*Erosive disease (%)	52	617	34	460	0.000
Tender joints (out of 28)	6.4	3 219	4.3	2 330	0.000
Swollen joints (out of 28)	5.9	3 220	3.6	2 331	0.000
Disease activity (DAS28)	4.6	2 821	3.9	2 009	0.000
Physician's global assessment of disease activity (PGA, 0-4)	2.0	3 109	1.6	2 237	0.000
*Patient's global assessment of health (VAS, 0-100mm)	50.9	3 156	44.7	2 169	0.000
Disability					
Pain (VAS, 0-100mm)	50.1	3 131	44.3	2 151	0.000
HAQ Disability Index (0-3)	1.0	2 976	0.8	2 053	0.000
*Fatigue	49.7	625	46.5	442	0.000
Health related quality of life (HRQL)					
*EQ-5D	0.5	1 228	0.6	860	0.000

*: Not included in Models 1-4 due to a lack of data (anti-CCP, erosive disease, fatigue and EQ-5D) or that they did not add any extra information about the difference in prescription (age at onset of RA, current smoker and the patient's global assessment of disease).

Regression analysis

Among RA patients who had never tried bDMARDs but had at least one sDMARD, we identified 4010 patients who changed treatment to either biologic or synthetic DMARD therapy during the study period, with enough data to be included in the final models (Table 4).

Table 4. Regression analysis of factors associated with patients changing treatment from one sDMARD to a bDMARD, instead of another sDMARD.

	Model 1, n=4010 OR (95% CI)	Model 2, n=3853 OR (95% CI)	Model 3, n=3596 OR (95% CI)	Model 4, n=3579 OR (95% CI)
Patient Characteristics				
Sex (female vs. male)	0.81 (0.69-0.94)	*	0.84 (0.72-1.00)	*
Age (per 10 years)	0.80 (0.76-0.84)	***	0.81 (0.77-0.86)	***
Duration of RA at visit (per year)	1.04 (1.03-1.05)	***	1.04 (1.03-1.05)	***
Disease Activity and Treatments				
Seropositive RA (Yes vs. No)	1.51 (1.29-1.77)	***	1.54 (1.30-1.81)	***
N° of swollen joints (out of 28)	1.10 (1.08-1.13)	***	1.07 (1.04-1.09)	***
DAS28	1.17 (1.08-1.27)	***	1.04 (0.95-1.14)	NS
Pain (per 10-mm change on a 100-mm VAS)	0.94 (0.91-0.97)	***	0.93 (0.90-0.96)	***
HAQ Disability Index (0-3)	1.54 (1.34-1.78)	***	1.50 (1.30-1.74)	***
N° of previous DMARDs (during 2008-2012)	1.21 (1.07-1.38)	**	1.20 (1.05-1.36)	**
PGA (0)		Referent	Referent	Referent
PGA (1)		0.74 (0.55-1.00)	*	0.82 (0.59-1.13)
PGA (2)		1.51 (1.08-2.10)	*	1.80 (1.27-2.57)
PGA (3)		2.68 (1.76-4.06)	***	3.37 (2.16-5.26)
PGA (4)		5.64 (1.21-26.19)	*	9.17 (1.95-43.23)
Physician preference				
Physician prevalence proportion (lowest tertile)		Referent	Referent	Referent
Middle tertile		1.49 (1.25-1.70)	***	1.28 (1.05-1.57)
Highest tertile		3.62 (2.98-4.56)	***	2.80 (2.13-3.68)
Physician location				
Region 0...18				Not Presented [†]
C statistic	0.708	0.724	0.754	0.774

Model 1 includes demographic and clinical variables, **Model 2** includes Model 1 + Physician's global assessment of disease activity, **Model 3** includes Model 2 + Physician preferences, **Model 4** includes Model 3 + Regional prescription rates. Only parameter estimates for factors associated with the outcome, $p < 0.05$ in at least one model, are shown for brevity, and to reduce colinearity; however, the C statistic (the area under the ROC curve) reflects discrimination for the model with all a priori specified variables.

RA= rheumatoid arthritis; OR= odds ratio; 95% CI= confidence interval; VAS= visual analogue scale; HAQ= health assessment questionnaire; DMARDs= disease modifying antirheumatic drugs; PGA= Physician's global assessment of disease activity

*= $p < 0.05$, **= $p < 0.01$, ***= $p < 0.001$, NS= not significant at $p < 0.05$. †= compared to the region with the highest prescription of bDMARDs, the OR for the other regions was 0.16-0.66, $p = 0.000-0.73$.

Using a restricted set of demographic and clinical variables, results in Model 1 in the first column of Table 4 show the factors independently associated with prescription of bDMARDs. Being female was associated with a lower likelihood of prescription of bDMARDs ($p < 0.05$). Older age and high estimated pain were also associated with a lower likelihood of being prescribed bDMARDs ($p < 0.001$). Disease duration, swollen joint count, DAS28 and HAQ scores as well as the number of previous DMARDs during the study period were associated with increased likelihood of receiving biologic therapy.

After adding information about the physician's global assessment, the results in Model 2 show that most factors, apart from DAS28, remained independently significant. Moreover, most of the factors had similar odds ratios as in the first model. The model's discrimination increased slightly (~ 0.02 -unit change in the C statistic) after addition of the physician's global assessment of disease activity.

We then calculated the physician preference proportions among the 314 physicians with at least 50 unique patients during the study period. As shown in Model 3, the prevalence proportion of patients being prescribed bDMARDs was a significant factor, regardless of clinical factors such as disease duration, self-estimated pain, swollen joint count, HAQ, number of previous sDMARDs, and physician's global assessment of disease activity. The magnitude of the odds ratios of the physician's preference was most pronounced among the third of the physicians with the highest prescription rates. The C statistic improved from 0.72 in Model 1 to 0.75 in Model 3.

We then tested whether hospital type (university hospital vs. other hospital) influenced prescription. However, since no significant influence of hospital type could be shown regarding the choice between prescribing bDMARDs or sDMARDs, this was not further considered.

Including data on the regional prescription rate, still revealed that the physician's preference was independently significant. The C statistic improved further, from 0.75 in Model 3 to 0.77 in Model 4.

Factors influencing the prescription of bDMARDs (Paper IV)

Prescription factors were grouped into broader categories and are presented as they were mentioned and rated by the rheumatologists: 1) the intervention, 2) the prescriber, 3) the patient, 4) the inner setting, and 5) the outer setting (Table 5).

Intervention characteristics

Overall, the rheumatologists described a pattern where the decision to use bDMARDs was largely influenced by scientific evidence about the drugs. From initially restrained prescribing, prescriptions increased when an increasing number of clinical studies demonstrated good clinical effectiveness of bDMARDs together with acceptable side effects. A few rheumatologists pointed out that recent studies supported the use of a combination of sDMARDs as an alternative to bDMARDs. In addition to the scientific evidence, most rheumatologists emphasized the substantially higher costs of bDMARDs compared to treatment with sDMARDs as an influencing factor. The higher costs made them think twice before prescribing bDMARDs, since they knew that prescription of these drugs would have a significant budgetary impact.

Characteristics of individual prescribers

All respondents recognized that the individual rheumatologist's subjective judgment and experiences influenced prescription decisions. A common argument was that if the drug had good effect in one patient and no serious side effects emerged, the physician felt safe in choosing that drug for the next patient. A number of personal attributes were also mentioned as influencing factors, ranging from how well-informed and up-to-date the rheumatologists were to their general attitude towards innovations and risks. A few

respondents also mentioned years in practice as an influencing factor and suggested that junior physicians were more keen on using bDMARDs.

Patient characteristics

All physicians emphasized that the decision to prescribe bDMARDs was largely influenced by patient characteristics such as disease activity and joint destruction, where patients with higher disease activity were prescribed the drug to a greater extent. In addition, the age of the patient was considered important, as was the patient's level of education, since that could have a possible impact on compliance with taking the drug. The impact of medication on the patient's everyday life as well as whether the patient would be able to return to work were also mentioned as influential regarding the prescription decision. In addition, the patient's own will and preferences were important factors. According to the rheumatologists, many patients are well-informed about bDMARDs and they are active in the choice of drug and make demands. Hence, the patients influenced the prescription decisions to a large extent, both by their clinical indications as well as through their own preferences.

Table 5. Summary of the factors influencing prescribing by thematic categories, P= prescriber, CC= county council.

Category	Theme	Quotations
1. The intervention	Scientific evidence of effect	"There's been so much data on the ... biologics, their effectiveness ... and even side-effect profiles and above all perhaps the absence of serious side effects have meant that they have come earlier and earlier in the treatment arsenal." (P24, CC2).
	Cost of the drug	"The striking fact about the biological drugs when they arrived was that they were very expensive. So this led to far more expensive treatment than before." (P10, CC3).
2. The individual prescribers	Knowledge and beliefs about biologics	"How much you know about the drug, how much experience you have with it... If you have something that's gone wrong, you think it might be the same for the next patient... experiences and habit largely affect prescribing." (P6, CC3).
	Personal attributes	"Some physicians are also very conservative, they use what they've learned ... and don't want to test something else." (P24, CC2).
3. The patient	Patient characteristics	"The patient influences the decision the most, it all starts there... Because then I can always justify my decision if somebody questions it and says that I prescribed something very expensive, I can always say "we chose this based on the patient" and then I can't get any criticism for it. The patient is the factor with the most influence." (P3, CC4).
	Patient as an actor in decision-making	"But then of course there's also some pressure from the patients. They're very well informed. And if you decide not to prescribe biologics you'll presumably have to motivate that decision." (P26, CC2).

Category	Theme	Quotations
4. Inner setting	Structure of the department	"Another reason (for the varying prescription decisions) is that the number of rheumatologists varies substantially across the country, and if you're not a specialist in rheumatology you probably don't feel very accustomed to using that type of drug." (P23, R2)
	Networks and communication	"When we want to start biological medication in a new patient, we have a group discussion and the decision is made in the group... to get a common practice for the patients we treat. The choice of treatment is still made by the individual physician so it's more about the decision that it's okay to start with a biological drug for this patient." (P12, CC1).
	Leadership involvement	"One thing that influenced prescribing was that I was the medical chief [at the rheumatology department] and I sat down and prioritized the extra resources needed for the drugs at our department." (P23, CC2).
	Available resources	"We have the pharmaceutical budget, we have had a ... well, a limited budget, simply. And these treatments are expensive of course and it's hard to stick to the budget." (P11, CC3).
	Culture	"When discussing a patient that I want to put on biologics, my colleagues usually question whether I've tried this and that first... My opinion is that it's more restrictive that way." (P15, CC1).
5. Outer setting	Cost responsibility	"... I think that the budget still plays a role there... the stricter the budget you have at the department, the more careful you are with the money. I think there are other departments

Category	Theme	Quotations
		with higher prescription levels that do not really ... carry their own drug costs in the same way we do and of course that facilitates their prescribing more." (P5, CC4).
	Political and administrative influence	"Sometimes you're lucky and this is an area that is highly prioritized by the county council and then you're more willing to start treatments, but in other regions it has been quite the opposite and starting treatments has been banned, yes, there has simply been a total stop." (P20, CC5)
	External policies	"When the new guidelines came there was a clear increase in funding for the drugs in the region... then we also had the new guidelines from the SRF and they could of course also be used as an argument that there were many more [patients] that should have biological drugs so then we need to have more money." (P18, CC5).
	External peer pressure	"And that was actually what made it possible to increase our previous low level of prescription. When the Open Comparisons came they made it a bit freer to prescribe the drugs." (P10, CC3).
	Participation in clinical trials	"The studies facilitated understanding of the new drugs, because when you test the new drugs in clinical trials, you're always in the forefront of development, so we were familiar with the new drugs before they were even available. And I think that has facilitated their use." (P21, CC5).
	Influence from the pharmaceutical industry	"If companies are very active in marketing at one department, then that can have an impact. Or if there are some personal ties between [physicians and reps] and they think they are nice or something. Then you can get a higher prescription level." (P7, CC3).

The inner setting

Departments with a larger number of rheumatologists were considered to be more familiar with bDMARDs and therefore likely to prescribe them to a larger extent. Physicians in smaller departments might have fewer colleagues but, on the other hand, might be more exposed to influence from pharmaceutical sales representatives. The physicians pointed out that they discussed and shared information informally within their professional network on an ongoing basis. Some departments had regular meetings where patient cases and drug prescription were discussed. Different treatment strategies were discussed and the various rheumatologists could express their opinions on treatment choice. The physicians contended that such meetings contributed to a greater degree of consensus on prescription strategies.

Furthermore, the attitude of department management had significant influence and could either facilitate or inhibit prescription of bDMARDs. Some chief managers promoted bDMARDs externally to obtain increased funding from county council management, and they could also allocate resources in the department specifically for bDMARDs. Many rheumatologists had experienced that staffing and financial resources at the department influenced the extent to which they prescribed bDMARDs. Some rheumatologists also declared that there were different local treatment traditions and different opinions about how early in the disease course bDMARDs should be instituted. Some rheumatologists pointed out that university hospitals had created a culture of early adoption of innovative treatments in general. Therefore they tested drugs, also including new treatment indications, earlier than what might be done elsewhere.

The outer setting

A common argument among the rheumatologists was that differing reimbursement regimens for bDMARDs were behind much of the variation in

prescribing. Many respondents argued that responsibility for the drug budget at the department level had lowered the prescription levels. The rheumatologists also described that different forms of management at the central political and administrative levels of the county councils influenced prescription, by priority of rheumatology compared to other diseases in the county councils and compared to treatment practices in other county councils. The physicians also pointed at influence from external policies, such as the SRF guidelines and the national guidelines from the National Board of Health and Welfare, on the pharmaceutical funding for the department. Furthermore, the annual report comparing health care in the Swedish county councils, Open Comparisons, had also influenced prescription practices. In addition, participation in early trials on bDMARDs in the 1990s was emphasized as an incentive for increased prescription, since participating departments were well prepared to continue these treatments when the drugs eventually were registered. Some respondents also believed that there was external influence from pharmaceutical company representatives through their promotional activities.

Rating of predefined factors that influence prescribing practice

In the respondents' rating of predefined factors that may influence the prescription decision, three broad categories of factors could be distinguished (Table 6).

Among the predefined factors ranked by the respondents as having the highest impact on the prescribing decision were those concerning scientific evidence and professional and national guidelines (Table 6). More precisely, they concern the evidence of the efficacy and patient benefit of the drug, the strength and quality of the scientific evidence, the prescriber's knowledge and experience, the patient's level of disease activity, the influence of colleagues, and national, local and professional guidelines.

Factors rated as having moderate influence were associated with formal and informal influence from colleagues and leaders at the department, cost and budget issues, and the prescriber's own attitude and experiences from participating in studies of bDMARDs. Finally, factors rated as having the lowest impact on prescription decisions were the patients' expressed requests and wishes and non-disease specific patient attributes, as well as influence from pharmaceutical companies and the media.

Table 6. Rating of predefined factors that influence prescription decisions.

Factor	Mean	Min- Max	SD
Proven effect and patient benefit of the drug	2.96	2- 3	0.19
Strength and quality of the scientific evidence	2.85	2- 3	0.36
Prescriber's knowledge and experience	2.52	1- 3	0.58
Patient's level of disease activity	2.40	0- 3	1.01
National and professional guidelines	2.39	1- 3	0.63
Colleagues	2.11	1- 3	0.58
Local guidelines	2.08	0- 3	0.92
Prescriber's attitude toward bDMARDs	1.96	0- 3	0.98
Cost-effectiveness of bDMARDs	1.93	0- 3	0.78
Formal leaders at the department	1.85	1- 3	0.66
Economic resources and pharmaceutical budget	1.78	0- 3	0.75
Cost of the drug	1.70	0- 3	0.87
Economic consequences for the department	1.70	0- 3	0.87
Study participation by the prescriber	1.44	0- 3	0.88
Informal leaders at the department	1.41	0- 3	0.84
Feedback (from colleagues, leaders, statistics)	1.31	0- 3	0.61
Mode of prescription (if taking it is complicated)	1.29	0- 3	0.70
Patient's expressed requests and wishes	1.04	0- 2	0.50
Non-disease related attributes of the patient	0.93	0- 3	0.62
Information/ marketing from the pharmaceutical company	0.81	0- 2	0.48
Media attention in newspapers, TV	0.43	0- 1	0.49

Influences to a large extent=3, quite a lot=2, to some extent=1, not at all=0.

N=26.

Implementation of National Guidelines (Paper V)

The responses to the National Guidelines for Cardiac Care (NGCC) among the different groups at the county councils will be presented using Oliver's (1991) framework on institutional factors that influence the strategic responses: the cause, the constituents, the content, the control and the context of the implementation of the NGCC in Swedish county councils (33).

The cause

When the NGCC were released in 2004, all categories of informants; politicians, administrators and medical management, supported the goals of the NGCC. Their social legitimacy was high and they were perceived as an important document. However, interpretation of the goals varied between different categories of informants. For example, several politicians asked whether the goal of equal care was realistic for such a complex sector as health care.

The constituents

The organization of healthcare in Swedish county councils is confronted with multiple interests, pressures and expectations. Some expectations are related to the respective roles of the various actor groups in the county councils. Elected politicians face expectations from the general public, interest groups, and state authorities as well as internally from the medical profession (120). Medical management encounters the expectations of patients and their relatives, but also those of politicians, administrators and interest groups (121).

Additionally, there are a number of external pressures that confront the county council. These can be in the form of laws and regulations, comparisons with performances in other county councils, and recommendations such as the

national guidelines. The National Board of Health and Welfare, which produced the national guidelines, was perceived as a legitimate authority by many of the informants. Although the county councils are not directly dependent on this agency, if the guidelines are not implemented this could result in pressure from patients and the general public.

The content

The NGCC is a multifaceted policy instrument with different parts that put a varying amount of pressure on the implementing environment. The guidelines are mainly based on medical norms that are formulated as a system for ranking specific treatments. The informants perceived the suggested strategies for reaching the goals in NGCC as vague. They did not initially express that the NGCC provided an input to local healthcare programs, or that it supported explicit and needs-based prioritization or increased the dialogue between decision-makers. A clear view of how to handle the NGCC was lacking, and there was great ambiguity concerning the way the guidelines should be managed. Gradually, however, this changed in the county councils and a clearer view of how to handle the guidelines emerged, as will be described below in the section about strategic responses.

The control

The consequences of nonconformity with the NGCC are not directly punitive or strictly enforced. The guidelines are recommendations and it is up to each county council to locally implement them through voluntary diffusion. However, quality indicators are created to follow compliance with the national guidelines, and county councils that greatly deviate from the guidelines can be questioned by patients and the public.

The context

The context in Swedish county councils has undergone a transformation from stability to increased uncertainty due to the rapid influx of health technologies, more demanding patients, public-private mix, as well as changes in the interplay between central and regional government (122). In the external environment the county councils are highly interconnected to the national level and to state agencies. Several respondents, especially among the administrators and politicians, mentioned the diverging demands facing the county council.

Strategic responses to the NGCC

As previously mentioned, the different groups had different goals and norm systems within their respective parts of the county council. Although it is clearly expressed that the NGCC, when they were released, were intended for decision-makers throughout the entire health care organization, the politicians and administrators initially considered the guidelines as an issue for clinical management and the medical profession. Medical management initially shared this view, and reception and implementation of the guidelines was left to clinical management and the medical profession. In several of the county councils there were examples of local information meetings for the medical profession from both primary and secondary care that focused on integrating the guidelines into everyday clinical work in an attempt to comply with the guidelines.

Medical management expressed that some requirements in the NGCC, specifically concerning resources and prioritization connected to the NGCC, needed to be tackled at other levels of the county council. Eventually, local-level coalitions consisting of professional networks, became more involved in discussions with politicians and administrators about the guidelines in order to negotiate and to reach a balance regarding the different expectations of the multiple constituents. The professional networks acted as a collective opinion leader, intending to promote a positive view of the NGCC, for example by

organizing multi-actor seminars, in order to incorporate the NGCC in local healthcare programs as well as to promote explicit priorities with reference to the NGCC.

The increased involvement of local professional networks in the work with the NGCC eventually raised questions of more funding directed to the administrative and political levels of the county council. In several cases the networks demanded increased funding either for implementing some of the recommendations in the guidelines or for working indirectly with them by, for example, performing audits of cardiac care to explore if the care given was aligned with the guidelines. This resulted in debates with the administrative and political levels, leading to an increased level of conflict. The administrative and political levels tried to avoid the broad prioritization demanded by the NGCC, pointing to the need to also take health care areas besides cardiac care into account.

DISCUSSION

This chapter discusses the main results of the five papers and some of the lessons learned during the work with this thesis. It is divided into four sections according to the following headings: diffusion and variations, economic consequences of the diffusion, factors influencing the use of the health technology, and implementation of the national guidelines. Thereafter follows a discussion concerning methodological considerations and the implications of this thesis for policy and research.

Diffusion and variations

During the 2000s there has been rapid diffusion of the bDMARDs in basically all Western countries and between 7 and 16 percent of the diagnosed adult RA patient population in Europe are being treated with bDMARDs (20, 123). However, there are significant differences between countries in patients per 100,000 population who are being treated with bDMARDs, ranging from 5 percent in Austria to almost 30 percent in Norway in 2007 (123-127)

Compared to other EU member states, Sweden has been among the countries with the highest prescription rate of bDMARDs (20). The rapid diffusion of bDMARDs, as presented in Paper I, did not occur at the same pace in all regions in Sweden. Previous research has reported large variations between the different regions in the prescription rate of bDMARDs to patients with RA, both in Sweden and in other countries. In line with Mercuri et al. (2012), and Curtis et al. (2010), this thesis also exhibits individual variations in the treatment of RA (26, 128). Individual variations in prescription were seen both in the patient cases and in the register study (Papers II and III). To our knowledge, our patient cases study was the first to examine the differences in

the prescription of bDMARDs among individual rheumatologists in a Swedish setting, and the results indicate a substantial disparity in treatment choices for RA patients. This was also seen in the register study (Paper III) where the individual prescriber's preferences was an important predictor for prescription, even when adjusting for patient characteristics, disease activity and the physician's local context.

The fact that wide variations are seen among different countries, different regions as well as between individual physicians, raises the question as to whether these variations are unwarranted. This depends on how treatment with bDMARDs is viewed, since some variations might be more problematic than others (50). In accord with Wennberg (2011), variations in treatment that is considered both clinically efficient (and cost-effective) are probably a result of underuse due to limitations in supply or insufficient use of available evidence. Such variation is problematic from the perspective of equity, since the treatment is withheld from groups of patients in some areas but not in others. Furthermore, such variation can be inefficient if patients in low-use areas receive too little care. Wennberg (2011) does not include cost-effectiveness in his analysis of unwarranted treatment, but cost-effectiveness is important to consider since, together with the principle of human dignity and the principle of need and solidarity, it is a core principle intended to guide decision-makers in priority-setting at all levels in the Swedish healthcare system (16).

However, if the treatment has a similar clinical effectiveness as an alternative treatment, variations are probably induced by the preferences of the patients or physicians, or by supply (50). In this case the areas with low use of the studied treatment might get just as good clinical outcomes. Unequally distributed treatment that is not superior in clinical effectiveness will not lead to the same equity concerns as inequalities in the distribution of highly effective treatments (129). However, there may be concerns for patients in high-use areas receiving too much treatment, resulting in unfavourable risk-benefit or cost-effectiveness profiles.

Unfortunately, it is still unclear whether higher or lower prescription of bDMARDs is desirable in Swedish county councils, as the cost-effectiveness of bDMARDs is not well known in subgroups of patients with shorter disease duration or lower disease activity (81). Studies of such subgroups may help to better define optimal levels of treatment with bDMARDs. Recently, 'induction-maintenance' and 'dosing down', two alternative approaches to simply restricting, on economic grounds, the use of bDMARDs, have shown promising results (130, 131). These approaches could be a possible alternative to prescribing for all patients who would benefit from bDMARDs - resulting in a large budget impact in the long term, and full restriction- resulting in unreached potential in patient benefits. These conclusions highlight the importance of a joint analysis of the evolution of both the total rate of prescription and the evolution of the variation. A subgroup analysis of which patients would benefit the most from the treatment with bDMARDs, and which patients are currently receiving it is essential in further research.

Economic consequences of the diffusion

This thesis also contains the first study of the costs of RA covering 10 years before and 10 years after the introduction of bDMARDs. Paper I showed that bDMARDs in Sweden have increased the costs for drug treatment of RA patients from €8 million in 1990 to approximately €250 million in 2013 (132). Our results for specific years are comparable to those in previous studies (133, 134). Although bDMARDs constitute an extreme case, this is only one example of large technology shifts in health care. Based on the cost increases exhibited in Paper I it can be questioned as to whether new health technology drives the cost increases in health care, as is sometimes contended (12, 13). One explanation for cost increases in health care may be that innovative health technologies lead to an increased demand, i.e. an expansion in both the types and numbers of patients treated, at the same time as they are more expensive than previous treatments. Another explanation is that health technologies are introduced before their long-term efficiency is fully understood (135).

The total costs and effects of the introduction of new health technology have been evaluated for some disease areas, for example cardiac care (136, 137), and positive economic benefits for the investments in innovations have been shown. However, there is still a lack of data that definitely determine the total contribution of new health technologies to cost development in health care. In this thesis the disease area of RA has been examined, and a large increase in direct costs was seen. From a broader perspective, there was also a substantial increase in the total societal costs of this disease between 1990 and 2010, especially since 2000 when bDMARDs were introduced. However, it should be noted that there is slight downturn in total costs at the end of the period and that the health benefits of bDMARDs were not included in the calculation of total costs.

Factors influencing the use of the technology

The variations in treatment can be explained by different factors. The variations in treatment of RA between countries have been related to differences in national GDP as well as to different reimbursement policies, budgetary restrictions, and access to specialists and waiting times until diagnosis (138, 139). Small-area variations in general have been related to organizational, economic and social factors as well as to characteristics of the intervention and of the individual physicians (15, 47). In Papers II-IV, this thesis has explored the influences on treatment of patients with RA. These factors were found to comprise characteristics of the drug intervention; the actors involved, including the patients; the inner setting; and the outer setting.

Characteristics of the drug intervention

The scientific evidence on the effect of the drugs was both described and rated as having a highly significant influence on prescription (Paper IV). However, general agreement on the evidence for biologicals was lacking, and there were diverging interpretations of the evidence, something that was also seen in the responses to the described patient cases in Paper II. Some physicians pointed

out that research supports the extended use of biologicals while, on the contrary, others indicated that several recent studies have demonstrated similar outcomes using combination treatment with traditional DMARDs. The diverging views are interesting and might reflect that some applications of biologicals are still relatively new. They might also reflect the growing evidence leading to the question as to whether the initial general expectations of effect and cost-effectiveness of biologicals are being fulfilled.

A review has identified when disagreement over the choice of care is particularly prevalent (123). Firstly, disagreement over the choice of care is particularly prevalent when there is rapid development of scientific knowledge within the disease area. Secondly, disagreement over the choice of care may also occur when clinical trial evidence does not provide adequate information about the timing of treatment in relation to disease progression, or it provides little information on specific disease sub-groups. Thirdly, disagreements may also occur, since the disease is sufficiently heterogeneous in its impact on patients, with a wide range of disease complications, so that it is difficult to extrapolate clinical trial findings to the general patient population and even more difficult to apply as a ground for treatment decision of an individual patient. All of these factors apply to bDMARDs for RA, which could help explain the exhibited individual variations in treatment.

Characteristics of the individual prescribers

In addition, the diverging prescription patterns seen in Papers II and III further emphasize that other issues besides evidence and guidelines are of importance in clinical decision-making. Subjective judgments and experience were emphasized by the rheumatologists, and 'prescriber's knowledge and experience' was the third highest rated factor in the quantitative rating in Paper IV. Diverging knowledge and experience among rheumatologists might contribute to the individual variations in prescriptions for patient cases seen in Paper II.

The finding that prescription largely varied with the region of activity of the physician (Paper III) can be interpreted as indicating that some of the prescribing is supply-sensitive, and dependent on factors at the county council level. But even when controlling for the regional prescription rate, differences between individual physicians are evident. This highlights the finding that prescribing of bDMARDs is partly dependent on the preferences of the individual physicians.

Characteristics of the patient

In the interviews in Paper IV, the majority of the respondents expressed that patient attitudes and preferences were influential regarding the prescription decision, and in responding to the patient cases (Paper II), several physicians noted that they would like to consider the patient's preferences. This is indicative of the currently widespread discussions on shared decision-making, where clinicians and patients share the best available evidence when faced with the task of making decisions, and where patients are supported to consider options, to achieve informed preferences (140-142). At the core of the shared decision-making approach is the recognition that professional knowledge is necessary but not sufficient for good decision making (141).

Surprisingly enough, although they were an often discussed theme in the interviews, patient preferences were rated relatively low in the quantitative rating. This might reflect the simultaneous discussion about fair treatment and the physician's integrity in relation to the influence of individual patients. The principal-agent relationship lies at the base of health care, where the principal, i.e. patients, delegate making clinically adequate choices for them to the agents, i.e. healthcare professionals (143). Furthermore, for patients who express preferences for a specific treatment, the question remains as to where they gather their information. Some information might come from the manufacturing companies while other sources might include patient associations, who do not necessarily base all their information on systematically gathered best available evidence or guidelines. Also, to meet

patient preferences, adequate resources are required at the department, which might not always be the case.

Inner setting

The importance of social knowledge, such as professional networks and collegial discussions (144, 145), was raised by many of the interviewed physicians (Paper IV). Colleagues were also quantitatively rated relatively high. The importance of colleagues has also been shown by others (146-148). McGettigan et al. have suggested that "the medium is more important than the message" (148). In a survey comprising 230 hospital physicians, the vast majority declared that their primary sources of information on new drugs were colleagues and clinical meetings (148). The fact that professional networks and colleagues were important indicates the significance of the characteristics of the inner setting. This finding can indicate a rapid dissemination of information and new evidence, both from science and experience, among the professionals. However, this may also contribute to therapy traditions being preserved within the clinic if the professional network is not more extensive.

In Paper IV, several rheumatologists suggested that the inner setting at university hospitals encouraged openness to innovations which they expected in turn led to higher levels of prescription of bDMARDs. However, this could not be seen in the register study in Paper III. The discrepancy in findings is perhaps due to the fact that only rheumatologists at university hospitals were included in the interviews, along with the widespread belief that university hospitals, where a great deal of research is performed, are also more open for innovations. It could also be due to the period included in the register study; 2008-2012 is several years after the initial introduction of bDMARDs, when there were perhaps larger differences in use. However, an important lesson to be drawn from this is the value of having multiple approaches, both quantitative and qualitative, in order to cover several aspects of a research phenomenon.

Outer setting

In the interviews in Paper IV, several factors at the organizational level, such as budget responsibility, were mentioned as influencing the prescription decisions. Financial incentives have previously been shown to influence on the uptake of new drugs (149, 150). A recent review showed that the mere presence of financial incentives may influence prescriptions (151). Based on 13 studies, this review concluded that when a group of physicians, or individual physicians, manage their own budget, they prescribe fewer and less expensive drugs. The participating physicians in paper IV had experience of having costs for bDMARDs included in a regional global budget as well as having drug cost responsibility at the rheumatology department. Many physicians argued that department responsibility for the drug budget had lowered prescription levels. Whether or not budget responsibility lay at the department level had an impact on prescriptions, which is an important lesson regarding the formulation of pharmaceutical reimbursement.

Another influential factor in the outer setting was the priority level of rheumatology compared to other disease areas in the county councils. National registries and audits through the Open Comparisons Reports were mentioned as a powerful factor and a tool for making administrative leaders and policy-makers aware of variations in prescriptions, which in turn led to increased resources for biologicals in county councils that lagged behind. Treatment guidelines were rated as being of similar importance as the patient's level of disease activity and were repeatedly mentioned as being used to influence the political and administrative leadership in the county council. It would therefore be interesting in future research to evaluate the implementation of the treatment guidelines for RA. One possibility after the guidelines have been in effect for some time is to follow treatment changes in the Swedish Rheumatology Quality Register.

Interaction of factors

Given the broad range of factors that were mentioned in interviews in Papers II and IV as influential regarding the prescription of bDMARDs, and that were identified in the register study in Paper III, the large regional variations are not unexpected. Since these factors differ among county councils, departments and prescribers, they contribute to varying levels of prescription. The identified factors act at either an organizational or an individual level. The organizational factors can be suspected to cause much of the variation between different areas, but individual factors probably increase regional variations and cause the variations among physicians at the same department. The factors should not be seen as single influences, but rather as acting in an interactive, nonlinear manner, where one factor could have an immense influence on the others and cause a chain-reaction in one setting, while barely having an impact in another setting. An implication of these results is that in addition to scientific knowledge, attempts to influence prescription behavior need to be multifactorial and account for interactions of factors among different actors.

Implementation of the National Guidelines

National Guidelines are one of the most important instruments used in Swedish health care to influence physician behavior as well as policy decisions and have received an attention in the political debate in recent years. They are unique in their combination of best evidence on effectiveness and cost-effectiveness and their aim to be used in decisions throughout the health care organization, within clinical, administrative as well as political settings. Paper V in this thesis has studied the implementation of national guidelines for cardiac care (NGCC) in four county councils in Sweden. Being the first issued guidelines in Sweden, the NGCC provided an opportunity for a long-time follow up of the response in the county councils, which was not possible considering the RA guidelines.

As presented in Paper V, the NGCC is a complex policy instrument incorporating scientific evidence as well as health economic evidence and patient needs. The goals of the NGCC are seemingly explicitly stated but it is not entirely clear what is meant by their goals, and several informants raised the issue of inherent ambiguity. The fact that a policy draws heavily on evidence, as in the case of the NGCC, does not necessarily reduce its inherent ambiguity. On the contrary, few evidence-based policies are undisputed (152, 153). In the words of Greenhalgh and Russel, "a narrowly 'evidence-based' framing of policymaking is inherently unable to explore the complex, context-dependent, and value-laden way in which competing options are negotiated by individuals and interest groups" (153).

Unilateral responses to the NGCC within the county councils were rare, but there were attempts at compromise and a balance between multiple constituents. Examples have been noted of local information meetings, use of the NGCC in local health care programs, and performing audits with NGCC as a base. We have seen clear examples of strategies to avoid performing "explicit priority-setting", by engaging in procedures that signal a will to conform to latest evidence, as suggested by the NGCC, but not through far-reaching reallocation of resources. The manifestation of compliance is important for the county council as an organization in order to maintain its legitimacy in relation to the national level, but also in relation to patients and the public. However, performing explicit prioritization is connected with a risk, particularly for politicians since they risk critique among their constituencies.

An important "goal" within the organization of the Swedish county councils is to retain stability. The NGCC can contribute to increasing the degree of "uncertainty" and instability within the county council in that they contain demands for redistribution of resources, within as well as between, clinical service areas. Although redistribution might be desirable from a societal perspective, represented, for example, by the state authority the National Board of Health and Welfare, internally it can be difficult to reconcile it with the different organizational goals of the political and professional decision-

makers. This can increase the degree of conflict both within the medical profession and the political sphere.

A lesson from this study is that in the handling of ambiguity, the alternative roads forward become visible, which can spark conflicts. The form of institutional pressure represented by the NGCC is of two kinds. A "standardization" of the allocation of healthcare resources, which NGCC implies, should be attractive to both the political and the professional branches of the county council. The political branch since it is often attractive for political decision-makers to adapt to national "standards" to reduce the risk of "blame" in times of uncertainty (154), and the professional branch since scientific evidence is an important part of their norm system. Extensive use of evidence-based medicine to accomplish a high degree of standardization in health care could, however, collide with another part of professional norms, self-governance (155). Concerns have also been raised about the limited applicability of evidence-based guidelines that are based on RCTs, particularly with respect to elderly patients with multi-morbidity (156).

A further lesson is the importance of having a long-term perspective when exploring the implementation of national guidelines. The ambition of the NGCC – to influence different decision-making groups with evidence, is far from self-propelling. However, during the years since the first guidelines were issued, the implementing landscape has changed and the national guidelines are no longer a new instrument in Swedish healthcare. We have noted a gradual increase in activities connected to the guidelines, as well as in structural changes. This has taken a long time, but it also means that recent guidelines, such as those presented for RA, are implemented in another context than the first guidelines issued, which could facilitate their implementation.

Methodological considerations

The studies performed in this thesis have both strengths and limitations. A general issue with the studies about diffusion and its' consequences (Paper I-

IV), is that they are based on one case, that of biological drugs. Case studies enable a deeper understanding of the specific case and are particularly suitable when the focus of the study is to answer “how” and “why”, and when contextual conditions are relevant to the phenomenon under study. However, there might be limitations in the generalizability of the results from case studies to other cases (157).

Looking into the specific papers, using national register data in Paper I, selection bias has been avoided since the entire RA population was covered. We cannot distinguish the causality behind the cost changes, but we can present the trajectory of costs during this extended period. The present study differs from previous studies, which were based on cohorts and/or examined individual cost items and years. The limitations of Paper I are first of all that some relevant data are lacking. This is the case for care given by the municipalities, informal care and intangible costs. Intangible costs, such as pain and fatigue, are substantial for RA patients, but are difficult to quantify. As a result, cost estimates of this kind inevitably underestimate the total effect of the disease on the individual and society. We cannot deny that many patients’ quality of life may improve with bDMARDs, but that was not within the scope of this study. Second, data for outpatient care and sick leave were not complete for all years in the 1990s, and average values were used, leading to possible over- or underestimation of total costs. Finally, as is always the case with cost-of-illness studies, it is not possible to state reasons for cost changes or correlation between changes. For example, costs and effects may be affected not only by the introduction of bDMARDs, but also by the intensification of treatment with traditional DMARDs in the 1990s.

Descriptions of patient cases, such as those used in Paper II have previously been widely used to evaluate practice procedures (158, 159), although the validity of this approach has been criticized, particularly with respect to the extent to which the cases correspond to actual behavior (160). Prescription choices in clinical practice often require extensive information and a stepwise approach, while case simulations provide limited information and ask for a straight answer. The limited information does not specify, for instance, the

patient's preferences and coping style, the physician's global assessment, which joints were affected and their chronicity, or the dosage and administrative route of MTX, all possibly important for treatment choice. The yes/no answer concerning the need for bDMARDs might overestimate the difference in opinion, especially when evaluating borderline cases. Alternative ways to monitor prescription choices include electronic medical records or clinical registries (103), although these strategies might entail limited data sets and reporting bias. Written case simulations have the advantages of being convenient to use, because questions can be posed directly to respondents about their treatment decisions. This technique also ensures that all participants receive the same information, which enables comparisons. We tested the validity of our approach in a small pilot study, and based on the results obtained in that preliminary evaluation, we made minor changes in the patient descriptions before they were used in the interviews.

Due to the limitations of revealing physicians' preferences based on hypothetical patient cases, we complemented this study with a registry study (Paper III) and an explorative qualitative study (Paper IV), asking the rheumatologists themselves about the factors that influence prescription. The strengths of our analysis in Paper III include the use of a comprehensive register, enabling analysis of a large number of RA patients. Various rheumatology registers have been established in Sweden as well as in other countries in the past decade, providing an opportunity to analyze the treatment of patients with rheumatic diseases. The advantages of such registers are that multiple questions can be addressed and that they mirror real-life situations, which in general enables a greater generalization of the results (161, 162). The growing number of observational drug registers has resulted in a task force appointed by EULAR (the European League against Rheumatism) with recommendations for studies from biological registers of RA. These recommendations include the setting, the participants, the variables, the statistical methods, the descriptive data and the analysis (163). Some of these recommendations indicate weaknesses in our study that need to be discussed. The setting in the study is Swedish, and in Sweden all RA patients are eligible for treatment with bDMARDs based on the decision of the

rheumatologist in charge. Varying criteria for drug treatment in different countries might have implications for the direct applicability of our results in different settings (164). However, the general conclusion from our study, that physician preference influences prescription independent of disease activity and patient characteristics, has been supported in previous rheumatology studies as well as studies from other healthcare areas (26, 128, 165). Furthermore, in real-life RA treatment, patients start and stop drug treatments, switch drugs and restart previous treatments. Despite improvement within the past decade, a number of patients are still not included in the register until they are prescribed bDMARDs. The total number of prevalent patients in the SRQ during the period 2008-2012 was 30 127. We used the cleanest exposed cohort; i.e. biologic-naïve patients with at least one sDMARD, who started treatment during this period with either bDMARD or sDMARD (n=4010). By choosing this smaller cohort, we adjusted for the fact that a number of patients first enter the register when bDMARDs are prescribed, and thus we could obtain more reliable results.

In Paper IV, the qualitative approach of the study is both a strength and a weakness. It works well in fulfilling the main purpose of increasing the understanding of possible factors which could influence prescribing practice. However, it might not reveal actual behavior. There is a potential risk of response bias, with the respondent not being aware of, or even wanting to admit, what influences his/her behavior. Accordingly, the responses in the interview and the rating may be biased, and there might be an effect of social desirability at play. We cannot rule out that we have missed important factors in the analysis of the data, despite carefully reading the original transcripts several times after categorizing the themes. Further, the transferability of this study to settings outside of university hospitals might have limitations. However, in Sweden approximately 50 percent of RA-patient visits to rheumatologists occur at university hospitals (SRQ). Despite the limitations in Papers II-IV, using these complementary approaches to explore prescription behavior has, overall, been an asset that can be recommended in further research.

Paper V also has a number of limitations, one of which involves the selection of informants. A pitfall in strategically selecting informants is that some views that are not represented by the experts might be overlooked. A further limitation, as is always the case with qualitative research, is the analysis and whether it has captured the important aspects needed to achieve the aim of the study. Two researchers did the coding separately and then discussed it together to decide on the final themes for analysis, with the ambition of increasing the reliability of the study. This study has the strengths of covering the perspectives of different actor groups in the organization. In addition, as previously advised (58, 166), it combines two widely used theoretical frameworks in the analysis of the implementation process in order to explore both the characteristics of the policy and the institutional factors in the responding organization.

IMPLICATIONS FOR POLICY AND RESEARCH

The diffusion of new health technology was influenced by a wide array of factors, both at individual and organizational levels, as well as by their interaction. Given the wide array of influencing factors, policy attempts to produce and disseminate evidence-based guidelines will unlikely result in automatic implementation. The study on Swedish national guidelines highlights that even when scientific evidence is gathered in policy recommendations, the implementation process is still complex and context-dependent and at large a negotiation between different interest groups. Attempts to influence healthcare decisions need to have a systems perspective (44), and to account for the interaction of factors between different actors.

Future research is warranted on subgroups of patients with RA to define optimal levels of treatment with bDMARDs, from both effectiveness and cost-effectiveness perspectives. This is imperative to get further ahead with the large variations seen in practice between regions, as well as between individual prescribers. In view of the ambiguity perceived in the evidence for treatment of RA, future research could precisely focus on this aspect in decision-making. This is especially important, since the ambitious attempt to consolidate best evidence in the national guidelines, was still perceived ambiguous by the targeted actor groups.

In both the case of RA and that of national guidelines, a significant influence was noted by patient involvement and by comparisons of healthcare performance with other areas, such as that condensed in the Swedish Open Comparisons. Further research could elaborate deeper in these topics. Moreover, several studies in this thesis made fruitful use of the healthcare registries that cover much of healthcare statistics in Sweden, and that are growing in other countries as well. Such registers could be used in future research even more than they are today.

CONCLUSIONS

This thesis provides new knowledge concerning empirical aspects of the diffusion and economic consequences of biological drugs for treatment of RA, as well as concerning the implementation of the national guidelines for cardiac care. The results show that the costs of RA increased over the period, especially following the introduction of biological drugs. A wide array of factors both at individual and organizational levels, and their interaction, influenced rheumatologists' prescribing decisions. Implementation of the national guidelines for cardiac care was not a simple, straightforward process, but occurred gradually and required the involvement of multiple actors. The results show that the simple existence of evidence-based guidelines does not mean that they will automatically be applied, since healthcare decision-making is influenced by many different factors in addition to guidelines. The findings further demonstrate the importance of having a system perspective and taking into account the various factors that influence practice when elaborating evidence-based policy instruments.

Specific conclusions from the analyses of the empirical factors:

- Despite that there was a decrease in the utilization of RA-related inpatient care, sick leave and disability pension in Sweden during 1990-2010, there was a 32 percent increase in the total fixed cost of RA during the same period. This is to a great extent an effect of expensive new medical treatments for RA.
- Choosing to initiate bDMARDs varied substantially among rheumatologists presented with hypothetical patient cases, and there were also disparities between rheumatologists practicing in the same clinic. Treatment choices were primarily motivated by medical reasons.
- Physician preference, adjusted for patient characteristics, disease activity and the physician's local context, was an important predictor for

prescription of bDMARDs, based on data from the Swedish Rheumatology Quality Register.

- A constellation of various factors and their interaction influenced the prescribing decisions according to interviewed rheumatologists, and these included the individual rheumatologist's experiences and perceptions of the evidence, the structure of the department including responsibility for costs, peer pressure, political and administrative influences, and participation in clinical trials. The patient as an actor emerged as an important factor. Hence, factors both at organizational and individual levels influenced the prescribing of bDMARDs.
- Unilateral responses to the National Guidelines within the county councils have been rare, but there have been attempts to compromise and to attain a balance between multiple constituents. There are examples of local information meetings, the use of the NGCC in local healthcare programs, and performing audits with NGCC as a base. However, performing explicit prioritization as advised in the NGCC is associated with the risk of blame, particularly for the politicians. Over time, however, a more systematic use of the National Guidelines has been noted.

SUMMARY IN SWEDISH (SAMMANFATTNING PÅ SVENSKA)

Utveckling inom medicinsk teknologi ökar förhoppningarna om bättre behandlingsresultat och en mer effektiv hälso- och sjukvård. Processerna för spridning och implementering av ny medicinsk teknologi har dock visat sig vara komplicerade, och medför ett antal utmaningar för sjukvården. Många försök har därför gjorts för att hantera och påverka införandet och spridningen av medicinsk teknologi. Ett betydande exempel är de svenska nationella riktlinjerna som syftar till att påverka både kliniskt och politiskt beslutsfattande i hälso- och sjukvården.

Det övergripande syftet med denna avhandling är att beskriva och analysera de faktorer som påverkar spridningen och de ekonomiska konsekvenserna av införandet av en ny teknologi med stora variationer i användning, samt att undersöka implementeringen av nationellt producerade riktlinjer som syftar till att göra hälso- och sjukvården mer effektiv och rättvis. Avhandlingen fokuserar på två empiriska fall. Det första är de biologiska läkemedlen (bDMARDs) för behandling av reumatoid artrit (RA), som valdes eftersom de inneburit en väsentlig behandlingsförändring och är relativt kostsamma. Det andra fallet är de nationella riktlinjerna för hjärtsjukvård, som valdes eftersom de var de första nationella riktlinjerna med rekommenderade prioriteringar, vilket möjliggör ett långsiktigt perspektiv i utforskandet av deras implementering.

Artikel I presenterar en registerstudie som baseras på data från nationella och regionala register för vårdförbrukning och sjukfrånvaro av patienter med RA och uppvisar en 32-procentig ökning av de totala fasta kostnaderna för RA under 1990-2010, främst efter införandet av bDMARDs. Artikel II visar att beslutet att påbörja behandling med bDMARDs varierar kraftigt bland 26 reumatologer som presenteras hypotetiska patientfall, även bland reumatologer inom samma klinik. Artikel III baseras på data från 4010 patienter med RA från Svensk Reumatologis Kvalitetsregister. Genom multivariat logistisk regression visas att läkarens preferenser är en signifikant faktor för förskrivningen av bDMARDs, justerat för

patientkaraktistika, sjukdomsaktivitet och landsting där läkaren var verksam. Artikel IV är en kvalitativ studie om förskrivningsbeslut, som visar att en konstellation av olika faktorer och deras samverkan påverkar förskrivningsbeslut enligt 26 intervjuade reumatologer. Bland de faktorerna ingår den enskilde reumatologens erfarenheter och uppfattningar om evidensen, strukturen på kliniken inklusive kostnadsansvaret, politiska och administrativa influenser, och deltagande i kliniska prövningar. Patienten som aktör förekom som en viktig faktor. Artikel V är en longitudinell kvalitativ studie som genom 155 intervjuer med politiker, administratörer och kliniska chefer undersöker hur fyra landsting implementerat de nationella riktlinjerna för hjärtsjukvård. Resultaten visar att entydiga svar på de nationella riktlinjerna inom landstingen har varit sällsynta, men att det har förekommit försök att kompromissa och att uppnå en balans mellan olika aktörsgruppers intressen. Lokala informationsmöten, användning av de nationella riktlinjerna i lokala vårdprogram samt revisioner utförda med de nationella riktlinjerna som bas, framkom som exempel. Explicit prioritering, såsom det rekommenderas i riktlinjerna nämndes dock sällan. Med tiden har ändå en mer systematisk användning av de nationella riktlinjerna noterats.

Sammanfattningsvis påverkas spridningen av ny medicinsk teknologi av en mängd olika faktorer både på individ- och organisationsnivå, samt av deras interaktion. Spridningen av den nya metod som studerades i denna avhandling har medfört stora ekonomiska konsekvenser och ojämlig tillgång på grund av praxisvariationer, även på klinisk nivå. Eftersom beslutsfattande i sjukvården påverkas av många olika faktorer, kommer framtagande av evidensbaserade riktlinjer osannolikt att resultera i automatisk implementering och vara tillräckligt. Försök att påverka hälso- och sjukvårdsbeslut behöver ha ett systemperspektiv och ta hänsyn till samspelet mellan olika faktorer och aktörer.

APPENDIX A

Questionnaire Paper IV

- *Introduce oneself and the study* (Participants were emailed an information document before the interview).

This study is part of my PhD project about implementation in health care. The specific focus of this study is regional variation in drug prescription and the aim is to explore the variation in prescription of biological drugs for RA. The study is managed independently as part of my PhD thesis and does not have any connections to the pharmaceutical industry or any interest organization.

- *Explain the purpose of the interview*

I would like to use this time to talk to you about prescription, what you see as influential factors on prescription and what you take into account when you prescribe drugs to patients with RA. We have chosen to study the choice between traditional disease-modifying antirheumatic drugs (DMARDs) and biologics, disregarding which brands of biologics are used.

We will be interviewing several physicians at your department to gain multiple perspectives. We will also interview a number of physicians at four other university hospitals. Now we are really interested in learning more about your own experience with prescription.

- *Describe the audio recording and how we will assure confidentiality and answer any questions*

I will start the interview with some general questions about your experience of prescription to RA-patients. Then we will continue with open ended questions about prescription and finally we will talk about specific parts more in detail.

This interview will be audio recorded so that we have an accurate record of your thoughts. Nobody outside of the research team will have access to any of your responses. In any use of your quotations, they will be unidentified and it will not be possible to link the responses to you personally. Our study has an approval from the Regional Ethical Review Board in Linköping. Is it OK that I record the interview?

You may skip any questions you wish during the interview. The interview usually takes about 30-45 minutes.

Do you have any questions for me before we begin?

Introduction

- Will you please describe your background and your role within your department?
 - How long have you been active as a rheumatologist?
 - Are you engaged in research?
 - Are you involved on a local or national level in developing clinical guidelines for treatment of patients with RA?
- What proportion of your total number of patients are patients with RA?
- Where do you gain new knowledge about treatment of RA? (Scientific papers, conferences, colleagues, guidelines, pharmaceutical companies?)

Description of prescribing

- How did your department start to prescribe biologics? How were they introduced?
- How are prescription decisions taken today? How have they been taken previously?
- What influences prescription decisions? What factors do you see are important when prescribing biologics to RA-patients?
 - What influencing factors do you see that are connected to the drug itself?
 - What influencing factors do you see that are connected to the prescriber?
 - What influencing factors do you see that are connected to the department?
 - What influencing factors do you see that are connected to the county council?
 - What factors do you see have facilitated / hindered prescription?
- Do you have any systematic meetings where you discuss the prescription? Have you had such meetings previously? How do you believe they have influenced the prescription?
- Do you see anything that has been controversial with the biologics?
- There are reported variations in prescription of biologics to RA-patients between different regions in the country (Open Comparisons 2012). What do you think can cause such variations?
- Do you think that there are variations **within** regions/county councils? Do you think that there are variations between different departments? Do you think that there are variations between different prescribers? What do you think can cause such variations?

Rating of predefined factors

In previous research a number of factors have been identified that could influence prescription, and we would like you to rate the following factors according to how relevant they are in your prescription decisions. We have categorized the factors in characteristics of the drug, the patient, the prescriber, the department and external influence. We would like you to rate whether they influence your prescription to a large extent=3, quite a lot=2, to some extent=1, not at all=0.

How are prescription decisions influenced by characteristics of the drug:	Not at all	To some extent	Quite a lot	To a large extent
Proven effect and patient benefit of the drug				
Strength and quality of the scientific evidence				
Cost-effectiveness of biologics				
Cost of the drug				
Mode of prescription (if taking it is complicated)				
How are prescription decisions influenced by the patients				
Patient's level of disease activity				
Patient's expressed requests and wishes				
Non-disease related attributes of the patient				
How are prescription decisions influenced by the prescribers				
Prescriber's knowledge and experience				
Prescriber's attitude to biologics				
Study participation by the prescriber				
How are prescription decisions influenced by the the department				
Colleagues				
Formal leaders at the department				
Informal leaders at the department				
Economic resources and pharmaceutical budget				
Economic consequences for the department				
Feedback (from colleagues, leaders, statistics)				
How are prescription decisions influenced by external factors				
National and professional guidelines				
Local guidelines				
Information/ marketing from the pharmaceutical company				
Media attention in newspapers, TV				
Which other factors could influence prescription? Which three factors influence the most?				

APPENDIX B

Questionnaire Paper V

Introduce the project

As you know, the purpose of this study is to better understand the process of implementation of the national guidelines for cardiac care (NGCC) over time. We will use interview data from four county councils on three occasions. We want to take this time to talk to you about your experience, so far, with the implementation of NGCC.

We want to understand the attitudes to the goals and means of NGCC, the actors involved and their interplay in the implementation of NGCC, how the implementation process has evolved and what it has resulted in. Your interview will help us to better understand these questions at your county council. We will be interviewing multiple people at your county council to gain multiple perspectives. Now, we are really interested in learning more about your own experience with the NGCC.

We are going to ask you questions about your experience as a [medical manager/ administrator/ politician] at your county council.

Describe the audio recording and how we will assure confidentiality and answer any questions

This interview will be audio taped so that we have an accurate record of your answers. Please be assured that the tapes and your transcript will be kept confidential and only the research group will have direct access to it. If using any quotes they will first be anonymous. Our study does have approval by the Ethic Board in Linköping. If, at any time, you feel that the questions are too sensitive, you may also skip any questions you wish. The interview usually takes 45min-1 hour.

Do you have any questions before we start?

INTRODUCTION

1. Can you tell me about yourself i.e. name, background, role within the county council?
2. How is your role connected to the National Guidelines (NG) and National Guidelines for Cardiac Care (NGCC)?
3. Have you in some way participated in or been in contact with the development of the NGCC?

PERSPECTIVE ON THE NATIONAL GUIDELINES

4. How do you view the NG?
5. What is, in your view, the goal with NG?
6. Who do you consider to be the target group for the NG?
7. Do you consider it to be clear how the guidelines should be used in practice?
8. Do you think that the content of the NG is in line with current changes within Swedish healthcare?
9. Do you see anything controversial about the NG?
10. *Do you think that the guidelines in any aspect intrude or strengthen the autonomy of the county councils? (question to politicians only)*

We have spoken about the NG in general and now we will talk about the NGCCs specifically.

ACTORS AND INTERPLAY

11. What role have politicians/administrators/medical professionals had in the implementation of NGCC in your county council?
12. How have the politicians/administrators/medical professionals acted based on the guidelines in your county council?
13. Has anyone particularly taken initiative in the implementation process of NGCC?
14. *Has there been any change in the county council organization that may have affected the conditions to implement the NGCC? (question to administrators only)*
15. What decisions based on the NGCC can the medical profession take in the county council without participation of others? In what contexts are political decisions required?
16. Do you think that NGCC has played any role to initiate or enhance the dialogue between politicians and/or administrators and/or the medical profession?
17. Is there any knowledge exchange between medical professionals, administrators and politicians on the basis of NGCC?
18. Is the NGCC used in this county council in any way to create consensus around the development and organization of cardiac care?

IMPLEMENTATION

19. *Why do you think that some people within the medical profession start to act according to the guidelines? Why not? (question to medical profession only)*
20. *What do you see as the driving force for the medical professionals to act according to the guidelines? Major difficulties? (question to medical profession only)*
21. Have you as a politician/administrator/medical professional used the NGCC as a support for decision-making? In what way?

22. *Have you as a politician used the NGCC to lead and govern in any other way? (question to politicians only)*
23. Have you used the content of NGCC related to:
- Analysis of needs within cardiac care in your county council?
 - To follow up cardiac care?
 - Discussions with other groups/within your group in your county council?
 - Discussions with patient organizations in your county council?
 - Educational or informational activities (participated/arranged)?
24. Has the use of NGCC changed over time?
25. Has the introduction of NGCC been a planned process or more ad hoc?
26. What has facilitated the introduction of the content in NGCC?
27. What has hampered or prevented the introduction?
28. *Have any political structures been elaborated to handle the NG/NGCC? (question for politicians only)*
29. What besides the NGCC has affected the development within cardiac care?
30. Is there anything else that may have had an impact on the conditions for implementation?

RESULTS

31. Has the content of the NGCC in some way affected the composition of cardiac care?
32. Do you think that NGCC in some way has been a support for decision-making concerning allocation of resources within your county council? How?
33. *How do you think the NGCC has affected the medical professionals as an actor group in relation to other groups? (question to administrators only)*
34. Can you see any negative effects that have appeared within your county council because of the NGCC?
35. To conclude: how do you think the NGCC have affected the conditions to run cardiac care in your county council?
36. Is there anything else that you would like to add?

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