Quality of rheumatic care

QUALITY
OF RHEUMATIC CARE

Monitoring and patient-centered care

by
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The research presented in this thesis was conducted at CAPHRI Care and Public Health Research Institute, Department of Internal Medicine (Rheumatology Division), of Maastricht University. CAPHRI participates in the Netherlands School of Public Health and Care Research (CaRe).

Provided by thesis specialist: Persoonlijk Proefschrift | www.persoonlijkproefschrift.nl
Cover en lay-out: Hans Schaapherder | Persoonlijk Proefschrift
Printing: Ridderprint | www.ridderprint.nl

ISBN: 978-94-6469-592-2
DOI: https://doi.org/10.26481/dis.20231121eb)

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PROEFSCHRIFT

ter verkrijging van de graad van doctor
aan de Universiteit Maastricht,
op gezag van de Rector Magnificus, Prof.dr. Pamela Habibović
volgens het besluit van het College van Decanen,
in het openbaar te verdedigen op
dinsdag 21 november 2023 om 16:00 uur

door

Esther Anna Bartholomeus Beckers

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CHAPTER 1

General introduction

General introduction RMDs

Rheumatic and musculoskeletal diseases (RMDs) are a diverse group of more than 200 diseases commonly affecting the joints, tendons, ligaments, bones and/or muscles[1,2]. Inflammatory rheumatic diseases are an important subgroup of RMDs. The most prevalent diseases in this subgroup comprise rheumatoid arthritis (RA), axial spondyloarthritis (SpA) and psoriatic arthritis (PsA)[3-6]. Examples of non-inflammatory rheumatic diseases are osteoarthritis and fibromyalgia. RMDs can affect individuals at any age and develop through a diverse range of pathogenic pathways, most of which are not completely understood[1]. Inflammatory rheumatic diseases are associated with an increased risk of comorbidities compared to the general population, which can be partly explained by the chronic inflammation[7-9]. From a clinical perspective, all RMDs may result in a substantial decline in both physical and mental health-related quality of life (HRQoL) and are the leading cause of disability in developed countries[10-12]. On that line, RMDs are also a major cause of health resource utilisation and loss of work productivity resulting in significant healthcare and social support costs[13,14]. In this thesis, we primarily focus on RA and SpA.

Rheumatoid arthritis

RA is a chronic auto-immune rheumatic disease that typically manifests as a poly-articular, symmetrical arthritis of the joints of the hand and feet, and can also affect extra-articular organs and tissues, including the heart, lungs, skin and eyes[13]. Patients with insufficiently controlled disease may experience progressive and irreversible joint damage and deformities, further contributing to functional impairments[15]. Early diagnosis and treatment are crucial for optimal therapeutic success, especially in patients with risk factors for poor outcomes, such as high disease activity, the presence of autoantibodies, and early joint damage[13]. In the past decade, the improved understanding of the pathogenesis resulted in new and highly effective pharmacological drugs. An earlier diagnosis, combination of (innovative) drugs in treatment, and management strategies that target towards low disease activity or remission have dramatically improved the long-term outcome of RA[13,16].

Spondyloarthritis

SpA is an umbrella term for a group of inflammatory rheumatic conditions related to the human leukocyte antigen (HLA) B27 and sharing common clinical features and pathophysiological mechanisms[17]. SpA historically comprises ankylosing spondylitis (AS), PsA, reactive arthritis and arthritis associated with inflammatory bowel disease or uveitis[5]. In response to new insights into clinical characteristics of SpA and unmet needs, the Assessment of SpondyloArthritis international Society (ASAS) has developed classification criteria for SpA to differentiate between axial and peripheral disease according to the predominant clinical manifestations[18,19]. Axial SpA is characterized by inflammation in the sacroiliac joints (sacroiliitis) and the spine (spondylitis). Axial SpA encompasses both patients with structural damage visible on radiographs of the sacroiliac joints (radiographic axial SpA, historically termed AS) and patients without structural damage on radiographs (non-radiographic axial SpA)[20,21]. Peripheral SpA is predominantly characterized by arthritis, enthesitis and dactylitis of the peripheral joints. Concomitant extra-mus-

culoskeletal manifestations may occur, such as anterior uveitis, psoriasis and inflammatory bowel disease. Similar to other auto-inflammatory diseases, SpA is associated with the onset of comorbidities, including cardiovascular diseases, osteoporosis and mood disorders[22]. The long-term prognosis of SpA has improved in the past decades due to earlier diagnosis and initiation of treatment with highly effective pharmacological drugs.

Quality of healthcare

Every patient deserves to receive high quality of healthcare. Quality of healthcare has been defined as "the degree to which health services for individuals and populations increase the likelihood of desired health outcomes and are consistent with current professional knowledge"[23]. In the landmark Institute of Medicine (IOM) report '*Crossing the Quality Chasm: A New Health System for the 21st Century'* six pillars for improving the quality of healthcare have been defined, which state that provided care should be effective, safe, patient-centered, timely, efficient and equitable[23]. These six aspects are complementary, and improvements in one will enhance the performance of others. To evaluate the quality of healthcare, three interrelated components of Donabedian's conceptual framework can be used, which are 'structure of care', 'processes of care', and 'outcomes of care'[24]. This frequently used framework can be applied in several healthcare settings, such as primary care or hospital care settings[25].

The first component, 'structure of care', includes all structural healthcare needs in order to be able to provide high quality of healthcare, such as facilities with adequate resources and qualified healthcare providers (HCPs). These elements can be assessed with structural measures, which make for example an inventory of the availability of an electronic medical record or physician-patient ratios. The second component of Donabedian's framework, 'processes of care', includes all actions from HCPs and patients that contribute to maintaining and improving health. These processes can be assessed with process measures, for example checking whether patients had unexpected care delays, whether patients were adequately informed about treatment options, or by assessing the degree to which HCPs and patients adhere to evidence-based quality standards and clinical guidelines[26]. The third component of Donabedian's framework, 'outcomes of care', includes all consequences of provided care, such as changes in disease outcomes, knowledge, behaviour, and use of services or costs. These aspects can be assessed with outcome measures, such as patient-reported outcome measures (PROMs), survival rates, patients' knowledge or costs per quality-adjusted life-year (QALY). The component 'outcomes of care' may seem to represent the gold standard in assessing the quality of healthcare, however, these outcomes might be affected by numerous structural and process-related factors, of which many are beyond the control of HCPs and patients[27].

The results of the structural, process and outcome measures from the perspectives of different stakeholders can contribute to improving the quality of healthcare in several ways[28]. First, these results can be used for providing external accountability towards stakeholders, who have the right to be informed on the quality of provided healthcare, such as patients, policy makers and

the society[29]. This requires healthcare services to be transparent on results from quality of healthcare assessments, as these results can be used by patients for selecting their preferred healthcare services, by insurance companies for drafting contracts and by healthcare inspections to identify incidents. Second, quality assessments can provoke continuous internal quality improvements at the level of individual HCPs, healthcare departments or entire healthcare settings. Healthcare services should therefore assess their performances to identify areas for improvements. Third, outcomes of care at the individual patient level can inform HCPs and patients on disease prognosis and treatment effects. In this way, monitoring disease outcomes in practice can contribute to clinical reasoning and treatment decision making.

Quality standards, treatment recommendations and treat-to-target

To provide care that is in line with the above principles of quality of care, HCPs can be guided by quality standards and evidence-based treatment recommendations for performing optimal quality of healthcare. Quality standards are sets of statements that cover areas with variation in care and identify resources and processes that need to be optimized in order to achieve quality improvement[30]. The overall aim of evidence-based treatment recommendations is to translate health research findings on managing and treating conditions into clinical practice. For patients with RMDs, several quality standards and numerous management recommendations have been developed by the European League Against Rheumatism (EULAR) and the American College of Rheumatology (ACR)[30-34].

In 2010, a management strategy called 'treat-to-target' (T2T) was introduced for patients with RA[35]. This strategy recommends regular monitoring of disease activity with validated outcome measures and adequate treatment of patients towards pre-identified targets to prevent long term structural damage. The treatment target should be relevant for modification of the course of the disease. The modifiable target is usually inactive disease/remission or low disease activity. This T2T approach showed superiority in achieving clinical, functional and structural outcomes and was found to be cost-effective compared to routine care in patients with RA and PsA[16,36]. Furthermore, low disease activity was associated with better work productivity, less comorbidity and lower cardiovascular risk. For patients with axial SpA, a T2T approach has also been recommended, however only observational studies were available at the time of development of the recommendations[37,38]. Studies have demonstrated a longitudinal association between disease activity and radiographic progression in patients with axial SpA and that the impact of TNF inhibitors on spinal radiographic progression is mediated by their effect on disease activity[39-41]. Furthermore, in patients with non-radiographic axial SpA, achieving the treatment target of inactive disease was associated with improved physical activity, HRQoL and work productivity[42]. Recently, results have been published from the first RCT in axial SpA on the effect of a T2T approach towards predefined disease activity targets on health status compared to routine care (Tight Control in SpA (TICOSPA))[43]. Although the primary outcome of this RCT was not achieved (superiority of T2T compared to usual care in the proportion of patients expe-

riencing 30% improvement in the overall functioning and health), several secondary outcomes (including disease activity, physical functioning and work impairment) showed a general trend in favour of T2T with a comparable safety profile. Furthermore, a T2T approach was favoured over usual care from a societal health economics perspective.

Patient-centered care

One of the six pillars of the IOM framework for evaluating healthcare that receives increasing attention in the past two decades concerns 'patient-centered care'[44]. This pillar has been defined as "providing care that is respectful of and responsive to individual patient preferences, needs, and values and ensuring that patient values guide all clinical decisions"[45]. In an attempt to operationalize patient-centered care from the patient perspective, the Pickers institute has formulated eight principles that represent the most salient issues of patients' experiences with hospital care, which are 1) respect for patients' values, preferences and expressed needs, 2) coordination and integration of care, 3) information, communication and education, 4) physical comfort, 5) emotional support and alleviation of fear and anxiety, 6) involvement of family and friends, 7) continuity and transition, 8) access to care[46]. Patient-centered care has been shown to be beneficial compared to a more traditional paternalistic healthcare approach, in which physicians make unilateral decisions about patients' care, even at the expense of patients' autonomy[47]. For example, there is emerging evidence that patient-centered communication in primary care settings results in decreased utilization of medical resources, such as diagnostics and referrals, which consequently results in lower annual costs[48]. This association might be explained by the interplay between patients who actively participate in their own care and HCPs who become more knowledgeable on patients' needs and worries, as this may result in decreased anxiety among patients and increased trust in their HCPs. In addition, the degree to which patients are involved in their care has been demonstrated to have a significant impact on the safety and effectiveness of their treatment[49]. Furthermore, better patient care experiences have been associated with higher levels of treatment adherence[50]. However, the relationship between providing patient-centered care and disease outcomes is less clear, as this might be mediated by factors such as medication adherence and self-management[51].

In clinical practice, this entails that HCPs should get to know the person behind the patient in order to engage him/her as an active partner in his care and treatment, rather than focusing exclusively on the disease[51,52]. This also entails that patients should be educated on their disease and symptoms, available procedures, treatment options, possible outcomes and on identifying their personal values and preferences. Ultimately, patients need to be empowered to be involved in their own care as this requires self-monitoring, self-management and decision-making skills. One way in which healthcare settings can facilitate these needs for patient-centered care is by offering patients insights into their medical records and disease outcomes.

Shared-decision making

One of the key principles of patient-centered care is shared-decision making (SDM), which is the process of HCPs and patients jointly participating in making health decisions after discussing the options, the benefits and harms, and considering the patients' values, preferences, and personal circumstances[53]. The importance of SDM in clinical practice is emphasized in the overarching principles of the EULAR and ASAS management recommendations for patients with RA, SpA and PsA, which all state that treatment of patients should aim at the best care and must be based on a shared decision between the patient and the rheumatologist[14,37,54]. SDM is grounded in the paradigm that care should be based on the best evidence, and should be respectful of, and responsive to, individual patient preferences, needs and values[23]. Therefore, it is essential for HCPs to provide information on patients' current medical situation, as well as evidence-based information on available courses of action and the consequences on their personal lives[55].

Evaluation of care from the patient perspective

To evaluate the quality of provided healthcare, several approaches have been proposed, such as quality indicators that operationalize quality standards. However, the actual experiences with provided care can only be reported by patients themselves. Patient perspectives on experienced care within a certain period can be evaluated with patient-reported experience measures (PREMs), which include questions related to the structure and/or process of provided care and might include questions relating to outcomes of care other than health and disease outcomes. For example, PREMs include questions such as "When you needed help, were you able to access different members of my health team?" and "Did you receive information about your treatment?". The results of PREMs can be beneficial for patients as it helps them to choose high quality healthcare settings and for HCPs who can reflect on their own and their team's performance, identify areas of improvement at clinical and organizational levels, and evaluate the impact of introduced changes within organizations.

Challenges addressed in this thesis

In continuous efforts to improve care provided by medical specialists in the Netherlands, the Federation of Medical Specialists publish every few years a vision document with ambitions, goals and expectations for the role and position of medical specialists in the near future[56]. When we initiated this thesis, the most recent vision document formulated the aspiration that by 2025 Dutch specialist medical care is among the most innovative, efficient and best-quality care worldwide[57].

To achieve this ambition, all HCPs should collaborate even more intensively based on outcomes of healthcare and they should strive to organize care around the principles of patient-centered care. To drive the necessary improvements and innovations, medical specialists should be facilitated to monitor patients' health outcomes, experiences and perceptions with care using PROMS and PREMs in order to anticipate on these results. In addition, patients and HCPs should have the knowledge and skills for making joint decisions. Furthermore, healthcare settings

should be transparent on results from structure, process and outcomes indicators of care towards all stakeholders to improve the quality of healthcare and enhance stakeholders trust. In rheumatology care, HCPs and patients encounter some challenges in implementing this vision into clinical practice. In this thesis, we address some challenges related to monitoring of disease outcomes and providing patient-centered care.

Challenges related to monitoring of disease outcomes in practice

Monitoring of disease and health outcomes is a relevant process indicator for providing high quality value-based and patient-centered care[28]. Despite evidence-based recommendations, regular monitoring of disease outcomes has been applied to only a limited extent in patients with RA and SpA in clinical practice[58]. For example, an observational study in seven academic medical centres in Israel showed that disease activity was assessed in 38% of the patients with RA during three consecutive visits in 2015[59]. Another review of medical files from France care-settings in 2013 showed that outcome measures for disease activity were only assessed in a small proportion of patients with axial SpA, ranging from 1% for the Ankylosing Spondylitis Disease activity Score (ASDAS), to 51% for C Reactive Protein (CRP) levels[60].

The limited extent to which clinical outcomes are assessed might be explained by structural and process barriers in daily clinical care. One structural barrier is using paper-based questionnaires in daily clinical care, as these are resource demanding in terms of distribution, gathering, score calculation and transfer of data into the local hospital's electronic medical record (EMR)[61]. A solution for this barrier might be electronically collecting PROMs (ePROMs), as this has several advantages compared to paper-based outcomes measures. For example, completing ePROMs generally provides high-quality data, is faster, results in better data capture, and is preferred by patients with RMDs in routine practice[62-67].

Systematic monitoring of patients in clinical practice can further be facilitated by disease-specific web-based tools. Such tools have the advantages that newly entered data are immediately saved, ongoing data-storage and maintenance are facilitated and complex scores are calculated automatically, which decreases the risk of errors and the workload of HCPs[61]. Ideally, such a tool should be easily accessible by both patients and HCPs in remote and outpatient settings and should graphically visualize the course of the disease over time. Consequently, such web-based tools can contribute to providing personalized, high quality and efficient care, as they can inform patients and HCPs about the course of the disease and management options, and they might improve communication between patients and HCPs[67].

For patients with RA in the Netherlands, a disease-specific personalized tool for comprehensive disease management, including facilitating monitoring of disease outcomes, has been developed, called Dutch Rheumatoid Arthritis Monitoring (DREAM-RA), available at www.mijnreumacentrum.nl[68]. DREAM-RA was established in 2003 as an ongoing cohort study for patients with RA who started using tumour necrosis factor (TNF) inhibitors. Moreover, the data

collected within this web-based registry have been used to study the efficacy of TNF inhibitors in patients with RA in clinical practice[69,70]. Unfortunately, such a disease-specific personalized tool for patients with SpA was lacking at the time of start of this thesis.

When healthcare settings are facilitated with such web-based tools for systematic monitoring of patients in clinical practice the collected data can also be used for evaluating the principles of T2T. That is, evaluating the proportion of patients in which disease activity is monitored at regular intervals and whether pre-identified treatment targets are achieved, and if not, evaluating the proportion of patients in which treatment is intensified. For patients with axial SpA, no data existed to what extent the T2T recommendations were applied in clinical care. Moreover, there was no insight into whether a T2T approach is feasible in clinical practice, where patient populations are more heterogeneous, variation in behaviours of HCPs exists and stronger restrictions are present in time, costs and resources compared to RCTs.

Outcome measures for disease activity in peripheral SpA

Although a T2T approach is also recommended in peripheral SpA, a validated outcome measure for assessing disease activity in a comprehensive way in clinical practice is lacking[38]. Disease activity in peripheral SpA is commonly assessed by physician-oriented measures, such as the number of tender and swollen joints, and the presence of enthesitis or dactylitis, as well as by PROMs by means of a visual analogue scale of pain or patient global assessment of disease activity. However, there is no composite score for disease activity available, such as the Disease Activity score of 28 joints (DAS28) for RA or the ASDAS for axial SpA[71,72].

Several disease activity composite scores for related RMDs could potentially be used in peripheral SpA. For example, the Disease Activity Index for Psoriatic Arthritis (DAPSA) score and the PsA Disease Activity Score (PASDAS), specifically developed for PsA, a disease overlapping with peripheral SpA[73,74]. The DAPSA and PASDAS are joint-based composite scores and their performance has been studied in patients with peripheral SpA with psoriasis, but not yet in the total peripheral SpA population, including also patients without psoriasis[73,75]. Alternatively, the ASDAS, which has been developed to assess disease activity in axial SpA, might also be useful in patients with peripheral SpA, as this composite score includes one general question on joint pain and swelling, besides questions on duration of morning stiffness and global disease activity, which are also relevant to patients with peripheral SpA. The ASDAS has already been used in peripheral SpA in clinical trial settings and specific patient populations, but not yet in clinical practice[76-78]. Studying the performances of the DAPSA, PASDAS and ASDAS in patients with peripheral SpA could contribute to finding an instrument for measuring disease activity in these patients in daily clinical practice.

Challenges related to providing patient-centered care

Providing patient-centered care encompasses care in which HCPs and patients act towards symptoms that matter to both of them. This principle is covered in the recent proposal that the management of RA should be guided by a 'dual target' strategy[79]. This strategy implies that treatment should not only aim to control inflammation (biological remission), which is important from the HCP perspective, but treatment should also aim to control disease impact (symptom remission), which is important from the patient perspective.

In continuous efforts to improve quality of healthcare for patients with RMDs, the Dutch Arthritis Society organised panel discussions among patients with RMDs to gain insight into the knowledge gaps that should be addressed to improve daily care. Patients ranked 'fatigue and its treatment' as the area with the highest priority[80]. The literature in RMDs indicates that over two-thirds of patients with RMDs experience severe or very severe fatigue and that patients with RMDs are more affected by fatigue compared to the general population, despite having adequate controlled disease activity[81-84]. Many patients feel that fatigue surpasses pain as a source of disability and that this symptom is insufficiently addressed by HCPs[84].

The number of peer-reviewed clinical studies addressing fatigue in RMDs is substantial and many studies have already been summarised in literature reviews. Notwithstanding, knowledge across various research areas remains fragmented, as studies/reviews frequently focus on one rheumatic condition or address a specific topic in a larger research area. As a result, the available knowledge from various areas is insufficiently integrated and fails to recognise differences and similarities related to fatigue across RMDs. This fragmentation also hampers translation of knowledge into the management of fatigue and hinders identification of potentially unaddressed research questions. There is therefore a need for summarizing available knowledge aspects of fatigue that are relevant for clinical practice. Such an extensive summary can identify current knowledge gaps and support HCPs in composing a personalized treatment plan for fatigue.

Decision aids

For applying SDM, patients should be fully informed on their medical situation and on the expected effect of treatment options on disease outcomes and their personal life[55]. Patients can be informed verbally but also by paper-based or electronic tools, such as patient information leaflets, health education materials and in a more standardized manner by using decision aids. The latter are evidence-based tools designed to support patients in making specific and deliberated choices among healthcare options and to support patients in communicating their considerations with healthcare providers[85]. Decision aids can help empower patients to make well-informed personal treatment decisions, thereby potentially increasing long-term satisfaction with the provided care[86]. A systematic Cochrane review concluded that patients who faced a treatment or screening decision and who used a decision aid compared to care as usual, had more knowledge on their options, had increased accuracy of risk perceptions and experienced more agreement between informed values and care choices[87]. Also, the proportion of patients

who were passive in decision-making or who experienced a decisional conflict, related to feeling uninformed, decreased. Moreover, this Cochrane review suggested that the use of decision aids might have a positive effect on the communication between patients and HCPs.

In patients with axial SpA and persistent high disease activity (despite symptomatic or conventional Disease-Modifying Anti Rheumatic Drug (DMARD) treatment), the decision-making process for initiating a biologic or targeted synthetic DMARD (bDMARD or tsDMARD, respectively) has become more complex due to the availability of different drug classes that differ in mode of action, currently including five TNF-inhibitors, two IL-17 inhibitors and two JAK-inhibitors for patients with radiographic axial SpA[21,88]. These b/tsDMARDs have comparable effectiveness for axial manifestations, but differ in individual characteristics, such as the route of administration (subcutaneous, intravenous or oral), frequency of administration (daily, weekly, monthly or every few months), expected effect on extra-musculoskeletal manifestations (uveitis, psoriasis, inflammatory bowel disease (IBD)) and potential adverse effects. A decision aid could therefore be useful to support these patients in the decision-making process.

In 2017, one high-quality web-based decision aid has been developed in the Dutch language to support SDM in patients with inflammatory arthritis who are about to initiate or switch a b/tsDMARD[89]. However, the decision aid was not specifically developed for the axial SpA patient population. Consequently, important information on the effectivity of the b/tsDMARDs on extra-musculoskeletal manifestations is missing. Furthermore, this decision aid has never been updated and recently approved treatment options are also lacking. There is therefore a need for a new evidence-based and web-based decision aid, feasible for supporting SDM in patients with axial SpA who face a treatment decision to initiate or switch a b/tsDMARD.

PREMs for rheumatology settings

Patient perspectives on the quality of experienced healthcare can be assessed with generic or disease-specific PREMs depending on the overall goal of evaluating the quality of healthcare. As implied, disease-specific PREMs include questions that are weighted towards a specific condition and are therefore preferred over generic PREMs for assessing the quality of healthcare within one specific setting[90].

Two PREMs have been used to evaluate all types of healthcare services for patients with RA in the Netherlands: the Consumer Quality Index for patients with Rheumatoid Arthritis (CQ-Index RA) and the Quality of Care Through the Patients' Eye for all Rheumatic Patients (QUOTE Rheumatic-Patients)[91,92]. A major drawback of these questionnaires is the large number of items (115 and 155 questions, respectively). Furthermore, these instruments are also generic for healthcare services, not specific for rheumatology settings and the CQ-Index RA is disease specific for RA, thus might not be applicable to other RMDs. A feasible PREM applicable to both patients with RA and SpA in Dutch rheumatology settings would therefore be useful for assessing the quality of healthcare in clinical practice.

Aims and outline of this thesis

This thesis focuses on improving the quality of healthcare by responding to encountered challenges in rheumatology care. Based on the current knowledge gaps, the main research objectives of this thesis are:

1. To develop and implement an integrated web-based tool for (tele)monitoring and reporting of health-related data of patients with SpA in the Netherlands, and to test the usability and acceptability of this system among patients and HCPs.
2. To investigate to what extent disease activity is monitored and results are used for re-evaluation and treatment intensification in clinical practice in patients with axial SpA in a clinical setting that is supported by an electronic monitoring tool.
3. To investigate concurrent validity and discrimination of the DAPSA, PASDAS and ASDAS in peripheral SpA in clinical practice.
4. To scope published reviews addressing fatigue in RA, SpA, osteoarthritis and fibromyalgia on research areas relevant for clinical practice.
5. To develop and implement an up-to-date evidence-based decision aid for patients with axial SpA in whom initiating a (new) b/tsDMARD is considered.
6. To evaluate the psychometric properties of the Commissioning for Quality in Rheumatoid Arthritis PREM (CQRA-PREM) in patients with RA and SpA and to implement this questionnaire in daily practice in the Netherlands.

In **chapter 2** of this thesis, we describe the development of a web-based integrated registry and quality management system for SpA in the Netherlands (SpA-Net), as well as its usability and acceptability of this system among patients and HCPs in clinical practice. In **chapter 3,** we evaluate to what extent the internationally agreed T2T recommendations are applied in clinical practice in patients with axial SpA in a clinical setting that is supported by SpA-Net. In **chapter 4,** we explore the concurrent validity and discrimination of the DAPSA, PASDAS and ASDAS in patients with peripheral SpA, without and without psoriasis, in clinical practice. In **chapter 5,** we present a scoping review on fatigue in four RMDs on 15 research questions that are important for managing fatigue in clinical practice, including the definition of fatigue, measurement instruments, determinants of fatigue, consequences of fatigue and interventions for fatigue. In **chapter 6,** we describe the development and implementation of an up-to-date evidence-based decision aid for patients with axial SpA in whom initiating a (new) b/tsDMARD is considered. In **chapter 7,** the face validity, feasibility, internal consistency, homogeneity and divergent validity of the translated CQRA-PREM is evaluated in patients with SpA and RA. Next, the CQRA-PREM was implemented in daily practice and results were evaluated through repeated Plan-Do-Check-Act quality improvement cycles. Finally, in **chapter 8** the findings of these studies are summarized and discussed and in **chapter 9** the scientific and societal impact of this thesis is described.

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CHAPTER 2

Development, usability and acceptability of an integrated eHealth system for spondyloarthritis in the Netherlands (SpA-Net)

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RMD Open 2019;5:e000860.
doi:10.1136/rmdopen-2018-000860

Abstract

Objective

To develop and test the usability and acceptability of a disease-specific integrated electronic health (eHealth) system for spondyloarthritis (SpA) in the Netherlands ('SpA-Net').

Methods

SpA-Net was developed in four phases. First, content and design were discussed with experts on SpA and patients. Second, the database, electronic medical record (EMR) and quality management system were developed. Third, multiple rounds of testing were performed. Fourth, the eHealth system was implemented in practice and feasibility was tested among patients through semi-structured focus interviews (n=16 patients) and among healthcare providers through feedback meetings (n=11 rheumatologists/fellows and 5 nurses).

Results

After completion of the first three steps of development in 2015, SpA-Net was implemented in 2016. All patients included have a clinical diagnosis of SpA. Information on domains relevant to clinical recordkeeping is prospectively collected at routine outpatient consultations and readily available to healthcare providers, presented in a clear dashboard. Patients complete online questionnaires prior to outpatient visits. In February 2019, 1069 patients were enrolled (mean (SD) age 54.9 (14.1) years, 52.4% men). Patients interviewed (n=16) considered SpA-Net an accessible system that was beneficial to disease insight and patient–physician communication, and had additional value to current care. Healthcare providers appreciated the additional information for (preparing) consultations. Barriers were the initial time required to adopt the EMR and the quantity of data entry.

Conclusion

SpA-Net enables monitoring of patients with SpA and real-life data collection, and could help improve knowledge and optimise communication between patients and healthcare providers. Both considered SpA-Net a valuable addition to current care.

Introduction

Spondyloarthritis (SpA) is a chronic inflammatory rheumatic disease with a heterogeneous clinical presentation. It may follow a disabling disease course, leading to substantial impairment of health-related quality of life (HRQoL), and to substantial costs for society due to healthcare utilisation and work productivity loss[1-3].

From the healthcare provider's perspective, regular and personalised monitoring of disease activity, physical functioning, medication use, side effects and comorbidities is essential to improve and maintain patients' HRQoL. Patient-reported outcome measures (PROMs) could further support this process and may also directly contribute to patient-centred care[4]. Measuring outcomes that matter to patients is becoming increasingly important, as a way to learn and improve healthcare, to support shared-decision making and to secure sustainable healthcare[5]. However, regular monitoring using PROMs has not yet been widely implemented into clinical practice. Barriers against use are time constraints, administrative burden, lack of a digital system to capture PROMs, lack of training, motivation and reluctance to change[6]. In addition, it is unknown whether routine collection of PROMs leads to improved outcome for the individual patient in clinical practice.

From the patient's perspective, access to results of regular monitoring using PROMs could provide insight into their own health state. Patient empowerment and shared decision making are advocated as essential elements of high quality clinical practice[7]. The patient and the rheumatologist decide together on the best possible management and define personal treatment goals, taking into account patient-specific context regarding comorbidities, adverse events, patient preference and preferred role, frequency of monitoring, and personal circumstances. To be involved in this process, patients need to be informed about their disease and management options, and vice versa, the patient's voice needs to be heard. Good mutual communication is therefore essential. Furthermore, regular monitoring using PROMs can also be done electronically (ePROMS), which allows for telemonitoring with the potential to decrease the number of visits and reduce the burden for the patient.

From the payer's perspective, governments and insurers increasingly demand transparency on outcomes, safety and efficiency/costs of care. The concept of value-based healthcare (VBHC) delivery, that is, a healthcare system where the health outcomes achieved per euro spent (value) are maximised, was introduced more than a decade ago[8]. Regular and comprehensive measurement of relevant health outcomes is one of the core principles of VBHC[8,9]. On a related note, variations in medical practice were already acknowledged 50 years ago but have recently been gaining attention[10]. The extent to which this variation is 'unwarranted', i.e. the consequence of a complex interaction between several medical and non-medical factors finally resulting in underuse or overuse of healthcare, should be minimised. Benchmarking and performance evaluation, as well as transparency on the results, can support this process. This requires an integrated, supported and cyclic process of improvement with a sufficient number of centres and patients.

Within the field of electronic health (eHealth, i.e. healthcare supported by information technology), new developments such as online monitoring tools could support high-quality, personalised and efficient care for patients with SpA. Most electronic medical records (EMRs) in their current form are not fit for chronic disease management, as relevant disease measures are often not available and ways to monitor the course of disease over time are lacking[11]. A disease-specific, integrated eHealth system, that is, a system that is central in the organisation of daily care, linked with existing EMRs and accessible for patients, can serve the needs of healthcare providers, patients, payers and society[8,12-18]. In addition, from a scientific perspective, it would capture data for research. While some aspects, such as regular collection of (e)PROMs, have been successfully implemented in SpA, to our knowledge, a system for comprehensive disease management was not yet available in the Netherlands.

In order to facilitate integration of the patient's and the healthcare provider's perspective on quality of care, we aimed (1) to develop and implement an integrated eHealth system for (tele) monitoring and reporting of health-related data of patients with SpA in the Netherlands ('SpA-Net'), including an EMR and real-time quality management system, and (2) to test the usability and acceptability of this system among patients and healthcare providers.

Patients and methods

Development of SpA-Net

The development of SpA-Net was carried out according to an iterative process of four phases: (1) content and design, (2) technical development of database and EMR, (3) internal and external testing, and (4) implementation. Rheumatologists, nurses experienced with care for patients with SpA and trained patient research partners were involved during various phases of development. Detailed information on the development of SpA-Net and the roles of the stakeholders is described in Supplementary file 2.1. SpA-Net is registered in the Netherlands Trial Registry.

Content and design

In 2014 and 2015, rheumatologists (experts in the field of SpA), nurses and two experienced patient research partners were consulted on the design and content of SpA-Net. To ensure that SpA-Net would capture all domains essential for clinical record-keeping in SpA, a 'core set' was defined. Based on evidence from literature review and expert opinion, domains and instruments were selected from existing Assessment of SpondyloArthritis international Society/ Outcome Measures in Rheumatology (ASAS/OMERACT) and Group for Research and Assessment of Psoriasis and Psoriatic Arthritis/OMERACT (GRAPPA/OMERACT) sets[19,20], and several other disease-specific as well as generic domains and instruments were added. Also, indicators of quality of care and patient experience of care were included. In order to prevent abundant and unnecessary data collection, intervals were set per questionnaire (Table 2.1). Whenever possible, use of free-text fields was avoided to allow for standardised and structured data capture.12 Altogether, we aimed for an inclusive, efficient core set with domains that were relevant for

daily practice (as opposed to research registries, which usually have extensive sets of questionnaires and are less efficient in daily practice). We further decided that aggregated data on quality indicators from participating centres should become available in SpA-Net to gain insight into practice variation. As SpA-Net aimed to closely follow the patient in daily practice, we decided that visits to the rheumatologist using SpA-Net should not be according to a predefined schedule but instead left to the discretion of the healthcare provider.

Technical development and infrastructure

The technical system behind SpA-Net was developed by Transparency in Healthcare (TiH, www.tihealthcare.nl) in 2015, specialised in the development of software for collecting and monitoring clinical and patient-reported data. The SpA-Net registry is incorporated within DREAM (Dutch Rheumatoid Arthritis Monitoring), a collaboration of Dutch rheumatology practices that aims to improve the quality of patient care, to provide transparency on treatment results and costs, and to produce data for scientific research. For the purpose of collecting, storing and using comprehensive data on patient outcomes, a web-based data acquisition and storage system was developed, which can be linked to, and integrated with, the EMRs of patients in local hospitals. Information on laboratory markers of inflammation can be extracted from the hospital information management system. Data storage and maintenance in SpA-Net meet all Dutch and European legal requirements, and is in line with regulations on the protection of personal data (NEN7510, ISO2700 and the EU General Data Protection Regulation).

Table 2.1 Domains, instruments and questionnaires included in SpA-Net

Domain	Reported by	Instrument	Interval (minimum)*
Demographic characteristics	Patient	Questionnaire (education, marital state, employment, alcohol, smoking)	1 year
Work, productivity	Patient	WPAI[21]	6 months
Quality of life, health state	Patient	SF-36[22], EQ-5D[23], ASAS Health Index[24]	1 month (SF-36), 6 months (EQ-5D, ASAS Health Index)
Physical function	Patient	BASFI[25], HAQ-S[26]	6 months
Patient global	Patient	NRS (global disease activity last week)	1 month
Fatigue	Patient	Fatigue question of BASDAI[27]	Every visit
Pain	Patient	VAS	1 month
Experience with care	Patient	Modified PREM[28]	1 year
Medical history, comorbidity	Physician	NA	Updated every visit
Medication use	Physician	NA	Updated every visit
Adverse events	Physician, patient	NA	Updated every visit

[continued on next page]

Table 2.1 [Continued]

Domain	Reported by	Instrument	Interval (minimum)*
SpA manifestations	Physician	Checklist: inflammatory back pain, peripheral arthritis, enthesitis, dactylitis, psoriasis, uveitis, IBD, elevated CRP, NSAID response, recent GI or urogenital infection, positive family history, sacroiliitis on X-ray/MRI, HLA-B27 status	Updated every visit
Disease activity	Physician, patient	ASDAS[29], BASDAI[27], CRP, ESR	Every visit
Physician global	Physician	VAS (disease activity)	Every visit
Spinal mobility	Physician	Chest expansion, occiput to wall, modified Schober, cervical rotation, lateral spinal flexion	On indication
Peripheral symptoms	Physician	SJC66, TJC68, presence and location of dactylitis, presence and location of enthesitis in 65 sites	Every visit
Skin/Nail involvement	Physician	Body surface area, presence of nail psoriasis	On indication
Laboratory results	Physician	Haemoglobin, white blood cell count, platelet count, liver/renal function	On indication

*Minimum interval between assessments of the domain. Visits to the rheumatologist are not predefined, but scheduled according to the opinion of the healthcare provider. Consequently, the interval between assessments of domains can vary among patients but will never be shorter than the minimum interval reported here.
ASAS = Assessment of SpondyloArthritis International Society, ASDAS = Ankylosing Spondylitis Disease Activity Score, BASDAI = Bath Ankylosing Spondylitis Disease Activity Index, BASFI = Bath Ankylosing Spondylitis Functional Index, CRP = C-reactive protein, EQ-5D = EuroQoL-5D, ESR = Erythrocyte Sedimentation Ratio, GI = Gastrointestinal, HAQ-S = Health Assessment Questionnaire for Spondyloarthropathies, HLA-B27 = Human Leucocyte Antigen B27, IBD = Inflammatory Bowel Disease, NA = Not Applicable, NRS = Numerical Rating Scale, NSAID = Non-Steroidal Anti-Inflammatory Drug, PREM = Patient-Reported Experience Measure, SF-36 = Short Form 36 Health Survey, SJC66 = Swollen Joint Count of 66 joints, SpA = Spondyloarthritis, TJC68 = Tender Joint Count of 68 joints, VAS = Visual Analogue Scale, WPAI = Work Productivity and Activity Impairment

Testing

After the initial development phase, SpA-Net was evaluated in a test environment during multiple rounds of internal and external testing in 2015 and 2016. These rounds were aimed at both improving different aspects of the system and bug-testing. Results from testing were reported monthly to the development team to ensure rapid cycles of improvement.

Implementation

After identification of barriers and facilitators for successful implementation, a multifaceted implementation strategy was developed[30,31]. SpA-Net was initially implemented into clinical practice in two centres, followed by an extension to other centres. Part of the implementation strategy was engaging those who have to record data[32]. To motivate rheumatologists and stimulate dynamic refinement of SpA-Net, staff meetings were organised every 2 months to

evaluate the usability of SpA-Net in practice, discuss bugs encountered, demonstrate updated system features and provide feedback to healthcare providers on the use of SpA-Net. After every meeting, feedback from staff was communicated to the development team. Healthcare providers thus helped shape SpA-Net and embed it into clinical practice. As part of the implementation strategy, patients were informed about SpA-Net on an individual basis during outpatient visits and accompanied by a demonstration of SpA-Net.

Usability and acceptability of SpA-Net

A usability and acceptability study was planned to evaluate satisfaction, accessibility and experiences with SpA-Net in clinical practice from the users' perspective (patients and healthcare providers).

In November and December 2017, a sample of patients with SpA were recruited from the Maastricht University Medical Center to participate in focus group interviews (see Supplementary file 2.2 for a detailed description of the methodology). Interviews were planned with approximately five patients each, until data saturation was reached. Inclusion criteria were a clinical SpA diagnosis, age ≥18 years, at least two visits to the rheumatology clinic since implementation of SpA-Net and mastery of the Dutch language. Eligibility for inclusion was considered on a case-by-case basis, aiming for a sample that reflected the full spectrum of the SpA population. To prevent selection bias, patients did not have to actively participate in SpA-Net. Prior to the interviews, SpA-Net was briefly demonstrated to any patients in the focus groups that had no experience with the system. In semi-structured focus group interviews, the accessibility and usability of SpA-Net, and whether patients perceived SpA-Net had an effect on disease understanding and on quality of care in daily practice, were assessed. In the same period, rheumatologists and nurses were interviewed in multiple group sessions on the usability of SpA-Net, the role of SpA-Net in (preparing) consultations and the perceived effect of SpA-Net on the quality of care.

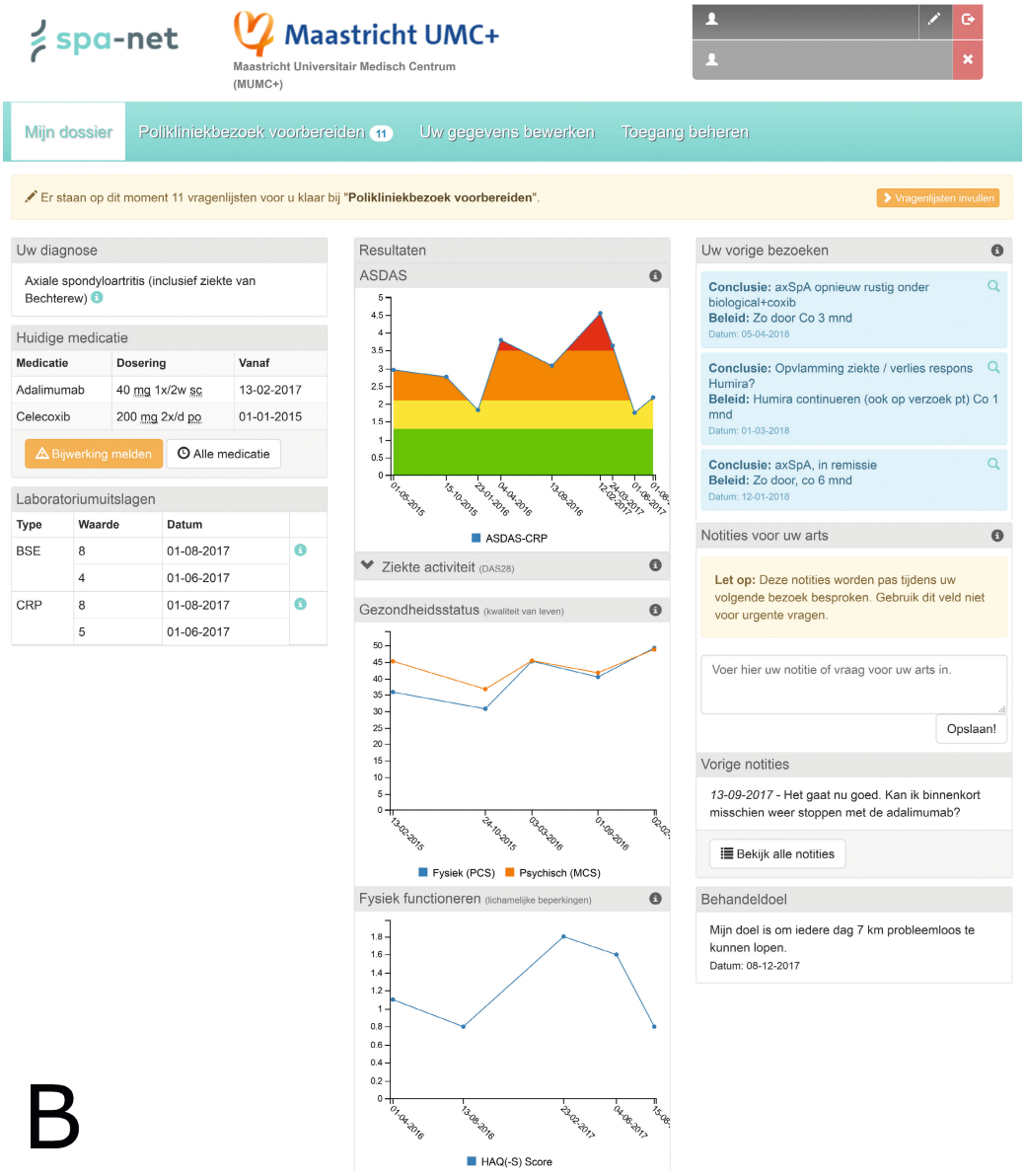
Data analysis

Descriptive statistics were used to summarise the characteristics of the total population in SpA-Net and the participants in the focus group interviews. Patient interviews were audiotaped and transcribed verbatim. Using NVivo V.11 software, transcripts were coded and meaningful quotes were structurally classified into themes and subthemes for analysis (see Supplementary file 2.2)[33]. All statistical analyses were performed using R V.3.1.4.

Results

In order to serve its purpose as an integrated (tele)monitoring system, SpA-Net was designed and developed as a secure web page (http://www.mijnreumacentrum.nl) compatible with tablet devices. TiH provides technical support to healthcare providers and patients.

Figure 2.1 Side-by-side view of the healthcare provider's dashboard (A) and the patient's dashboard (B) in SpA-Net. The healthcare provider's dashboard (A) includes the patient's personal information, (past) presence of SpA features, current medication use, summary of most recent visits, patient's notes, and graphical representations of ASDAS, SF-36 and HAQ-S. The patient's dashboard (B) presents an excerpt of their EMR, which contains information regarding diagnosis, recent laboratory results, results from questionnaires, current medication and most recent outpatient visits. In addition, patients have the option to report possible side effects and can leave notes for their healthcare provider. For patients, all items are accompanied by understandable explanations and information is presented in graphs whenever possible.



B

ASDAS = Ankylosing Spondylitis Disease Activity Score, EMR = Electronic Medical Record, HAQ-S = Health Assessment Questionnaire for Spondyloarthropathies, SF-36 = Short Form 36 Health Survey, SpA = Spondyloarthritis.

Development: content

SpA-Net is meant to provide a comprehensive view of the patient. Domains captured by PROMs include disease activity, physical function, pain, global assessment of disease activity, work participation and HRQoL. These data are complemented with clinical measures on spinal mobility and peripheral joint involvement, physician's global assessment of disease, laboratory values and imaging data. In addition, demographic and socioeconomic status, medical history, comorbidities and extra-articular manifestations, lifestyle factors, medication use, and adverse events are collected (Table 2.1). Of note, data on all medications, prescribed for SpA or another condition, are collected. A patient-reported experience measure is included to assess patient experiences with care. Finally, individual treatment goals can be registered and monitored.

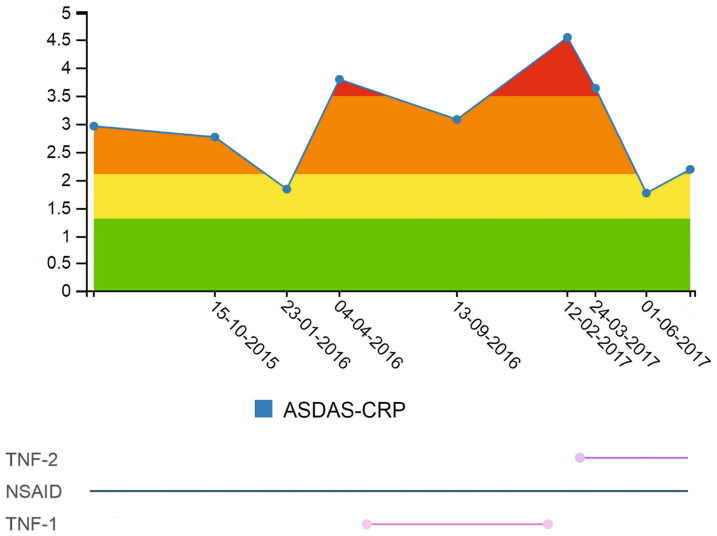


Figure 2.2 Graph in SpA-Net reporting the evolution of ASDAS in relation to medication use over time, healthcare provider's perspective. In SpA-Net, detailed graphs of ASDAS (shown), SF-36 (not shown) and HAQ-S (not shown) are presented together with the patient's medication use over time. The ASDAS graph is colour-coded (traffic light, using the cut points as recommended by the ASAS) to aid quick interpretation.

ASAS = Assessment of SpondyloArthritis International Society, ASDAS = Ankylosing Spondylitis Disease Activity Score, CRP = C-reactive protein, HAQ-S = Health Assessment Questionnaire for Spondyloarthropathies, NSAID = Non-Steroidal Anti-Inflammatory Drug, SF-36 = Short Form 36 Health Survey, TNF =Tumour Necrosis Factor

Development: design

SpA-Net was designed to replace the existing EMR for patients with SpA, thereby also avoiding double entry. For healthcare providers, SpA-Net is split into three tabs: (1) Dashboard, (2) Visit and (3) Data Input & Reporting. The Dashboard provides an overview, and includes patients' personal information, presence of SpA features, current medication use, summary of recent visits, patients' notes and graphical representations (graphs) of disease activity, HRQoL and functioning (Figure 2.1). The disease activity graph is colour-coded to aid quick interpretation,

using the cut-offs as defined by ASAS (Figure 2.2)[34]. The Visit tab allows healthcare providers to enter a new outpatient visit, and includes a selection of items relevant for clinical record-keeping, such as a manikin for joint involvement and enthesitis. These items are completed on indication. Adverse events are recorded for record-keeping, and are also automatically reported to the Netherlands Pharmacovigilance Centre (Lareb).

The Data Input & Reporting tab includes all items of SpA-Net and can be used to complete missing items outside of visits. Besides these three tabs, there is an additional dashboard where healthcare providers can access aggregated data on clinical indicators for quality improvement, comparing their centre with other centres (Figure 2.3). Patients can also access SpA-Net (Figure 2.1). After being introduced to SpA-Net, they receive a login and password. Two-factor verification is mandatory for all patients. For them, all clinical information is accompanied by clickable pop-ups with understandable explanations in lay language. The clinical information includes the diagnosis, a list of current and past medication, recent laboratory results, graphs of disease activity, HRQoL and functioning, and healthcare provider's notes of recent outpatient visits. Patients can report possible side effects to medication and leave notes for their healthcare provider, for example on topics they wish to discuss during their next visit. For urgent matters, such as serious suspected side effects, patients are explicitly instructed to contact the outpatient clinic by phone or email. Questionnaires are available for the patient to complete prior to each consultation. In between visits, patients can complete questionnaires for self-monitoring, depending on the minimum interval (Table 2.1).

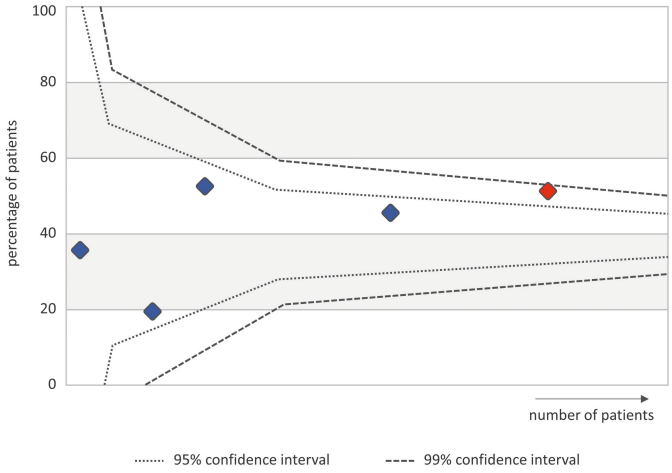


Figure 2.3 Example of graph of aggregated data on clinical indicators for quality improvement in SpA-Net, healthcare provider's perspective. In order to stimulate performance evaluation and benchmarking, aggregated data on relevant clinical indicators of care are presented in a separate dashboard in SpA-Net. For illustrative purposes, an example is shown presenting the proportion of patients with an ASDAS<2.1. For the healthcare provider's centre (light grey dot) in comparison with other participating centres (dark grey dots).

ASDAS = Ankylosing Spondylitis Disease Activity Score

Development: testing

A multitude of bugs and errors were encountered during 10 rounds of testing. These included error screens, incomplete questionnaires, errors in formulas used to calculate composite scores and accepting extreme values. All bugs and errors were fixed. The most recent version (V.1.11.0) of SpA-Net was launched in June 2018.

Development: implementation and use in practice

SpA-Net was launched into practice in May 2016 in two rheumatology centres. All rheumatologists and nurses were trained with a manual and practised in a test environment before use in practice. Use of SpA-Net was not mandatory for healthcare providers in participating centres, but strongly encouraged through motivational interviewing and peer pressure. Some healthcare providers quickly adopted SpA-Net, whereas others were more hesitant. Personal assistance for healthcare providers was available, if needed.

Outpatients with a clinical diagnosis of SpA were consecutively included in SpA-Net and prospectively monitored. On inclusion, patients were educated on SpA-Net, received an information booklet and were instructed to prepare each visit by completing the PROMs in the week prior to the consultation date.

A number of additional actions were taken to increase participation in SpA-Net. First, a dedicated nurse was tasked with assisting those who need help with logging in or using SpA-Net. Second, we introduced a touch-screen tablet PC at the clinic, for those without internet access or who have forgotten to complete the questionnaires at home. Third, monthly open evenings were organised for patients with questions and general information meetings for patients twice a year. Of note, the open evenings had very low attendance, likely due to the availability of the dedicated nurse at the time of outpatient visits (a more feasible option for patients). Internal and external benchmarking is done annually and summarised results are published in an annual report.

Once SpA-Net was successfully implemented in the two initial adopting centres, steps were undertaken to increase awareness on SpA-Net among Dutch rheumatologists by presentations at the annual meeting of the Dutch Rheumatology Society, local hospital visits with demonstrations and written information in the Dutch Rheumatology journal. In February 2019, 1,069 patients from five centres had been enrolled in SpA-Net (Table 2.2), and inclusion is ongoing.

Usability and acceptability study

Accessibility, usability, satisfaction of use and experiences with SpA-Net in clinical practice from the perspective of both patients and healthcare providers were assessed through focus group interviews and feedback meetings, respectively. Sixteen patients were interviewed (4 groups, 3–5 patients per interview), after which information saturation was reached. Included patients had axial, peripheral, or combined axial and peripheral SpA with or without concomitant psoriasis, inflammatory bowel disease and/or anterior uveitis (Table 2.3). Fifteen of these 16 patients (94%) had been introduced to SpA-Net before, and 8 (50%) considered themselves

to actively and consistently use SpA-Net. Patients considered the layout of SpA-Net to be clear, well accessible and intuitive. They felt SpA-Net was a valuable addition to current care, and improved communication and patient involvement. Patients appreciated having access to their EMR with lay-term explanations. In addition, they valued the increased insight into their disease over time and the option to add notes. Points of improvement were the login process and providing insight into the conclusion and plan from the healthcare provider after each visit. Patients not actively using SpA-Net did so because of either long-term stable disease or because they did not want to be occupied with their disease in their spare time. Of note, patients who were initially not enthusiastic about SpA-Net became interested when they learnt about the possibilities. A member check was carried out, and interviewed patients had no comments on the summarised results of the interviews.

Table 2.2 Characteristics of patients included in SpA-Net as of February 2019

Variable	Total group (n = 1,069)	Completed, n (%)
Age, years	54.9 (14.1)	1,069 (100.0)
Male, n (%)	560 (52.4)	1,069 (100.0)
Symptom duration, years	16.0 (11.3)	528 (49.4)
HLA-B27 positive, n (%)	300 (46.2)	650 (60.8)
Diagnosis*		1,069 (100.0)
Axial SpA, n (%)	339 (31.7)	
Peripheral SpA, n (%)	96 (9.0)	
Axial and peripheral SpA, n (%)	55 (5.1)	
Psoriatic arthritis, n (%)	510 (47.7)	
Reactive arthritis, n (%)	5 (0.5)	
IBD-associated arthritis, n (%)	28 (2.6)	
Undifferentiated SpA, n (%)	36 (3.4)	
ASDAS-CRP	2.3 (1.0)	500 (46.8)
BASDAI	4.3 (2.2)	640 (59.9)
BASFI	3.3 (2.5)	550 (51.4)
HAQ-S	0.7 (0.6)	465 (43.5)
VAS pain	3.9 (2.6)	706 (66.0)
Patient global	4.0 (2.6)	674 (63.0)
Physician global	1.6 (1.7)	693 (64.8)
SJC	0.5 (1.3)	606 (56.7)
TJC	1.1 (3.1)	606 (56.7)
SF-36PCS	39.9 (10.0)	551 (51.5)

[continued on next page]

Table 2.2 *[continued]*

Variable	Total group (n = 1,069)	Completed, n (%)
SF-36MCS	48.8 (11.3)	549 (51.4)
EQ-5D	0.8 (0.2)	382 (35.7)
ASAS-HI	5.7 (3.4)	382 (35.7)
Medication use, current†		1,021 (95.5)
NSAID, n (%)	554 (54.3)	
csDMARD, n (%)	418 (40.9)	
bDMARD, n (%)	391 (38.3)	
tsDMARD, n (%)	2 (0.2)	

Values expressed as mean (SD) unless stated otherwise
If a patient had multiple scores on an instrument, the first score since enrolment in SpA-Net was used.
*Clinical diagnosis as made by the rheumatologist.
†Percentages apply to population with registered medication. In 48 patients (4.5%), no medication was registered.
ASAS = Assessment of SpondyloArthritis International Society, ASDAS = Ankylosing Spondylitis Disease Activity Score, BASDAI = Bath Ankylosing Spondylitis Disease Activity Index, BASFI = Bath Ankylosing Spondylitis Functional Index, bDMARD = Biological Disease-Modifying Antirheumatic Drug, CRP = C-reactive protein, csDMARD = conventional synthetic Disease-Modifying Antirheumatic Drug, EQ-5D = EuroQoL-5D, HAQ-S = Health Assessment Questionnaire for Spondyloarthropathies, HLA-B27 = Human Leucocyte Antigen B27, IBD = Inflammatory Bowel Disease, MCS = Mental Component Summary, NSAID = Non-Steroidal Anti-Inflammatory Drug, PCS = Physical Component Summary, SF-36 = Short Form 36 Health Survey, SJC66 = Swollen Joint Count of of 66 joints, SpA = Spondyloarthritis, TJC68 = Tender Joint Count of 68 joints, tsDMARD = targeted synthetic Disease-Modifying Antirheumatic Drug, VAS = Visual Analogue Scale

Table 2.3 Characteristics of patients participating in the focus group interviews

Variable	Total group (n = 16)
Age, years	62.6 (41–78)
Male, n (%)	6 (37.5)
Household composition	
Living alone, n (%)	2 (12.5)
Partner without children, n (%)	10 (62.5)
Partner with children, n (%)	3 (16.7)
Other family member(s), n (%)	1 (6.3)
Educational attainment	
Low, n (%)	3 (18.8)
Middle, n (%)	8 (50)
High, n (%)	5 (31.3)
Employment	
Full-time/part-time, n (%)	3 (16.7)
Retired/house-keeping/caregiver, n (%)	9 (50)

[continued on next page]

Table 2.3 *[continued]*

Variable	Total group (n = 16)
Unemployed, n (%)	2 (11.1)
Work disabled, n (%)	4 (22.2)
Smoking status	
Never, n (%)	7 (43.8)
Current, n (%)	3 (18.8)
Former, n (%)	6 (37.5)
Alcohol consumption, yes, n (%)	11 (68.8)
Phenotype	
Axial SpA, n (%)	5 (31.3)
Peripheral SpA, n (%)	5 (31.3)
Axial and peripheral SpA, n (%)	6 (37.5)
Symptom duration, years	17.5 (1–66)
Extra-articular manifestations	
Psoriasis, n (%)	7 (43.8)
Anterior uveitis, n (%)	4 (25.0)
Inflammatory bowel disease, n (%)	3 (18.8)
Any extra-articular manifestation, n (%)	11 (68.8)

Values expressed as median (range) unless stated otherwise.
SpA = Spondyloarthritis

Furthermore, seven rheumatologists, four residents in rheumatology and five nurses were interviewed during group meetings on the use of SpA-Net in daily practice. Healthcare providers appreciated the additional information for (preparing) their consultations, the insight gained into the evolution of important outcomes such as disease activity and HRQoL over time in relation to medication use, and the ease of prescribing medication. Barriers against use were the initial time required to adopt the EMR, the number of 'clicks' and the quantity of data entry during consultations. Rheumatologists felt the latter could be at the expense of patient–clinician interaction, especially for patients who did not complete the questionnaires prior to their visit. Of note, rheumatologists supported by nurses during visits experienced less barriers when using SpA-Net. All remarks were converted into action plans for further improvement. During subsequent interviews, rheumatologists stated they used SpA-Net more frequently and consistently.

Discussion

Here, we described the successful development and implementation in daily practice of an integrated eHealth system and quality registry for patients with SpA in the Netherlands. Both patients and healthcare providers considered SpA-Net feasible and acceptable for use in clinical care. Over the last two decades, a multitude of cohorts and registries have been developed for SpA. While patients registries can technically be considered to be cohorts, registries such as SpA-Net have an important advantage over typical cohort studies[32,35], as they provide a real-world view of all aspects of clinical practice and can be used to evaluate care as it is actually provided[35]. What sets SpA-Net apart from most existing registries is its full integration in daily care as an EMR, inclusion of all subtypes of SpA, and the key role for the patient. In the Netherlands, SpA-Net is the first quality registry for all subtypes of SpA. Similar quality registries have been successfully operating in Denmark and Sweden[36-38].

Increasingly, healthcare is shifting from physician-centred to patient-centred. Patients feel the need to be informed and involved.39 PROMs are considered essential in patient-centred care. Sharing PROM results with patients in a comprehensible way can improve the patient's knowledge, communication and trust.40 ePROMs have several advantages over paper-based assessments[18]. Remote collection of questionnaires is usually faster[41] and results in better data capture with less missings[42]. Furthermore, ePROMs are accepted, and even preferred, by patients with rheumatic disease in routine practice[41,43,44]. ePROMs and paper-based PROMs lead to comparable results in most studies[45]. SpA-Net combines these facets, by remote collection and presentation of PROMs over time in relation to the treatments provided, to the healthcare provider and patient in an understandable way. Notwithstanding, it has yet to be shown whether regular collection of PROMs in daily practice really leads to improved outcome for the individual patient. Personalised monitoring systems such as SpA-Net will play a pivotal role in this regard.

As became evident during the current study, most patients who were interviewed appreciated SpA-Net, especially the way it improved communication, stimulated patient involvement and provided the opportunity to monitor their own health state. These findings are in line with previous studies on eHealth in rheumatology[14,46]. In a pretest–posttest study investigating an online portal in rheumatoid arthritis (RA), a relevant proportion of patients felt that using the web portal increased their involvement in disease management (44%) and understanding of healthcare providers' explanation (24%)[14]. Another study supported the potential benefits of eHealth for quality of care, as the use of a newly developed, disease-specific eHealth system in patients with RA was associated with achieving low disease activity over time while at the same time maintaining patient satisfaction and improving physicians' productivity[11].

SpA-Net was usable and acceptable in clinical practice. At the same time, several barriers were found. From the healthcare provider's perspective, especially time constraints and burden of data entry during consultations were frequently reported. The burden of data registration is a factor that hinders how a quality registry can lead to quality improvement, as the time spent on data registration could instead be spent on other improvement efforts.47 In this regard, inte-

gration in daily care is necessary[15,16]. By using SpA-Net as an EMR, data collection by healthcare providers has become part of the standard clinical workflow. In order to further ease this burden for both healthcare providers and patients, we strived towards a simple, yet comprehensive and intuitive system, and developed a core set of domains with a limited number of instruments. Also, the rheumatologists in this study reported that the burden of data entry decreased over time, and thus at least partly could be attributed to the initial transition period. Additionally, support by a dedicated nurse seemed to lower the burden for rheumatologists.

About half of the interviewed patients did not feel the need to actively use SpA-Net. These patients provided us insight into possible barriers to becoming an active user. Two previous studies showed that, if online access was provided, about half of the respondents accessed their EMR[14,48]. Reasons for not using the portal were lack of internet access, lack of spare time or not being interested. Furthermore, patients who are older, lower educated, have lower health literacy and/or lower computer literacy could be less likely to use eHealth systems such as SpA-Net[14,42,43,48]. It is essential that systems meant to assess and improve quality of care are inclusive, especially as those patients who are less likely to participate might be those who would benefit most from improvements in care delivery[7]. In 2017, 97% and 88% of Dutch residents aged 12 years or older and 65 years or older, respectively, had internet access[49]. With the support of a nurse, we strived to involve as many patients as possible in SpA-Net. It should be noted that currently no data on the actual usage of the system by patients are available, and a future study will address this.

In order to successfully implement and maintain integrated monitoring and quality managements systems, overcoming barriers of change is essential. Besides a strong commitment of both healthcare providers and patients as discussed above, the social (culture, current practice), organisational (resources, support) and economical (financing of care) context are relevant[30,31]. For SpA-Net, a bottom-up approach was chosen, meaning that participation for centres is voluntary. The successful implementation of SpA-Net in both academic and general hospitals supports the transferability of this system within the Netherlands. As long as regular monitoring of outcome relevant to patients is not mandatory, full implementation of quality management systems will be difficult, if not impossible. Bundle payments, or payment for the care of a patient's medical condition across the entire care cycle, will stimulate implementation of quality management systems and acceptance of PROMs and other outcomes relevant to patients. In this regard, decreasing the administrative and reporting burden of process quality indicators to increase transparency on outcome could prove beneficial[5]. Systems such as SpA-Net will be necessary to capture those indicators relevant for high-quality care.

In conclusion, we developed and implemented an integrated eHealth system and quality registry (SpA-Net) for patients with SpA in the Netherlands. SpA-Net enables regular monitoring of patients with SpA and could help optimise knowledge and communication between patients and healthcare providers, facilitate treatment decisions, stimulate patient empowerment, support VBHC and provide data for patient-centred research. Both patients and healthcare providers considered SpA-Net a valuable addition to current care for SpA.

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CHAPTER 3

Performance of three composite measures for disease activity in peripheral spondyloarthritis

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J Rheumatol 2022;49(3):256-64
doi:10.3899/jrheum.210075

Abstract

Objectives

To investigate concurrent validity and discrimination of the Disease Activity Psoriatic Arthritis score (DAPSA), Psoriatic Arthritis Disease Activity Score (PASDAS) and Ankylosing Spondylitis Disease Activity Score (ASDAS) in peripheral spondyloarthritis (pSpA) in clinical practice.

Methods

Data from a Dutch registry for SpA (SpA-Net) were used. Predefined hypotheses on concurrent validity of the composite measures with 15 other outcome measures of disease activity, physical function and health-related quality of life were tested. Concurrent validity was considered acceptable if ≥75% of the hypotheses were confirmed. Discrimination was assessed by stratifying patients in DAPSA, PASDAS and ASDAS predefined disease activity states and studying mean differences in health outcomes by one-way ANOVA. Furthermore, the concordance in disease activity states was determined. All analyses were repeated in subgroups with and without psoriasis.

Results

DAPSA, PASDAS and ASDAS scores were available for 191, 139 and 279 patients with pSpA, respectively. The concurrent validity and discrimination of all composite measures were acceptable as the strength of correlations were as hypothesized in ≥75% of the studied correlations. With increasing disease activity states, scores in nearly all outcome measures worsened significantly. The DAPSA, PASDAS and ASDAS classified 22%, 56% and 48% of the patients, respectively, in the two highest disease activity states. Stratified analyses for concomitant psoriasis revealed no relevant subgroup differences.

Conclusions

The performance of DAPSA, PASDAS and ASDAS in pSpA was acceptable, and independent of concomitant psoriasis. Due to discrepancy in classification, the validity of existing thresholds for disease activity states warrants further study in pSpA.

Introduction

Peripheral spondyloarthritis (pSpA) is characterized by the presence of arthritis, enthesitis and/or dactylitis. Concomitant extra-musculoskeletal manifestations such as uveitis, psoriasis and inflammatory bowel disease may occur[1]. The treatment of pSpA usually consists of a combination of education, exercise therapy, and pharmacotherapy[2-4]. Response to treatment can be evaluated with the Peripheral SpondyloArthritis Response Criteria (pSpARC40)[5]. Such response criteria have been developed to assess how many and which patients have responded adequately to treatment in randomised controlled trials, to facilitate comparison across different trials, and to assess factors that predict treatment response[6]. In clinical practice, response criteria may not be useful for monitoring disease activity as there is no "baseline visit" against which to compare[7]. Furthermore, their dichotomous scores only show whether the criteria are met, but they do not give any information on the degree of disease activity nor are they able to identify disease activity states.

Currently, a tool specifically developed and validated to quantify and monitor disease activity in a comprehensive way in clinical practice is lacking for pSpA. Assessment of disease activity in pSpA is commonly physician-oriented and single or multiple components of the construct 'disease activity' are considered, such as the number of tender and swollen joints or the presence of enthesitis or dactylitis, but these are not explicitly integrated into a composite score to support management decisions.

For psoriatic arthritis (PsA), a subpopulation of pSpA, the Disease Activity in Psoriatic Arthritis (DAPSA) score has been recommend as an instrument to measure disease activity in a treat-to-target strategy[8], while the Group for Research and Assessment of Psoriasis and Psoriatic Arthritis (GRAPPA) recently voted to use the Psoriatic Arthritis Disease Activity Score (PASDAS) as the preferred measure for disease activity in clinical trials[9]. Both the DAPSA and PASDAS are joint-based composite scores. The PASDAS also assesses extra-articular involvement components and physical health-related quality of life (HR-QoL) (Box 3.1)[10-12]. The performance of the DAPSA and PASDAS have been studied in patients with PsA in clinical practice, but not yet in the total pSpA population, including those without psoriasis[10,13].

Alternative composite measures for disease activity in PsA are the Minimal Disease Activity (MDA) index, the modified MDA (mMDA), the Composite Psoriatic Disease Activity Index (CPDAI) and the GRAPPA Composite Exercise (GRACE) index[12,14-17]. However, these instruments may be less useful, as (except for the mMDA) the presence of psoriasis is included in their calculation, which is not applicable to patients without psoriasis.

For patients with axial SpA, the Ankylosing Spondylitis Disease Activity Score (ASDAS) has been developed to assess disease activity (Box 3.1)[19]. The ASDAS might also be useful for pSpA, as it also contains a question related to peripheral joint pain and swelling and one general question each on morning stiffness and global disease activity. To date, the performance of the ASDAS in pSpA has been studied only in clinical trial settings and specific patient populations. It was

shown that the ASDAS had a high sensitivity to change and a high ability to discriminate both between active and placebo treatment and between high and low disease activity[20,21]. Furthermore, the ASDAS improvement criteria were able to detect a clinically important or major improvement in patients with active treatment compared to placebo treatment[20,22]. Although promising in trials, the performance of the ASDAS in pSpA in daily practice is unknown.

Therefore, the primary aim of the present study was to investigate the concurrent validity of the DAPSA, PASDAS and ASDAS as well as their discrimination across thresholds of disease activity in pSpA in clinical practice. A secondary aim was to study the performance of these disease activity measures in subgroups of patients with pSpA with and without psoriasis. In addition, data on the performance of the ASDAS in axial SpA are provided as a benchmark for interpreting the findings of the ASDAS in pSpA.

Box 3.1 Components, formulas and cut offs of the DAPSA, PASDAS and ASDAS

DAPSA33	**PASDAS12**	**ASDAS32**
CRP [0-∞[(mg/dL)	CRP [0-∞] (mg/dL)	CRP [0-∞] (mg/L) or ESR (mm/h)
Patient global [0-10]	Patient global [0-100]	Patient global [0-10]
Overall pain [0-10]	Physician global assessment [0-100]	Pain and swelling in peripheral joints [0-10]
Tender joint count of 68 joints [0-68]	Tender joint count of 68 joints [0-68]	Back pain [0-10]*
Swollen joint count of 66 joints [0-66]	Swollen joint count of 66 joints [0-66] Leeds Enthesitis Count (LEI score) [0-6] Dactylitis count [0-20] SF-36 Physical component score (SF-36 PCS)	Duration morning stiffness [0 -10]
Formula = Tender joint count of 68 joints + Swollen joint count of 66 joints + CRP (mg/dL) + Overall pain + Patient global	*Formula PASDAS= ((0.18 √physician global VAS)* *+ (0.159* √patient global VAS)* *- (0.253*√ SF-36 PCS)* *+(0.101 * ln (swollen joint count+1))* *+ 0.048 *ln(tender joint count +1))* *+ 0.23 ln(Leeds Enthesitis Count + 1))* *+ 0.377 ln(Dactylitis count + 1))* *+ 0.102 ln(CRP (mg/L) + 1)) + 2) * 1.5*	*Formula ASDAS-CRP = 0.12 x Back Pain + 0.06 x Duration of Morning Stiffness + 0.11 x Patient Global + 0.07 x Peripheral Pain/Swelling + 0.58 x Ln(CRP (mg/L)+1)* *Formula ASDAS-ESR = 0.08 x Back Pain + 0.07 x Duration of Morning Stiffness + 0.11 x Patient Global + 0.09 x Peripheral Pain/Swelling + 0.29 x √(ESR)*
Thresholds for the DAPSA disease activity score are: remission ≤4, low disease activity ≥5 to ≤14, moderate disease activity ≥15 to ≤28 and high disease activity ≥29	Thresholds for the PASDAS disease activity score are: remission ≤1.9, low disease activity >1.9 and <3.2, moderate disease activity ≥3.2 and <5.4 and high disease activity ≥5.4	Thresholds for the ASDAS disease activity score are: inactive disease <1.3, low disease activity ≥1.3 to <2.1, high disease activity ≥2.1 to ≤3.5 and very high disease activity >3.5

*This question "How do you rate your back pain due to your AS?" was slightly adapted to "How do you rate your back pain due to your rheumatic condition?" in the present study
ASDAS = Ankylosing Spondylitis Disease Activity Score, CRP = C-reactive protein, DAPSA = Disease Activity Psoriatic Arthritis Score, ESR = Erythrocyte Sedimentation Rate, PASDAS = Psoriatic Arthritis Disease Activity Score

Methods

Study population

Cross-sectional data from an ongoing, disease-specific, prospective registry for SpA in daily practice in the Netherlands (SpA-Net) were used. SpA-Net started in April 2016 and is registered in the Netherlands Trial Registry (NTR 6740)[23]. For the current study, data collected in two medical centers participating in SpA-Net (Maastricht University Medical Center and Medisch Spectrum Twente) were used. All healthcare providers were trained to use SpA-Net in clinical practice and a standard operating procedure was provided for optimal record keeping. Patients with clinically diagnosed SpA were included if ≥1 DAPSA score, ≥1 PASDAS or ≥1 ASDAS could be calculated. Patients were categorized into axial SpA or pSpA according to current or past SpA-features (Figure 3.1). For sub-analyses, the group of patients with pSpA was further stratified for the presence or absence of psoriasis.

Methods of data collection

Clinical characteristics, outcome measures, results of clinical examinations and laboratory investigations were collected in SpA-Net at every outpatient visit. Clinical examination was performed for the number of tender and swollen joints (TJC68 and SJC66, respectively), presence of enthesitis (any location) and presence of dactylitis (any location), depending on the patient's presenting symptoms without structured examination. Outcome measures in this registry consisted of validated measures of disease activity, physical function, overall SpA specific health impact, generic HR-QoL and health utility. In SpA-Net, the ASDAS question related to back pain, "How do you rate your back pain due to your Ankylosing Spondylitis?", was slightly adapted to "How do you rate your back pain due to your rheumatic condition?" in order to make this also applicable to patients with other forms of SpA. The patient global assessment (PGA) on a visual analogue scale (VAS, 0-10) was defined as "How active was your disease on average in the last week?" and the physician global assessment (PhGA) on a VAS (0-10) was defined as "How active is the patient's disease on average?". Enthesitis and dactylitis were measured with the Leeds Enthesitis Index (LEI score) and dactylitis count, respectively[24]. Physical function was measured with the Health Assessment Questionnaire for Spondyloarthropathies (HAQ-S)[25]. Overall SpA specific health impact was measured with the ASAS Health Index (ASAS HI)[26]. HR-QoL was measured by the Health Survey Short Form (SF-36), having a physical component summary (SF-36 PCS) and a mental component summary (SF-36 MCS), and health utility was measured by the EuroQoL with 5 dimensions (EQ-5D)[27,28].

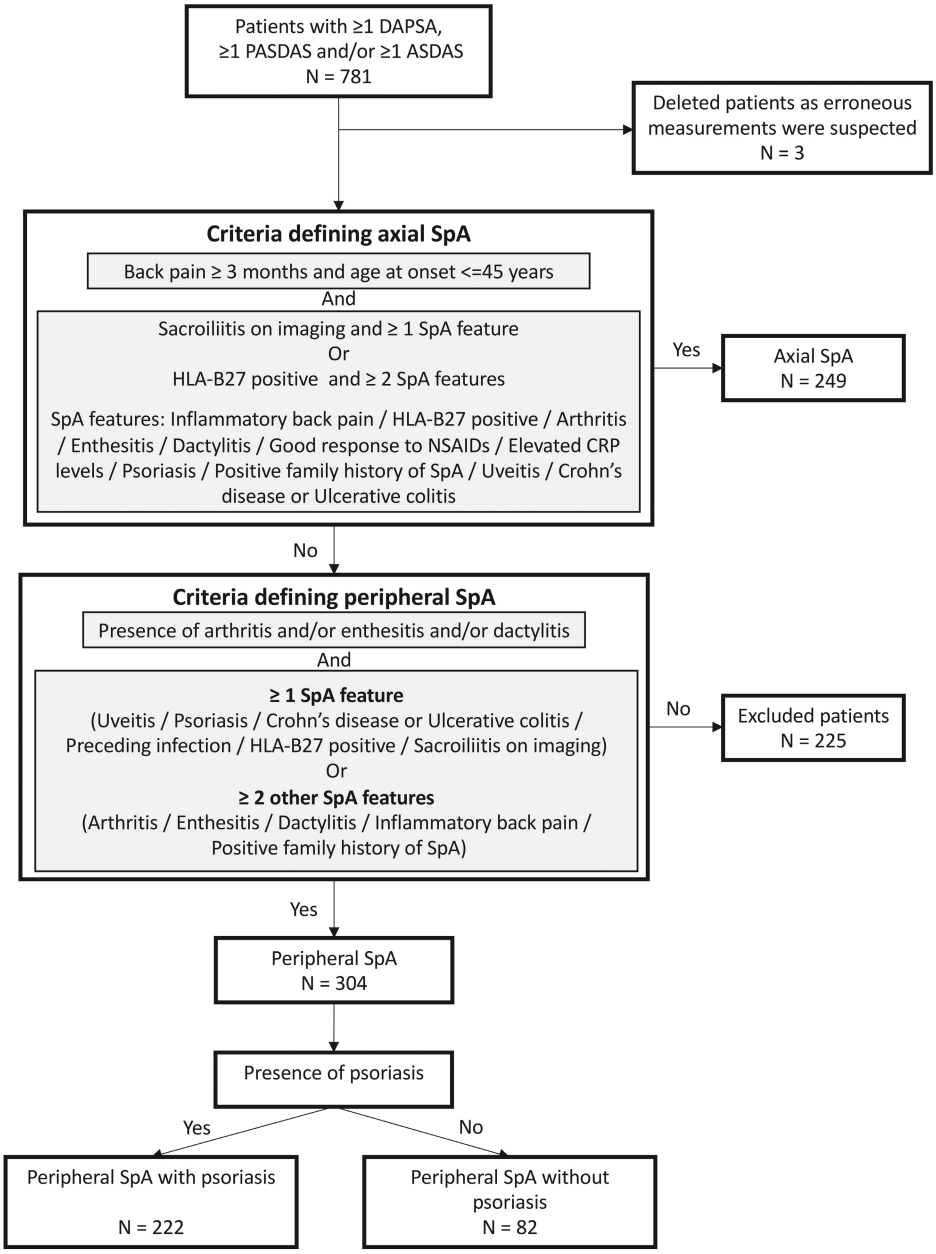

Figure 3.1 Flowchart of patients included in this study

ASDAS = Ankylosing Spondylitis Disease Activity Score, CRP = C-reactive protein, DAPSA = Disease Activity Index for Psoriatic Arthritis, NSAIDs = Non-Steroidal Anti-Inflammatory Drugs, PASDAS = Psoriatic Arthritis Disease Activity Score, SpA = Spondyloarthritis

Ethics considerations

The ethics committee of the Maastricht University Medical Center/Maastricht University determined that the Medical Research Involving Human Subjects Act did not apply as data were collected in routine care and official approval was not required for this study. Patients provided written informed consent for the data to be used for research purposes.

Statistical analyses

All data were checked for outliers using scatterplots and data were cleaned if erroneous measurements were suspected. Clinical and demographic characteristics were summarized using descriptive statistics.

Concurrent validity was assessed by Spearman correlations (r_s) of the DAPSA, PASDAS or ASDAS with all outcome measures, because not all assumptions for Pearson correlations checked with scatterplots were met in some of the outcome measures. The expected degree of correlation was hypothesized a priori (Supplementary file 3.1). The strength of correlation was based on predefined criteria: (r_s) ≤0.29 for very low correlation, 0.30 ≤ (r_s) ≤0.49 for low correlation, 0.50 ≤ (r_s) ≤0.69 for moderate correlation, 0.70 ≤ (r_s) ≤0.89 for high correlation and (r_s) ≥0.90 for very high correlation[29]. The frequency in which the hypotheses were confirmed between the DAPSA (11 hypotheses), PASDAS (8 hypotheses) or ASDAS (13 hypotheses) with other outcome measures that were not components of the composite score, was calculated (Box 3.1). Concurrent validity was considered acceptable if ≥75% of the observed correlations were as hypothesized[30]. This threshold for hypothesis testing has been accepted by international experts in a Delphi study[31]. Observed correlations were considered comparable if they had the same level of strength.

Discrimination across thresholds of disease activity in pSpA was assessed by stratifying patients according to established DAPSA, PASDAS and ASDAS disease activity states and subsequently comparing the means of several external health outcomes across these states by one-way ANOVA analyses[32,33]. We hypothesized that worsening in disease activity states would also be reflected in worsening of other health outcomes. In addition, we determined the concordance in DAPSA, PASDAS and ASDAS disease activity classification of patients.

Subgroup analyses were performed on data from patients who had all three disease activity measures available at the same point in time. Furthermore, all analyses were repeated after stratification for the presence of psoriasis. We hypothesized that the performance of the disease activity measures would be comparable in patients with or without psoriasis.

To allow benchmarking for the ASDAS performance, the results of the ASDAS in patients with pSpA were compared to the results of the ASDAS in patients with axial SpA, who were also included in SpA-Net (Figure 3.1). We hypothesized that the performance would be comparable in all subgroup analyses. Statistical analyses were performed using IBM SPSS Statistics 24.

Table 3.1 Clinical and demographic characteristics of patients with peripheral SpA

	DAPSA (n = 191)		PASDAS (n =139)		ASDAS (n = 279)	
Variable	Patients with an available assessment	Value	Patients with an available assessment	Value	Patients with an available assessment	Value
Age, years	191	56.1 (11.2)	139	57.2 (10.3)	279	55.7 (12.3)
Female, n (%)	191	103 (53.9%)	139	76 (54.7%)	279	145 (52.0%)
Symptom duration, years	140	13.4 (9.1)	112	13.2 (8.7)	213	12.6 (9.4)
Current NSAID use, n (%)	-	91 (47.6%)	-	70 (50.4%)	-	132 (47.3%)
Current csDMARD use, n (%)	-	117 (61.3%)	-	70 (50.4%)	-	158 (56.6%)
Current bDMARD use, n (%)	-	97 (50.8%)	-	77 (55.4%)	-	137 (49.1%)
Current glucocorticoid use, n (%)	-	10 (5.2%)	-	10 (7.2%)	-	14 (5.0%)
Disease activity						
DAPSA (0-∞)	191	9.9 (6.9)	129	9.5 (6.7)	159	9.6 (6.7)
PASDAS (0-10)	115	3.3 (1.4)	139	3.3 (1.4)	123	3.3 (1.4)
ASDAS (0-∞)	160	2.2 (1.0)	130	2.1 (1.0)	279	2.2 (1.0)
BASDAI (0-10)	161	4.2 (2.4)	132	4.1 (2.4)	279	4.1 (2.3)
PGA (0-10)	191	4.0 (2.7)	139	3.9 (2.7)	279	4.0 (2.6)
VAS pain (0-10)	191	3.9 (2.6)	129	3.7 (2.5)	230	3.9 (2.6)
PhGA (0-10)	144	1.7 (1.5)	139	2.0 (1.5)	184	1.8 (1.6)
CRP, mg/L (0-∞)	191	4.4 (6.0)	139	4.0 (5.4)	279	4.6 (9.1)
Psoriasis body surface area (0-100%)	142	1.4 (5.5)	127	1.4 (5.7)	166	1.3 (5.1)
Tender joint count (0-68)	191	1.2 (2.4)	139	1.1 (2.5)	197	1.1 (2.3)
Swollen joint count (0-66)	191	0.4 (0.9)	139	0.4 (0.9)	197	0.4 (1.1)
LEI score (0-6)	161	0.1 (0.4)	139	0.0 (0.2)	201	0.1 (0.3)
Dactylitis count (0-20)	161	0.1 (0.3)	139	0.0 (0.3)	201	0.0 (0.2)
Physical function and health impact						
HAQ-S (0-3)	128	0.8 (0.7)	106	0.8 (0.7)	194	0.8 (0.6)
ASAS-HI (0-17)	147	5.3 (3.6)	127	5.2 (3.6)	219	5.3 (3.5)
Health-related quality of life						
EQ-5D (0-1)	130	0.77 (0.18)	106	0.78 (0.20)	194	0.78 (0.19)
SF-36 MCS (0-100)	155	49.5 (10.9)	139	49.3 (10.9)	228	49.5 (10.8)
SF-36 PCS (0-100)	155	39.8 (10.4)	139	40.6 (10.7)	228	40.0 (9.9)

Values are presented as mean (SD) unless stated otherwise.

ASAS-HI = Assessment of SpondyloArthritis international Society Health Index, ASDAS = Ankylosing Spondylitis Disease Activity Score, BASDAI = Bath Ankylosing Spondylitis Disease Activity Index, bDMARD = biological Disease-Modifying Antitrheumatic Drug, BSA = Body Surface Area, csDMARD = conventional synthetic Disease-Modifying Antirheumatic Drug, CRP = C-Reactive Protein, DAPSA = Disease Activity Psoriatic Arthritis Score, EQ-5D = EuroQol 5D, HAQ-S = Health Assessment Questionnaire for Spondyloarthritis, LEI score = Leeds Enthesitis Index score, MCS = Mental Component Score, NSAID = Non-Steroidal Anti Inflammatory Drug, PASDAS = Psoriatic Arthritis Disease Activity Score, PCS = Physical Component Score, PGA = Patient Global Assessment, PhGA = Physician Global Assessment, SF-36 = Short Form 36 Health Survey, SJC66 = Swollen Joint Count of 66 joints, TJC68 = Tender Joint Count of 68 joints, VAS= Visual Analog Scale

Results

Study population

In 781 patients, at least one DAPSA, PASDAS or ASDAS score could be calculated (Figure 3.1). Three patients had to be excluded because of inconsistencies in the data. Of the remaining 778 patients, 249 patients had axial SpA, 304 patients had pSpA, and 225 patients could not be classified due to insufficient or missing variables. Of the patients with pSpA, 222 (73%) had concomitant psoriasis. In 124 of the 304 (41%) patients with pSpA all three disease activity measures were simultaneously available.

On average, disease activity in patients with pSpA was low according to the DAPSA, moderate according to the PASDAS and high according to the ASDAS (Table 3.1). Patients had low TJC68 and SJC66 scores and they experienced moderate difficulties in daily functioning based on the HAQ-S. Clinical characteristics and health outcomes were comparable between patients with and without psoriasis, except for gender distribution and csDMARDs use (Supplementary file 3.1). Patients with pSpA differed clinically from patients with axial SpA, but health outcomes were comparable (Table 3.1 and Supplementary file 3.2).

Concurrent validity by correlation with external measures

In the total population of patients with pSpA, the strength of correlation between the DAPSA and other outcome measures was as hypothesized for 10 out of 11 (91%), between the PASDAS and other outcome measures as hypothesized for 6 out of 8 (75%) measures and between the ASDAS and other outcome measures as hypothesized for 11 out of 13 (85%) measures measures (Table 3.2 and Supplementary file 3.3). The correlations were lower than expected between the PASDAS with SF-36 MCS, between the ASDAS with VAS pain, and ASDAS with PhGA (Table 3.2 and Supplementary file 3.3). Nearly all hypotheses were confirmed between the disease activity measures and measures of physical function, overall SpA specific health impact, HR-QoL and health utility.

Table 3.2 Spearman correlations of DAPSA, PASDAS and ASDAS with outcomes measures in peripheral SpA

	DAPSA							
	Total pSpA population n = 191		pSpA without psoriasis n = 49		pSpA with psoriasis n = 142		Total pSpA population n = 139	
Outcome measure Disease activity	Rs	Hypothesis	Rs	Hypothesis	Rs	Hypothesis	Rs	Hypothesis
DAPSA	NA		NA		NA		0.91*	- H
PASDAS	0.92*	- H	0.85*	+	0.91*	- H	NA	
ASDAS	0.81*	+	0.77*	+	0.80*	+	0.85*	+
BASDAI‡	0.76*	+	0.73*	+	0.76*	+	0.78*	+
PGA†,§ ‡	0.89*		0.87*		0.89*		0.92*	
VAS pain†	0.89*		0.86*		0.90*		0.74*	+
PhGA§	0.61*	+	0.61*	+	0.60*	+	0.81*	
CRP†,§ ‡	0.19*		0.33*		0.13		0.15	
Psoriasis BSA	-0.04		NA		0.01	- L	-0.08	
TJC68† §	0.67*		0.75*		0.67*		0.52*	
SJC66† §	0.46*		0.34		0.51*		0.43*	
LEI score §	0.12	+	0.18	+	0.07	+	0.10	
Dactylitis count §	0.22	+	ND		0.26*	+	0.19*	
Physical function and health impact								
HAQ-S	0.59*	+	0.62*	+	0.56*	+	0.68*	+
ASAS-HI	0.67*	+	0.57*	+	0.67*	+	0.68*	+
Health-related quality of life								
EQ-5D	-0.69*	+	-0.65*	+	-0.69*	+	-0.50*	+
SF-36 MCS	-0.30*	+	-0.31*	+	-0.28*	- L	-0.15	- L
SF-36 PCS §	-0.65*	+	-0.67*	+	-0.64*	+	-0.76*	

† DAPSA components, § PASDAS components ‡ ASDAS components, Individual components of the DAPSA, PASDAS and ASDAS were not included in the calculation of the frequency of confirmed hypotheses for concurrent validity

ND = Correlation could not be calculated as standard deviation was zero, *Correlation is statistically significant at the 0.05 level (two-tailed), + = strength of correlation as hypothesized, L = strength of correlation is lower than hypothesized, H = strength of correlation is higher than hypothesized

ASAS-HI = Assessment of SpondyloArthritis international Society Health Index, ASDAS = Ankylosing Spondylitis Disease Activity Score, BASDAI = Bath Ankylosing Spondylitis Disease Activity Index, bDMARD = biological Disease-Modifying Antitrheumatic Drug, BSA = Body Surface Area, csDMARD = conventional synthetic Disease-Modifying Antirheumatic Drug, CRP = C-Reactive Protein, DAPSA = Disease Activity Psoriatic Arthritis Score, EQ-5D = EuroQol 5D, HAQ-S = Health Assessment Questionnaire for Spondyloarthritis, LEI score = Leeds Enthesitis Index score, MCS = Mental Component Score, NSAID = Non-Steroidal Anti Inflammatory Drug, PASDAS = Psoriatic Arthritis Disease Activity Score, PCS = Physical Component Score, PGA = Patient Global Assessment, PhGA = Physician Global Assessment, pSpA = peripheral Spondyloarthritis, SF-36 = Short Form 36 Health Survey, SJC66 = Swollen Joint Count of 66 joints, TJC68 = Tender Joint Count of 68 joints, VAS= Visual Analog Scale

PASDAS						ASDAS			
pSpA without psoriasis n = 42		pSpA with Psoriasis n = 97		Total pSpA population n = 279		pSpA without psoriasis n = 82		pSpA with psoriasis n = 197	
Rs	Hypothesis	Rs	Hypothesis	Rs	Hypothesis	Rs	Hypothesis	Rs	Hypothesis
0.85*	+	0.90*	- H	0.80*	+	0.79*	+	0.89*	+
NA		NA		0.84*	+	0.80*	+	0.83*	+
0.81*	+	0.84*	+	NA		NA		NA	
0.67*	- L	0.80*	+	0.85*		0.83*		0.84*	
0.88*		0.91*		0.82*		0.79*		0.79*	
0.71*	+	0.74*	+	0.69*	- L	0.63*	- L	0.69*	- L
0.76*		0.80*		0.49*	- L	0.46*	- L	0.48*	- L
0.25		0.12		0.48*		0.56*		0.44*	
NA		0.00	- L	0.01		NA		0.14	- L
0.48*		0.58*		0.39*	+	0.35*	+	0.44*	+
0.27		0.50*		0.19*	+	-0.00	+	0.28*	+
0.17		0.05		0.11	+	0.15	+	0.09	+
ND		0.23*		0.08	+	ND		0.12	+
0.73*	- H	0.65*	+	0.63*	+	0.65*	+	0.60*	+
0.60*	+	0.68*	+	0.63*	+	0.64*	+	0.57*	+
-0.40*	+	-0.53*	+	-0.62*	+	-0.64*	+	-0.60*	+
-0.25	- L	-0.13	- L	-0.33*	+	-0.53*	+	-0.24*	- L
-0.82*		-0.72*		-0.67*	+	-0.69*	+	-0.64*	+

Table 3.3 Outcome measures stratified for DAPSA, PASDAS or ASDAS disease activity states in peripheral SpA

	DAPSA Total pSpA population n = 191							
	DAPSA cut-offs				One-way ANOVA			
Outcome measure Disease activity	**≤4 n = 49 (25.7%)**	**5 to ≤14 n = 99 (51.8%)**	**15 to ≤28 n = 41 (21.5%)**	**≥29 n = 2 (1.0%)**	**F-value**	**P-value**	**≤1.9 n = 23 (16.5%)**	**1.9 to <3.2 n = 40 (28.8%)**
DAPSA (0-∞)	2.1 (1.4)	9.5 (2.9)	18.9 (3.0)	34.7 (7.8)	346.6	<0.01	1.7 (1.9)	5.5 (2.9)
PASDAS (0-∞)	1.7 (0.9)	3.4 (0.7)	5.0 (0.6)	- (-)	132.6	<0.01	1.0 (0.5)	2.7 (0.4)
ASDAS (0-∞)	1.1 (0.5)	2.2 (0.7)	3.2 (0.8)	3.2 (-)	62.5	<0.01	0.9 (0.3)	1.5 (0.6)
BASDAI (0-10)	1.8 (1.6)	4.6 (1.8)	6.2 (1.9)	7.6 (-)	45.5	<0.01	1.0 (0.8)	2.9 (1.7)
PGA (0-10)	1.0 (0.9)	4.1 (1.8)	7.2 (1.6)	7.5 (0.7)	117.0	<0.01	0.4 (0.7)	2.2 (1.1)
VAS pain (0-10)	0.7 (0.7)	4.2 (1.9)	6.7 (1.4)	6.3 (1.0)	119.6	<0.01	0.9 (1.9)	2.6 (2.2)
PhGA (0-10)	0.8 (0.9)	1.6 (1.0)	3.2 (1.6)	8.0 (-)	34.7	<0.01	0.3 (0.6)	1.4 (0.8)
CRP, mg/L (0-∞)	2.3 (2.1)	4.0 (4.2)	7.5 (9.8)	13.5 (16.3)	8.3	<0.01	3.2 (2.9)	2.4 (3.0)
TJC68 (0-68)	0.0 (0.3)	0.6 (1.1)	3.2 (2.4)	15.5 (9.2)	94.5	<0.01	0.0 (0.2)	0.3 (0.6
SJC66 (0-66)	0.0 (0.3)	0.3 (0.6)	1.1 (1.3)	4.0 (1.4)	28.0	<0.01	0.0 (0.2)	0.2 (0.4)
LEI score (0-6)	0.0 (0.0)	0.1 (0.3)	0.2 (0.7)	0.0 (-)	1.3	0.29	0.1 (0.2)	0.1 (0.2)
Dactylitis count (0-20)	0.0 (0.0)	0.0 (0.1)	0.2 (0.6)	0.0 (-)	2.4	0.07	0.0 (0.0)	0.0 (0.0)
Physical function and health impact								
HAQ-S (0-3)	0.2 (0.3)	1.0 (0.6)	1.2 (0.7)	1.0 (-)	19.3	<0.01	0.1 (0.2)	0.5 (0.4)
ASAS-HI (0-17)	1.8 (1.7)	6.0 (3.1)	7.5 (3.3)	11.0 (-)	29.2	<0.01	1.5 (1.9)	3.3 (2.2)
Health-related quality of life								
EQ-5D (0-1)	0.94 (0.06)	0.76 (0.12)	0.64 (0.23)	0.41 (-)	25.7	<0.01	0.92 (0.13)	0.85 (0.11)
SF-36 MCS (0-100)	55.4 (7.1)	47.6 (10.9)	47.8 (11.4)	22.1 (-)	8.2	<0.01	54.3 (10.1)	49.4 (9.2)
SF-36 PCS (0-100)	49.7 (6.9)	38.5 (8.9)	32.1 (8.2)	35.9 (-)	31.2	<0.01	51.3 (7.5)	46.8 (7.6)

Values are presented as mean (SD) unless stated otherwise.
ASAS-HI = Assessment of SpondyloArthritis international Society Health Index, ASDAS = Ankylosing Spondylitis Disease Activity Score, BASDAI = Bath Ankylosing Spondylitis Disease Activity Index, bDMARD = biological Disease-Modifying Antitrheumatic Drug, BSA = Body Surface Area, csDMARD = conventional synthetic Disease-Modifying Antirheumatic Drug, CRP = C-Reactive Protein, DAPSA = Disease Activity Psoriatic Arthritis Score, EQ-5D = EuroQol 5D, HAQ-S = Health Assessment Questionnaire for Spondyloarthritis, LEI score = Leeds Enthesitis Index score, MCS = Mental Component Score, NSAID = Non-Steroidal Anti Inflammatory Drug, PASDAS = Psoriatic Arthritis Disease Activity Score, PCS = Physical Component Score, PGA = Patient Global Assessment, PhGA = Physician Global Assessment, pSpA = peripheral Spondyloarthritis, SF-36 = Short Form 36 Health Survey, SJC66 = Swollen Joint Count of 66 joints, TJC68 = Tender Joint Count of 68 joints, VAS= Visual Analog Scale

PASDAS Total pSpA population n = 139				ASDAS Total pSpA population n = 279					
PASDAS cut-offs		One-way ANOVA		ASDAS cut-offs				One-way ANOVA	
3.2 to <5.4 n = 69 (49.6%)	≥5.4 n = 7 (5.0%)	F-value	P-value	<1.3 n = 59 (21.1%)	1.3 to <2.1 n = 83 (29.7%)	2.1 to ≤3.5 n = 105 (37.6%)	>3.5 n = 32 (11.5%)	F-value	P-value
13.3 (5.2)	22.1 (3.6)	69.7	<0.01	3.2 (2.9)	7.2 (4.8)	12.9 (5.9)	17.1 (3.8)	50.2	<0.01
4.1 (0.6)	5.9 (0.4)	307.7	<0.01	1.8 (0.9)	3.1 (1.0)	4.2 (0.7)	4.9 (0.6)	64.2	<0.01
2.7 (0.7)	3.4 (0.8)	64.7	<0.01	0.9 (0.3)	1.7 (0.2)	2.7 (0.4)	3.9 (0.4)	717.4	<0.01
5.4 (1.7)	7.0 (1.7)	54.1	<0.01	1.5 (0.9)	3.2 (1.4)	5.3 (1.6)	7.0 (1.4)	151.8	<0.01
5.6 (1.8)	8.3 (1.1)	116.2	<0.01	1.1 (1.1)	3.2 (1.8)	5.2 (2.0)	7.4 (1.4)	119.0	<0.01
4.9 (1.8)	7.4 (0.8)	33.6	<0.01	1.6 (2.2)	2.9 (2.0)	5.3 (2.0)	6.3 (1.4)	56.2	<0.01
2.4 (1.0)	5.6 (1.6)	70.2	<0.01	1.0 (1.1)	1.5 (1.2)	2.3 (1.7)	3.3 (1.8)	14.5	<0.01
5.1 (6.8)	5.6 (5.8)	2.4	0.07	1.6 (1.1)	2.5 (2.5)	4.7 (5.6)	15.2 (21.9)	21.9	<0.01
1.7 (3.2)	3.1 (1.7)	6.5	<0.01	0.2 (0.5)	0.8 (1.3)	1.5 (3.1)	1.9 (2.0)	5.1	<0.01
0.4 (1.0)	1.9 (1.9)	9.2	<0.01	0.1 (0.4)	0.4 (0.8)	0.6 (1.4)	0.6 (1.2)	2.2	0.09
0.0 (0.2)	0.1 (0.4)	0.9	0.44	0.0 (0.0)	0.1 (0.3)	0.1 (0.4)	0.1 (0.3)	1.6	0.18
0.0 (0.4)	0.1 (0.4)	0.7	0.54	0.0 (0.3)	0.0 (0.1)	0.0 (0.3)	0.1 (0.3)	0.5	0.71
1.2 (0.6)	2.0 (0.4)	27.7	<0.01	0.2 (0.3)	0.6 (0.6)	1.1 (0.6)	1.3 (0.6)	30.1	<0.01
7.1 (3.2)	8.2 (3.3)	28.1	<0.01	2.2 (1.7)	4.3 (2.7)	6.9 (3.4)	8.3 (3.2)	38.2	<0.01
0.70 (0.23)	0.87 (0.11)	8.0	<0.01	0.93 (0.08)	0.81 (0.14)	0.71 (0.18)	0.63 (0.24)	22.9	<0.01
47.4 (11.4)	50.8 (13.8)	2.4	0.07	54.5 (7.4)	51.9 (9.9)	46.1 (11.1)	44.9 (12.4)	10.0	<0.01
35.2 (7.3)	24.5 (9.2)	47.0	<0.01	49.1 (7.0)	42.9 (8.9)	35.4 (8.1)	30.8 (5.0)	47.9	<0.01

Discrimination across thresholds of disease activity and concordance in classification

In the total population of patients with pSpA, we found with worsening DAPSA, PASDAS or ASDAS disease activity states, there was significant worsening for all other scores for measures of disease activity, physical function, overall SpA specific health impact, HR-QoL and health utility (all p<0.01, Table 3.3), except for enthesitis and dactylitis (all measures), CRP in worsening PASDAS disease activity states (F-value = 2.4, p-value = 0.07) and SJC66 in worsening ASDAS disease activity states (F-value = 2.2, p-value = 0.09).

Overall, substantially fewer patients were categorized as having high disease activity by the DAPSA (n=1 (0.8%) and PASDAS (n = 5 (4.0%)) compared to having high or very high disease activity by the ASDAS (n = 60 (48.4%), Table 3.4). When moderate disease activity was included in the definition of high disease activity by the DAPSA, the difference compared to the ASDAS remained substantial (n = 27 (21.8%) versus n = 60 (48.4%)), while including moderate disease activity into the definition of high disease activity by the PASDAS resulted in more patients classified as having high disease activity compared with the ASDAS (n=70 (56.4%) versus n=60 (48.4%).

Subgroup analyses

Subgroup analyses in patients with simultaneously available DAPSA, PASDAS and ASDAS measures showed that nearly all results for concurrent validity and discrimination across thresholds of disease activity were comparable to the total pSpA sample in which at least one disease activity measure was available (Supplementary file 3.4 and 3.5). The strength of correlations between the DAPSA, PASDAS or ASDAS with other outcome measures in patients with all three disease activity measures s available were as hypothesized for 9 out of 11 (81.8%) outcome measures, 5 out of 8 (62.5%) and 8 out of 13 (61.5%) outcome measures, respectively. The hypotheses for concurrent validity of the PASDAS with DAPSA and ASAS-HI, and ASDAS with HAQ-S and ASAS-HI were not met as the correlations were in fact higher than expected.
In patients with and without psoriasis, the strength of correlation between either the DAPSA, PASDAS or ASDAS with other health and clinical outcome measures was almost always comparable (Table 3.2).
Discrimination across existing thresholds of disease activity did not differ substantially after stratification for the presence or absence of psoriasis (Supplementary files 3.6, 3.7 and 3.8).

Benchmark analyses

As a benchmark, the performance of the ASDAS in the total population of pSpA was compared with the performance of the ASDAS in patients with axial SpA. The correlations between the ASDAS and other outcome measures were as hypothesized in axial SpA for 10 out of 12 (83%) measures and in pSpA for 11 out of 13 (85%) measures (Table 3.2 and Supplementary file 3.9).
The results for discrimination across thresholds of disease activity were comparable for the ASDAS in both pSpA and axial SpA populations, except that significant differences in TJC68 were found across ASDAS states in patients with pSpA, but not in patients with axial SpA (Table 3.3 and Supplementary file 3.10).

Table 3.4 Disease activity states of patients with pSpA with DAPSA, PASDAS and ASDAS scores simultaneously available

		PASDAS				ASDAS			
		Remission ≤1.9	Low >1.9 to <3.2	Moderate ≥3.2 to <5.4	High ≥5.4	Inactive <1.3	Low ≥1.3 to <2.1	High ≥2.1 to ≤3.5	Very high >3.5
	n = 124	n = 18 (14.5%)	n = 36 (29.0%)	n = 65 (52.4%)	n =5 (4.0%)	n = 30 (24.2%)	n = 34 (27.4%)	n = 46 (37.1%)	n = 14 (11.3%)
DAPSA									
Remission ≤4	n = 33 (26.6%)	16	17	0	0	22	11	0	0
Low ≥5 to ≤14	n = 64 (51.6%)	2	19	43	0	8	20	33	3
Moderate ≥15 to ≤28	n = 26 (21.0%)	0	0	21	5	0	3	12	11
High ≥29	n = 1 (0.8%)	0	0	1	0	0	0	1	0
ASDAS									
Inactive <1.3	n = 30 (24.2%)	15	15	0	0				
Low ≥1.3 to <2.1	n = 34 (27.4%)	3	17	13	1				
High ≥2.1 to ≤3.5	n = 46 (37.1%)	0	4	40	2				
Very high >3.5	n = 14 (11.3%)	0	0	12	2				

ASDAS = Ankylosing Spondylitis Disease Activity Score, DAPSA = Disease Activity Psoriatic Arthritis Score, PASDAS = Psoriatic Arthritis Disease Activity Score

Discussion

This study showed acceptable concurrent validity and discrimination across thresholds of disease activity of the DAPSA, PASDAS and ASDAS in clinical practice patients with pSpA, with on average a low degree of peripheral joint involvement. The strength of correlation between the disease activity measures with a variety of other outcome measures was correct in more than 75%. In addition, increasing DAPSA, PASDAS or ASDAS disease activity states were associated with worsening in patient and physician reported outcome measures for disease activity, impairment in physical function, overall SpA specific health impact, generic HR-QoL and health utility. Remarkably, classifying patients in the disease activity states showed discordance in the high disease activity states.

The results of the subgroup analyses in patients with simultaneously available disease activity measures were comparable to the results of the total pSpA population. Subgroup analyses in patients with and without psoriasis showed some differences in the performance of the disease activity measures. However, these results should be interpreted with caution as they may have been caused by the small number of patients without psoriasis.
As no gold standard exists to assess disease activity in pSpA, the performance of the DAPSA, PASDAS and ASDAS was studied in relation to multiple subjective and objective outcome measures capturing several disease aspects from both the physician and patient perspective. Overall, these analyses provided elaborated evidence on the performance of these disease activity measures in patients with pSpA with low peripheral joint involvement in the majority of the patients in clinical practice. The comparable performance of the ASDAS in patients with pSpA and axial SpA strengthens the hypothesis that the ASDAS could also be a valid measure in patients with pSpA.

An important finding was the substantial discordance when classifying patients into the disease activity states. The DAPSA classified 22%, the PASDAS 56% and the ASDAS 48% of the patients in the two highest disease activity states. These results might be explained by different individual components of each composite measure. Involvement of peripheral joints has substantially more weight in the cumulative calculation of the DAPSA, where the absolute number of affected joints is included, compared to the ASDAS, where only a general question on peripheral joint involvement is asked, and the PASDAS where joint involvement has a relative weight. Alternatively, the discrepancy could also be an indication that the existing thresholds for disease activity states of the DAPSA and PASDAS used for patients with PsA and the ASDAS for axial SpA might not be applicable to patients with pSpA, but this interpretation requires a cautious note, as the number of patients with a high number of swollen joints was limited in our study[32,33]. However, the discrepancy may have large implications for clinical practice. The number of patients with pSpA who did not achieve remission or low disease activity was much higher using the PASDAS and ASDAS compared to DAPSA and consequentially more patients would qualify for treatment intensification based on the PASDAS and ASDAS compared to the DAPSA. This discrepancy in classification and the validity of existing thresholds for disease activity states therefore warrants further study in pSpA.

Practically, the ASDAS might have some advantages over the DAPSA and PASDAS. First, assessment of the ASDAS is much faster than the DAPSA and PASDAS, which require full joint examination. Second, the ASDAS can be used for remote monitoring of disease activity as its components, including measuring C-reactive protein (CRP) levels, are assessor independent. Third, with the ASDAS, disease activity can be assessed in both axial SpA and pSpA with the same measure, allowing comparison as well as aggregation of the two populations. The DAPSA might also have an advantage over the PASDAS and ASDAS, as calculating these measures is complex and requires an online tool.

Some concerns about the usefulness of the DAPSA as measure of disease activity for patients with PsA have been expressed[34]. The DAPSA assesses peripheral joint disease, but does not take into account other aspects of disease activity, such as psoriasis, dactylitis and enthesitis which are important to patients. This limitation of the DAPSA also applies to the ASDAS.

Our study has several strengths. The performance of the disease activity measures in pSpA was evaluated in daily practice and the results therefore represent real-life rather than research settings, increasing the generalizability of the findings. Furthermore, data from all patients with pSpA and axial SpA were collected in one patient register using the same standardized method.

This study also has several limitations. First, patients in this study were adequately treated and had on average low CRP levels, and low tender and swollen joint counts, which limits the generalizability to other pSpA populations with more active disease. Second, the sample size of patients with pSpA without psoriasis was relatively low, which might have affected the results when comparing the performance of the disease activity measures between patients with or without psoriasis. Third, we have not tested the responsiveness of the DAPSA, PASDAS and ASDAS in pSpA in our population, because we have only limited follow up data from our patients thus far as SpA-Net is an observational cohort of well-treated patients with only a limited number of treatment adaptations.

In conclusion, this study showed that the DAPSA, PASDAS and ASDAS have acceptable concurrent validity and discrimination across thresholds of disease activity in pSpA, which was independent of the presence of psoriasis. Based on results of clinical trial data and our results in daily practice, the DAPSA, PASDAS and ASDAS could be useful for measuring disease activity in pSpA in clinical practice. However, the discrepancy in classification of individual patients in disease activity states currently limits their use for decision making in clinical practice and warrants further study in pSpA.

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CHAPTER 4

Treat-to-target in axial spondyloarthritis: an observational study in daily practice

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Rheumatology (Oxford) 2022;61(4):1396-407
doi:10.1093/rheumatology/keab516

Abstract

Objectives

To evaluate the extent to which internationally agreed treat-to-target (T2T) recommendations were applied in clinical practice in patients with axial spondyloarthritis (SpA).

Methods

Data were used from a web-based patient registry for monitoring SpA in daily practice in the Netherlands (SpA-Net). The extent to which T2T was applied was evaluated through four indicators: the proportion of patients 1) with ≥1 Ankylosing Spondylitis Disease Activity Score (ASDAS) assessed during a 1-year period, 2) having inactive disease/low disease activity (ID/LDA, i.e. ASDAS<2.1), 3) in whom re-evaluation of ASDAS within recommended intervals occurred, and 4) with high disease activity (HDA, i.e. ASDAS≥2.1) in whom treatment was adapted ≤6 weeks after obtaining ASDAS≥2.1. Patients with HDA with treatment adaptations were compared to patients with HDA without treatment adaptations.

Results

In 185 out of 219 patients (84%), disease activity was monitored with ≥1 ASDAS during a 1-year period, of whom 71 (38%) patients had a score below the target (ASDAS<2.1) at first measurement. Re-evaluation of ASDAS ≤3 months occurred in 11% and 23% of the patients with ID/LDA and HDA, respectively. Treatment adaptation occurred in 19 out of 114 patients (13%) with HDA. Patients in whom treatment was adapted, had significantly higher ASDAS ($p<0.01$), C-reactive protein levels ($p<0.05$), and physician global assessment ($p<0.05$) compared to patients without treatment adaptations.

Conclusions

T2T was applied to a limited extent in clinical practice in patients with axial SpA. Available disease activity scores seemed not to be used for determining the frequency of re-evaluation nor treatment adaptation.

Introduction

Treat-to-target (T2T) is recommended as a management strategy for axial spondyloarthritis (SpA)[1, 2]. The formulation of these T2T recommendations was justified by observational studies revealing a longitudinal association between disease activity and radiographic progression in ankylosing spondylitis (AS), and studies that showed that the impact of TNF inhibitors on spinal radiographic progression is mediated by their effect on disease activity[3-5]. In addition, achieving inactive disease (ID) is associated with improved physical activities and work productivity, all contributing to better overall functioning and health[6].

The international T2T recommendations for SpA, as well as the ASAS-EULAR management recommendations for axial SpA and the 2019 international ASAS quality standard set for optimising access, treatment and patient outcomes in axial SpA, all advise that disease activity should be monitored regularly with validated outcome measures to evaluate whether treatment targets have been achieved[1,2,7]. In axial SpA, the AS Disease Activity Score (ASDAS) is preferred; alternatively the Bath AS Disease Activity Index (BASDAI) can be used if CRP levels are not available[8]. Both the International T2T recommendations for SpA and the ASAS-EULAR management recommendations for axial SpA advice that treatment should be guided towards predefined treatment targets. However, only the T2T recommendations explicitly define the target as ID or low disease activity (LDA)[2]. In addition, experts from ASAS advise initiating or resumin treatment in patients who have demonstrated clinically important disease worsening, defined as an increase in ASDAS of 0.9 points or more[9]. Furthermore, the T2T recommendations explicitly advise that the frequency of re-evaluation should be dependent on prior disease activity scores. In patients who have not achieved the target, disease activity should be re-evaluated within 3 months. Evaluation within 6 to 12 months may be considered in patients whose target is achieved.

Although the guidelines and management recommendations propose regular monitoring of disease activity and treatment towards predefined goals, clinicians report feasibility concerns in daily practice[10]. In a review of medical files of patients with axial SpA in 2013, it was shown that outcome measures for disease activity were only collected in a limited proportion of patients, ranging from 1% for the ASDAS to 51% for C-reactive protein (CRP) levels[11]. Frequent monitoring of disease activity can be burdensome to both patients and healthcare providers. For example, paper-based questionnaires are resource demanding in terms of distribution, gathering, score calculation and transfer of data into the existing electronic medical records (EMRs)[12]. Integrating data collection into EMRs could provide a solution for these feasibility concerns, as patient reported outcome measures can be collected electronically (ePROMs) with equal or less investment of time required. ePROMs generally provide high-quality data and most patients prefer electronic data collection[13,14].

Since 2016, a web-based patient registry for monitoring patients with SpA in daily practice in the Netherlands (SpA-Net) has been in use, available at www.mijnreumacentrum.nl[15]. SpA-Net follows the patient journey in daily practice and facilitates monitoring of various disease aspects, including comorbidities, prescribed medication, adverse events, and patient- and

physician-centered outcome measures for disease activity, physical functioning and overall health status. Results over time are graphically visualized in a dashboard, using color-coding to aid quick interpretation. These comprehensive up-to-date individual patient data are readily available to the physician during consultations, which facilitate informed treatment decision making based on a complete overview of the patient's history. In this particular situation where an electronic monitoring tool is available, we were interested in what the uptake of the T2T recommendations was. Therefore, the aim of this study was to evaluate the extent to which internationally agreed T2T recommendations were applied in patients with axial SpA in rheumatology centers supported by SpA-Net.

Methods

Design of the study and data collection

Data were used from SpA-Net, an electronic monitoring tool, registered in the Netherlands Trial Registry (NTR 6740)[15]. The ethics committee of the university hospital Maastricht/Maastricht University determined that the Medical Research Involving Human Subjects Act did not apply as data were collected in routine care and official approval was not required for this study. Written informed consent was obtained from each patient to use data for research purposes.

Rheumatologists and (specialised) nurses were trained to use SpA-Net in clinical practice and a standard operating procedure was provided for optimal record keeping. Patients were instructed by their healthcare provider(s) to complete ePROMs in SpA-Net a few days prior to every visit at home or in the hospital's waiting room, where touch-screen tablets were available. If needed, a healthcare provider offered assistance in completing the ePROMs during the visit. Healthcare providers were not notified if patients have completed a new outcome measure, nor have a high disease activity (HDA).

Study population

We used SpA-Net data from three participating centers from different geographical areas in the Netherlands; Maastricht University Medical Center is an academic center where a couple of SpA expert rheumatologists work, Medisch Spectrum Twente is a large general teaching hospital, and VieCuri is a top clinical hospital.

For the present study, patients were selected if they had a clinical diagnosis of axial SpA for at least 6 months, were enrolled in SpA-Net before January 2018, and had at least one patient or physician reported outcome measure registered in 2018 (January to December). Patients were excluded if they had participated in other clinical studies within this period.

Assessments

In SpA-Net, disease activity could be evaluated by CRP-based ASDAS and/or BASDAI[8,16]. CRP levels were usually assessed prior to the clinical visit using standard measurements. ID/LDA

was defined as ASDAS<2.1 or BASDAI<4.0 and HDA was defined as ASDAS≥2.1 or BASDAI≥4.0[16,17]. Overall functioning and health was monitored with the ASAS Health Index (ASAS HI)[18]. Physical functioning was measured with the Bath AS Functional Index (BASFI)[19] and the Health Assessment Questionnaire for Spondyloarthropathies (HAQ-S)[20]. Health utility was measured with the EuroQoL 5 dimensions (EQ5D) and health-related quality of life (HR-QoL) with two summary scores of the Short Form Health Survey (SF-36): the physical and mental component summary (SF-36 PCS and SF-36 MCS, respectively)[21,22]. Symptom duration was calculated as the time between the onset of symptoms and the first ASDAS or BASDAI measurement in this study.

Study outcomes

The extent to which the T2T recommendations were followed were evaluated through four indicators: the proportion of patients (i) in whom disease activity was assessed with at least one ASDAS measurement during a 1-year period (January to December 2018); (ii) with ID/LDA at the first measurement; (iii) with ID/LDA or HDA in whom the ASDAS was re-evaluated within 3, 6 or 12 months after the first measurement; and (iv) the proportion of patients in whom pharmacological treatment for axial SpA was adapted within 6 weeks after a first measurement of ASDAS HDA.

Of note, for the third indicator, we used an extended time-window of 1 month, because in practice not all patients receive an appointment exactly within 3, 6 or 12 months, respectively. For the fourth indicator, treatment adaptation was defined as increasing the dosage and/or frequency of drugs, starting an additional drug or switching between drugs. We investigated adaptations of the following medications: non-steroidal anti-inflammatory drugs (NSAIDs), glucocorticosteroids, local steroid injections, conventional synthetic DMARDs (csDMARDs), targeted synthetic DMARDs (tsDMARDs) and biological DMARDs (bDMARDs). In parallel, we studied the proportion of patients with HDA in whom treatment was discontinued or the drug dosage and/or frequency of administration was decreased and reasons for this. For this fourth indicator a maximum period of 6 weeks was accepted between obtaining an HDA score and starting a new treatment, as time delays might occur in clinical practice. For example, time delays are expected as patients are instructed to complete the questionnaires several days prior to the actual visit and when patients need to be screened for latent infectious diseases before commencement of a biological after a visit.

In extension to the fourth indicator, we evaluated treatment adaptation based on clinically important ASDAS worsening[9]. This was done by calculating the proportion of patients in whom treatment was adapted among those patients with ASDAS ID/LDA at the first measurement, who showed a clinically important ASDAS worsening (ΔASDAS +0.9) at a second measurement, and consequentially changed from an ID/LDA state to an HDA state.
Nearly all analyses were repeated with BASDAI instead of ASDAS.

Statistical analyses

Patient and disease characteristics were calculated with descriptive statistics. Differences in characteristics between patients with ID/LDA versus HDA at the first available measure-

ment, and between patients with HDA in whom treatment was adapted versus not adapted were compared with an independent samples Student's t-test, Mann-Whitney U-tests or the Chi-square test, whichever was appropriate. Results were considered statistically significant when $p<0.05$. Analyses were performed in R version 3.5.1 (R Foundation for Statistical Computing, Vienna, Austria) and IBM SPSS Statistics 24 (IBM, Corp., Armonk, New York, USA).

Results

In total, 307 patients had a clinical diagnosis of axial SpA for at least 6 months, were enrolled in SpA-Net before January 2018 and did not participate in other clinical trials. Of these 307 patients, 219 (71%) also had at least one patient or physician reported outcome measure registered in 2018. A significant difference was found for the current and prior use of bDMARDs between patients with or without at least one completed outcome measure in 2018 (53.0% versus 34.1%, respectively) (Supplementary file 4.1). Disease activity was assessed at least once in 2018 in 185 out of 219 patients (84%) with the ASDAS, and in 214 out of 219 patients (98%) with the BASDAI (Figure 4.1 and Table 4.1). In patients with at least one available ASDAS or BASDAI score in 2018, the average age of the patients was 51 (SD 14) years at the first measurement, average symptom duration was 21 (SD 14) years and 41% were female (Table 4.2).

Table 4.1 Frequency of ASDAS or BASDAI measurements per patient during a 1-year period (2018)

ASDAS		BASDAI	
Number of measurements	**Frequency n (%)**	**Number of measurements**	**Frequency n (%)**
0	31 (14.4%)	0	2 (0.9%)
1	91 (42.1%)	1	101 (46.8%)
2	67 (31.0%)	2	69 (31.9%)
3	19 (8.8%)	3	32 (14.8%)
4	5 (2.3%)	4	6 (2.8%)
5	2 (0.9%)	5	2 (0.9%)
6	1 (0.5%)	6	3 (1.4%)
≥7	0 (0.0%)	≥7	1 (0.5%)

ASDAS = Ankylosing Spondylitis Disease Activity Score, BASDAI = Bath Ankylosing Spondylitis Disease Activity Index

Table 4.2 Patient and disease characteristics of patients at time of measurement of first ASDAS and/or BASDAI

	ASDAS					BASDAI				
	Total population with ≥1 ASDAS n = 185		ASDAS <2.1 n = 71 (38.4%)	ASDAS ≥2.1 n = 114 (61.6%)		Total population with ≥1 BASDAI n = 214		BASDAI <4.0 n = 83 (38.8%)	BASDAI ≥4.0 n = 131 (61.2%)	
Patient characteristics	**N patients**				**p-value**	**N patients**				**p-value**
Female, n (%)	76 (41.1)	185	23 (32.4)	53 (46.5)	0.06	88 (41.1)	214	29 (34.9)	59 (45.0)	0.14
Age, years	50.8 (13.8)	185	49.6 (14.6)	51.5 (13.3)	0.38	51.1 (13.7)	214	50.1 (14.2)	51.8 (13.4)	0.37
Occupational status					0.66					0.78
Employed, n (%)	67 (36.2)	-	29 (40.8)	38 (33.3)		70 (32.7)	-	31 (37.3)	39 (29.8)	
Retired, n (%)	13 (7.0)	-	6 (8.5)	7 (6.1)		14 (6.5)	-	6 (7.2)	8 (6.1)	
Disabled for work, n (%)	23 (12.4)	-	8 (11.3)	15 (13.2)		25 (11.7)	-	9 (10.8)	16 (12.2)	
Other, n (%)	9 (4.9)	-	2 (2.8)	7 (6.1)		10 (4.7)	-	3 (3.6)	7 (5.3)	
Unknown, n (%)	73 (39.5)	-	26 (36.6)	47 (41.2)		95 (44.4)	-	34 (41.0)	61 (46.6)	
Symptom duration, years	21.7 (13.6)	117	17.4 (12.7)	24.3 (13.6)	<0.01	21.1 (13.5)	129	17.5 (11.6)	23.3 (14.2)	<0.05
Disease duration, years	15.9 (12.9)	185	15.0 (13.1)	16.4 (12.8)	0.46	16.1 (12.9)	214	15.9 (13.4)	16.2 (12.7)	0.88
Current use of NSAIDs, n (%)	108 (58.4)	-	38 (53.5)	70 (61.4)	0.29	120 (56.1)	-	47 (56.6)	73 (55.7)	0.90
Current use of bDMARDs, n (%)	104 (56.2)	-	40 (56.3)	64 (56.1)	0.97	113 (52.8)	-	43 (51.8)	70 (53.4)	0.82
Number of current and prior bDMARDs					0.17					<0.05
None, n (%)	70 (37.8)	-	25 (35.2)	45 (39.5)		86 (40.2)	-	35 (42.2)	51 (38.9)	
1, n (%)	59 (31.9)	-	29 (40.8)	30 (26.3)		69 (32.2)	-	35 (39.8)	36 (27.5)	
2, n (%)	26 (14.1)	-	9 (12.7)	17 (14.9)		28 (13.1)	-	9 (10.8)	19 (14.5)	
≥3, n (%)	30 (16.2)	-	8 (11.3)	22 (19.3)		31 (14.5)	-	6 (7.2)	25 (19.1)	

[continued on next page]

Table 4.2 *[continued]*

	ASDAS					BASDAI				
	Total population with ≥1 ASDAS n = 185		ASDAS <2.1 n = 71 (38.4%)	ASDAS ≥2.1 n = 114 (61.6%)		Total population with ≥1 BASDAI n = 214		BASDAI <4.0 n = 83 (38.8%)	BASDAI ≥4.0 n = 131 (61.2%)	
Patient characteristics		**N patients**			**p-value**		**N patients**			**p-value**
Active peripheral arthritis (SJC66≥1), n (%)	6 (3.2)	84	0 (0.0)	6 (5.3)	<0.05	6 (2.8)	94	1 (1.2)	5 (3.8)	0.19
Active psoriasis (BSA ≥3%), n (%)	1 (0.5)	52	0 (0.0)	1 (0.9)	0.35	1 (0.5)	58	0 (0.0)	1 (0.8)	0.35
ASDAS (0-∞)*	2.4 (1.0)	185	1.4 (0.4)	3.0 (0.7)	<0.01	2.4 (1.0)	185	1.6 (0.6)	3.0 (0.7)	<0.01
BASDAI (0-10)	4.6 (2.1)	185	2.3 (1.2)	5.8 (1.6)	<0.01	4.6 (2.2)	214	2.4 (1.0)	6.0 (1.4)	<0.01
PGA (0-10)	4.5 (2.6)	185	2.4 (1.8)	5.7 (2.1)	<0.01	4.5 (2.6)	209	2.7 (1.9)	5.6 (2.4)	<0.01
CRP, mg/L (0-∞)	4.8 (7.0)	185	2.0 (1.7)	6.6 (8.4)	<0.01	4.8 (7.0)	188	3.6 (6.1)	5.6 (7.4)	<0.01
VAS pain (0-10)	4.3 (2.6)	71	2.3 (2.0)	5.7 (2.0)	<0.01	4.5 (2.7)	74	2.1 (1.8)	5.8 (2.1)	<0.01
PhGA (0-10)	1.8 (1.6)	79	1.2 (1.2)	2.2 (1.7)	<0.01	1.7 (1.5)	87	1.3 (1.3)	2.0 (1.6)	<0.05
ASAS-HI (0-17)	6.7 (3.3)	63	5.0 (3.1)	7.6 (3.0)	<0.01	6.9 (3.4)	66	5.0 (2.6)	7.8 (3.3)	<0.01
HAQ-S (0-3)	0.8 (0.5)	71	0.5 (0.4)	1.0 (0.5)	<0.01	0.9 (0.5)	74	0.5 (0.4)	1.1 (0.5)	<0.01
BASFI (0-10)	4.0 (2.3)	143	2.6 (1.7)	4.9 (2.2)	<0.01	4.2 (2.4)	165	2.5 (1.8)	5.1 (2.1)	<0.01
EQ-5D (0-1)	0.77 (0.19)	63	0.90 (0.10)	0.71 (0.19)	<0.01	0.76 (0.20)	66	0.86 (0.15)	0.71 (0.21)	<0.01
SF-36 MCS (0-100)	45.9 (12.6)	74	49.2 (13.2)	44.0 (11.9)	<0.05	45.9 (12.6)	79	51.1 (9.6)	43.1 (13.2)	<0.05
SF-36 PCS (0-100)	39.1 (9.5)	74	45.8 (7.4)	35.3 (8.4)	<0.01	38.7 (9.4)	79	44.2 (8.2)	35.8 (8.8)	<0.01

Values are expressed as mean (SD), unless stated otherwise.
Included number of patients might be lower due to missing outcome measures. Correlations are statistically significant at the 0.05 level (two-tailed). * On average, CRP levels were measured -1.4 (SD 5.7) days prior to completing the BASDAI.
ASAS-HI = Assessment of SpondyloArthritis international Society Health Index, ASDAS = Ankylosing Spondylitis Disease Activity Score, BASDAI = Bath Ankylosing Spondylitis Disease Activity Index, , BASFI = Bath Ankylosing Spondylitis Functional Index, bDMARDs = biological Disease-Modifying Antirheumatic drugs, BSA = Body Surface Area, CRP = C-Reactive Protein, EQ-5D = EuroQol 5D, HAQ-S = Health Assessment Questionnaire for Spondyloarthritis, MCS = Mental Component Summary, NSAIDs = Non-Steroid Anti-Inflammatory Drugs, PCS = Physical Component Summary, PGA = Patient Global Assessment, PhGA = Physician Global Assessment, SF-36 = Short Form 36 Health Survey, SJC66 = Swollen Joint Count of 66 joints, VAS= Visual Analog Scale

Table 4.3 Specifications of adapted treatment in patients with HDA at the first or second measurement within a 1-year period

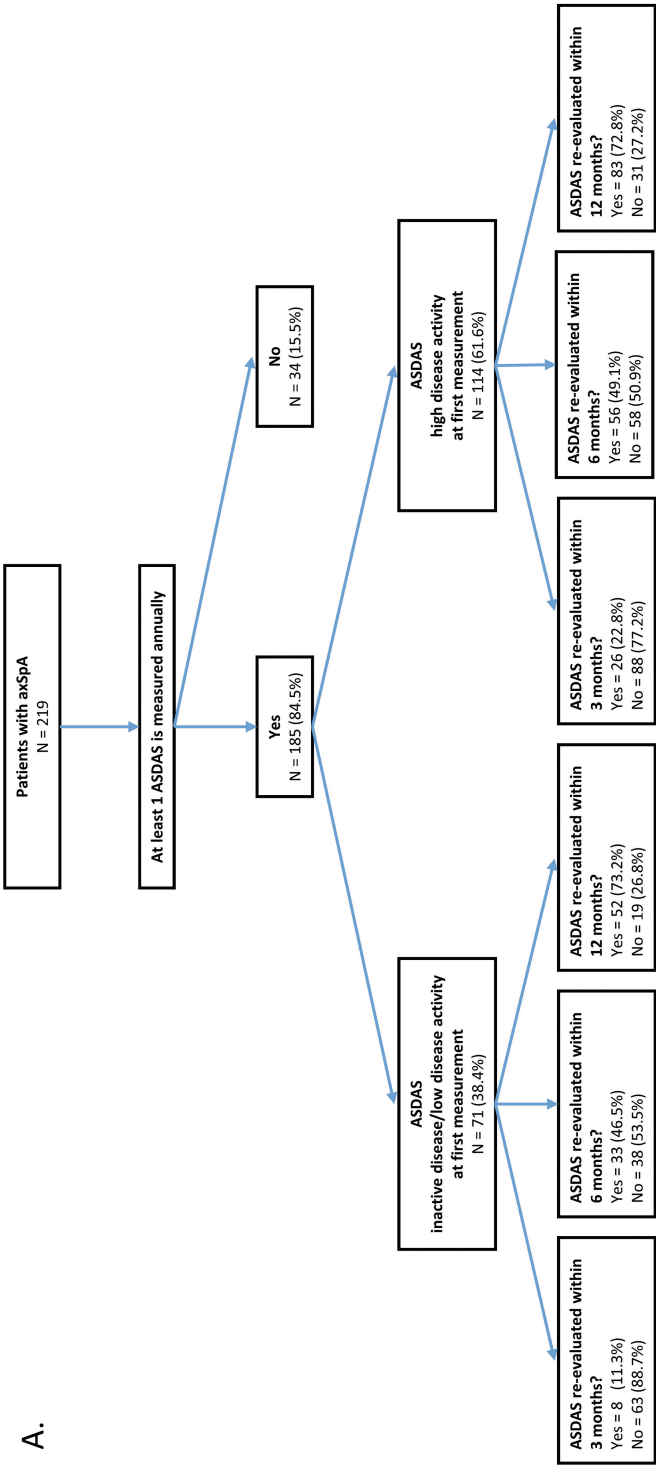
	Patients with ASDAS HDA (≥2.1) and adapted treatment N = 21	Patient with BASDAI HDA (≥4.0) and adapted treatment N = 21
Started (additional) treatment, n (%)	9 (42.9)	9 (42.9)
Intensifying dosage and/or frequency of drug treatment, n (%)	5 (23.8)	3 (14.3)
Switched within treatment class*, n (%)	6 (28.6)	8 (38.1)
Switched to another treatment class*, n (%)	1 (4.8)	1 (4.8)

*Treatments classes are non-steroid anti-inflammatory drugs, conventional synthetic disease-modifying antirheumatic drugs or biological disease-modifying antirheumatic drugs
ASDAS = Ankylosing Spondylitis Disease Activity Score, BASDAI = Bath Ankylosing Spondylitis Disease Activity Index, HDA = High Disease Activity

At the first measurement in 2018, 71 out of 185 patients (38%) had ID/LDA assessed with the ASDAS and 83 out of 214 patients (39%) had ID/LDA assessed with the BASDAI (Figure 4.1). The mean symptom duration was significantly lower in patients with ID/LDA compared to patients with HDA and patients with ID/LDA were more often male (Table 4.2). Scores for outcome measures assessing disease activity, physical function and overall functioning and health were significantly better in patients with ID/LDA compared to patients with HDA. Patient and disease characteristics of patients with BASDAI ID/LDA or HDA were comparable to ASDAS ID/LDA or HDA (Table 4.2).

In patients who had HDA at the first measurement, the ASDAS was re-evaluated within 3, 6 or 12 months in 26, 56 and 83 out of 114 patients (23%, 49% and 73%, respectively) and the BASDAI in 34, 76, and 105 out of 131 patients (26%, 58% and 80%, respectively) (Figure 4.1). The proportions of patients in whom disease activity was re-evaluated within 3 months was higher for patients with HDA compared to ID/LDA (23% versus 11% with the ASDAS and 26% and 19% with the BASDAI), while the proportions of patients in whom disease activity was re-evaluated within 6 or 12 months were comparable in patients with ID/LDA and HDA (Figure 4.1).

A.


Patients with axSpA
N = 219
At least 1 ASDAS is measured annually
No
N = 34 (15.5%)
Yes
N = 185 (84.5%)
ASDAS
inactive disease/low disease activity
at first measurement
N = 71 (38.4%)
ASDAS
high disease activity
at first measurement
N = 114 (61.6%)
ASDAS re-evaluated within
3 months?
Yes = 8 (11.3%)
No = 63 (88.7%)
ASDAS re-evaluated within
6 months?
Yes = 33 (46.5%)
No = 38 (53.5%)
ASDAS re-evaluated within
12 months?
Yes = 52 (73.2%)
No = 19 (26.8%)
ASDAS re-evaluated within
3 months?
Yes = 26 (22.8%)
No = 88 (77.2%)
ASDAS re-evaluated within
6 months?
Yes = 56 (49.1%)
No = 58 (50.9%)
ASDAS re-evaluated within
12 months?
Yes = 83 (72.8%)
No = 31 (27.2%)

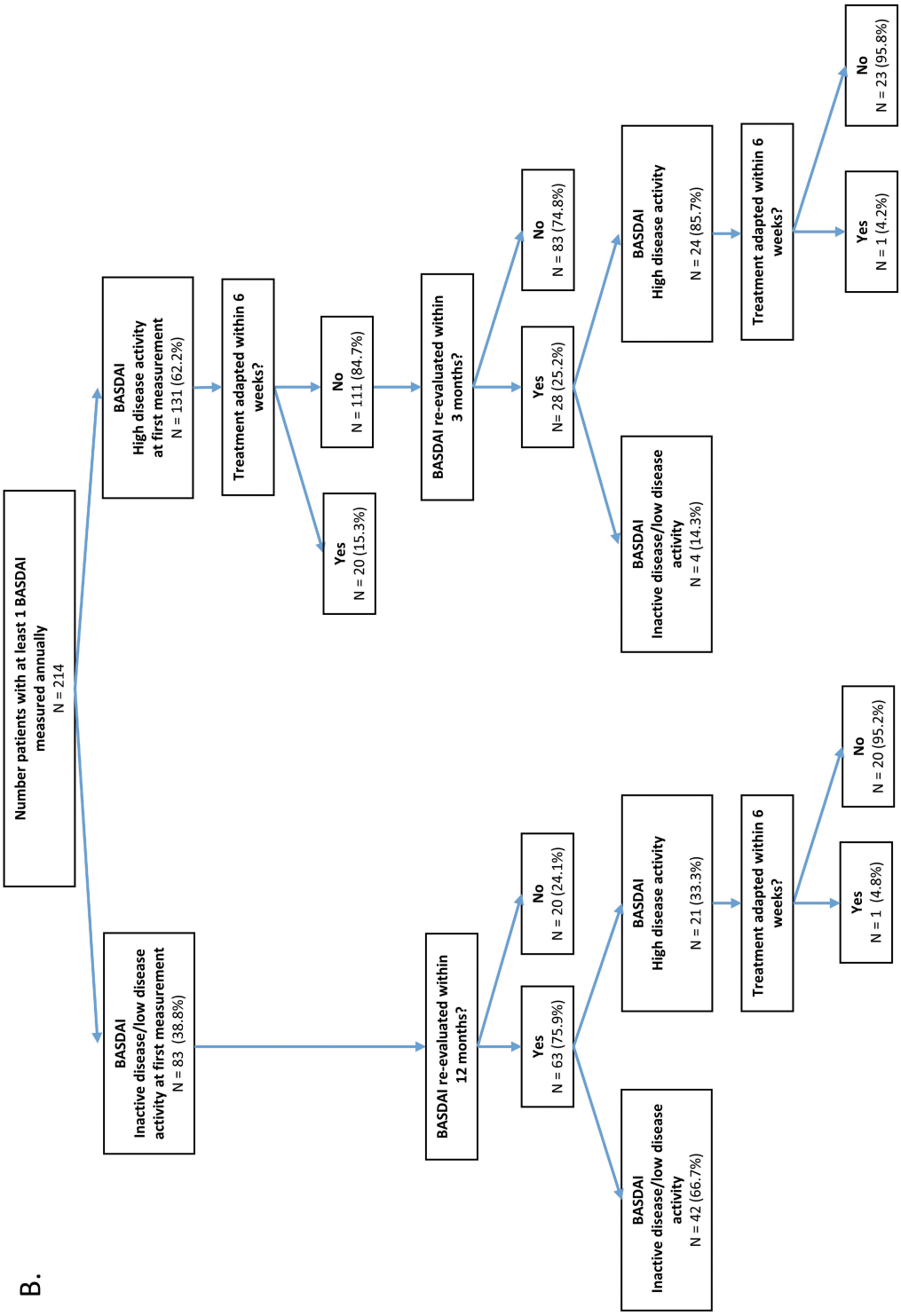
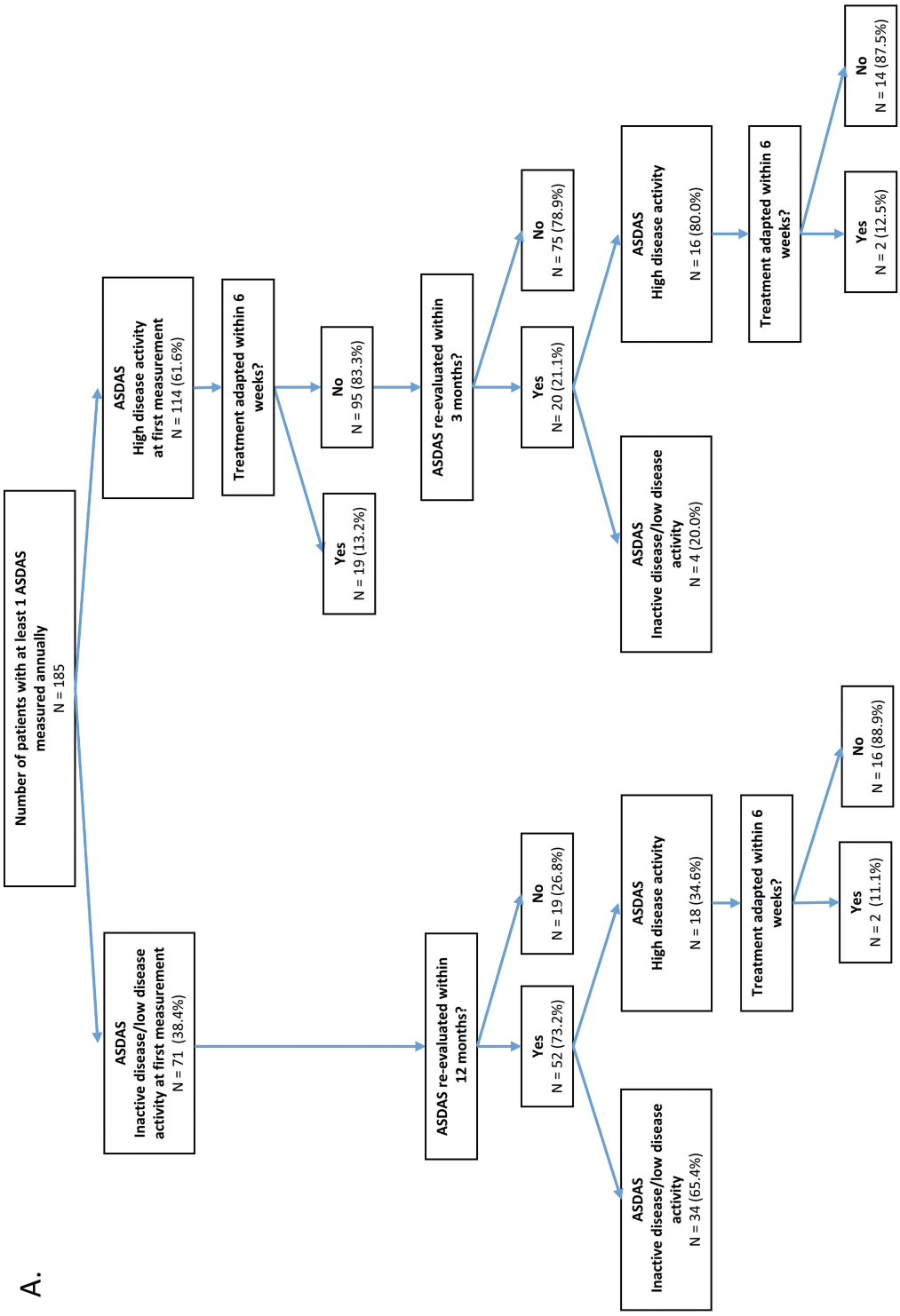


Figure 4.1 Flowchart of patients with axial SpA and measurements of ASDAS (A) and BASDAI (B) in SpA-Net

A.


Number of patients with at least 1 ASDAS measured annually
N = 185
ASDAS
Inactive disease/low disease activity at first measurement
N = 71 (38.4%)
ASDAS re-evaluated within 12 months?
Yes
N = 52 (73.2%)
No
N = 19 (26.8%)
ASDAS
Inactive disease/low disease activity
N = 34 (65.4%)
ASDAS
High disease activity
N = 18 (34.6%)
Treatment adapted within 6 weeks?
Yes
N = 2 (11.1%)
No
N = 16 (88.9%)
ASDAS
High disease activity at first measurement
N = 114 (61.6%)
Treatment adapted within 6 weeks?
Yes
N = 19 (13.2%)
No
N = 95 (83.3%)
ASDAS re-evaluated within 3 months?
Yes
N= 20 (21.1%)
No
N = 75 (78.9%)
ASDAS
Inactive disease/low disease activity
N = 4 (20.0%)
ASDAS
High disease activity
N = 16 (80.0%)
Treatment adapted within 6 weeks?
Yes
N = 2 (12.5%)
No
N = 14 (87.5%)

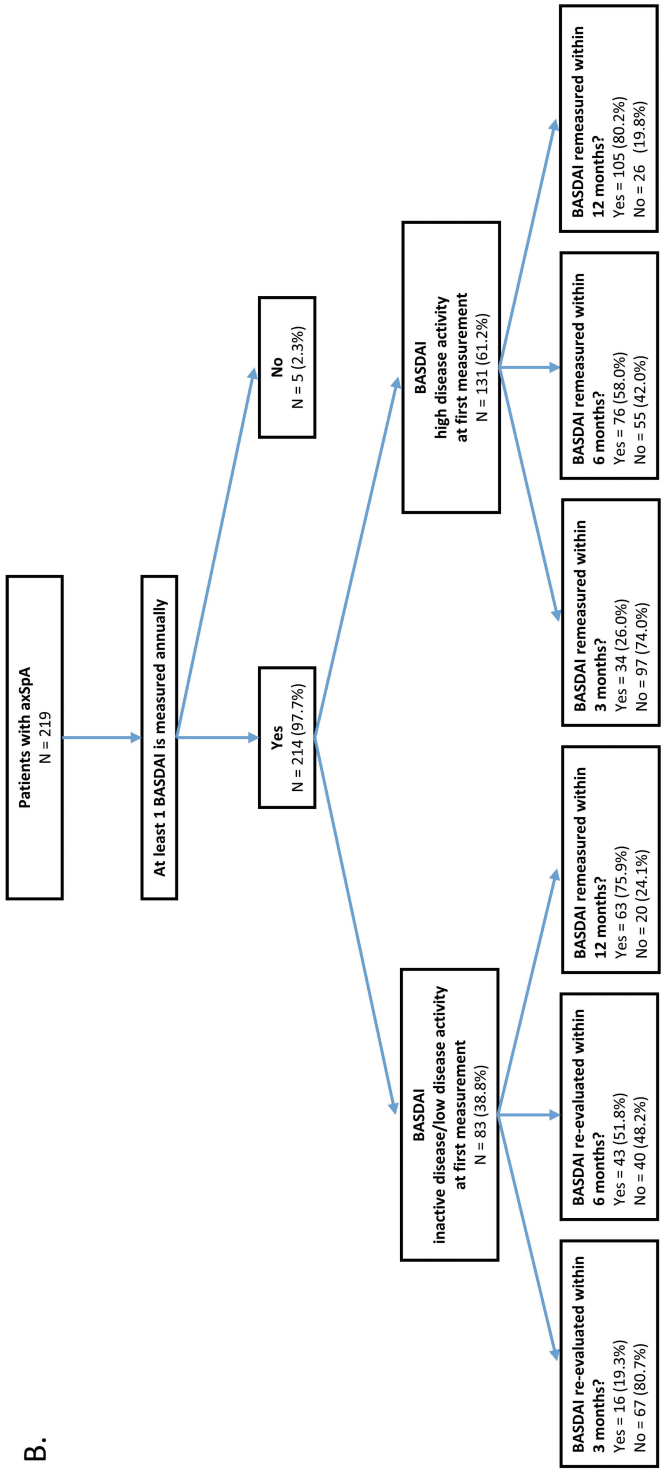


Figure 4.2 Flowchart of patients, re-evaluations and treatment adaptations based on ASDAS (A) and BASDAI (B)

In patients with ASDAS or BASDAI HDA at the first measurement, treatment was adapted within 6 weeks in, respectively, 19 out of 114 (13%) patients and 20 out of 131 (15%) patients (Figure 4.2). For ASDAS HDA, this was done within the first week in 12 out of 19 (63%) patients, in the second week in 3 out of 19 (16%) patients and between the third and sixth week in 4 out of 19 (21%) patients. In 5 out of 21 patients (24%) with treatment adaptations at either the first or second measurement, the dosage and/or frequency of administration of the drug was increased (Table 4.3). In 2 out of 16 (13%) patients without treatment adaptations despite HDA after the first measurement and with persistent ASDAS HDA at the next measurement, treatment was adapted after this second measurement (Figure 4.2). Interestingly, in 8 out of the 114 patients (7%) with ASDAS HDA at the first measurement, the treatment was decreased (n=3) or (partially) discontinued (n=5) within 6 weeks. Reasons for this were that the disease activity was considered low by the physician (i.e. HDA state was not related to axial SpA manifestations, n=3), drug ineffectiveness (n=2), drug side effects (n=1) or unknown reasons (n=1)).

In patients with ASDAS HDA and treatment intensification, the ASDAS, CRP and Physician Global Assessment (PhGA) were significantly higher and the Patient Global Assessment (PGA) was numerically, but non-significantly, higher compared to patients with ASDAS HDA in whom treatment was not adapted (Table 4.4). Similarly, in patients with BASDAI HDA having a treatment intensification, the ASDAS, PGA, CRP and PhGA were significantly higher compared to patients with BASDAI HDA in whom treatment was not adapted (Table 4.4).

Thirteen out of 52 (25%) patients with ASDAS ID/LDA at the first measurement and in whom the ASDAS was re-evaluated within 1 year, had a clinically important worsening leading to HDA. In 2 out of these 13 (15%) patients, treatment was intensified.

Table 4.4 Comparison of characteristics of patients with HDA in whom treatment was adapted or not adapted

	ASDAS ≥2.1			**BASDAI ≥4.0**		
Patient and disease characteristics	Treatment not adapted n = 93	Treatment adapted n = 21	p-value	Treatment not adapted n = 110	Treatment adapted n = 21	p-value
Female, n (%)	44 (47.3)	9 (42.9)	0.81	51 (46.4)	8 (38.1)	0.33
Age, years	51.8 (13.5)	50.0 (12.2)	0.58	52.3 (13.7)	49.1 (12.0)	0.32
Occupational status			0.10			0.16
Employed, n (%)	31 (33.3)	7 (33.3)	-	31 (28.2)	8 (38.1)	-
Retired, n (%)	7 (7.5)	0 (0.0)	-	8 (7.3)	0 (0.0)	-
Disabled for work, n (%)	9 (9.7)	6 (28.6)	-	11 (10.0)	5 (23.8)	-
Other, n (%)	7 (7.5)	0 (0.0)	-	7 (6.4)	0 (0.0)	-
Unknown, n (%)	39 (41.9)	8 (38.1)	-	53 (48.2)	8 (38.1)	-

[continued on next page]

Table 4.4 *[continued]*

Patient and disease characteristics	ASDAS ≥2.1			BASDAI ≥4.0		
	Treatment not adapted n = 93	Treatment adapted n = 21	p-value	Treatment not adapted n = 110	Treatment adapted n = 21	p-value
Symptom duration, years	24.6 (13.9)	22.8 (12.7)	0.73	23.9 (14.1)	20.4 (14.7)	0.45
Disease duration, years	16.6 (13.2)	15.5 (11.4)	0.80	16.8 (12.8)	13.2 (11.7)	0.14
Current use of NSAIDs, n (%)	57 (61.3)	13 (61.9)	1.00	59 (53.6)	14 (66.7)	0.34
Current use of bDMARDs, n (%)	49 (52.7)	15 (71.4)	0.15	57 (51.8)	13 (61.9)	0.48
Number of current and prior used bDMARDs			0.19			<0.05
None, n (%)	39 (41.9)	6 (28.6)	-	45 (40.9)	6 (28.6)	-
1, n (%)	22 (23.7)	8 (38.1)	-	25 (22.7)	11 (52.4)	-
2, n (%)	12 (12.9)	5 (23.8)	-	17 (15.5)	2 (9.5)	-
≥3, n (%)	20 (21.5)	2 (9.5)	-	23 (20.9)	2 (9.5)	-
Active peripheral arthritis (SJC66>=1), n (%)	4 (4.3)	2 (9.5)	0.52	3 (2.7)	2 (9.5)	0.39
Active psoriasis (BSA >=3%), n (%)	1 (1.1)	0 (0.0)	0.64	0 (0.0)	0 (0.0)	0.65
ASDAS	2.9 (0.6)	3.4 (0.7)	<0.01	2.9 (0.7)	3.4 (0.8)	<0.01
BASDAI (0-10)	5.7 (1.6)	6.0 (1.7)	0.50	6.0 (1.4)	6.3 (1.3)	0.21
PGA (0-10)	5.6 (2.1)	6.5 (1.7)	0.06	5.4 (2.4)	6.8 (1.9)	<0.05
CRP, mg/L (0-∞)	6.0 (8.2)	8.9 (9.1)	<0.05	5.0 (6.9)	8.5 (9.1)	<0.05
VAS pain (0-10)	5.5 (2.1)	6.3 (1.7)	0.26	5.7 (2.1)	6.7 (1.7)	0.15
PhGA (0-10)	1.8 (1.4)	3.3 (1.9)	<0.05	1.6 (1.4)	3.0 (2.0)	<0.05
ASAS-HI (0-17)	7.5 (2.7)	8.0 (3.9)	0.62	7.5 (3.3)	9.0 (3.2)	0.22
HAQ-S (0-3)	1.0 (0.5)	1.1 (0.5)	0.50	1.1 (0.5)	1.1 (0.5)	0.88
BASFI (0-10)	4.9 (2.2)	5.0 (2.4)	0.84	5.1 (2.1)	5.4 (2.2)	0.61
EQ-5D (0-1)	0.70 (0.21)	0.73 (0.13)	0.96	0.70 (0.22)	0.72 (0.13)	0.68
SF-36 MCS (0-100)	44.2 (12.8)	42.8 (9.6)	0.73	44.2 (12.9)	38.3 (13.7)	0.19
SF-36 PCS (0-100)	35.6 (8.7)	33.5 (8.3)	0.48	35.8 (8.9)	34.9 (9.9)	0.75

Values are expressed as mean (SD), unless stated otherwise, Included number of patients might be lower due to missing outcome measures, Correlations are statistically significant at the 0.05 level (two-tailed).
ASAS-HI = Assessment of SpondyloArthritis international Society Health Index, ASDAS = Ankylosing Spondylitis Disease Activity Score, BASDAI = Bath Ankylosing Spondylitis Disease Activity Index, BASFI = Bath Ankylosing Spondylitis Functional Index, bDMARD = biological Disease-Modifying Antitrheumatic Drug, BSA = Body Surface Area,
CRP = C-Reactive Protein, EQ-5D = EuroQol 5D, HAQ-S = Health Assessment Questionnaire for Spondyloarthritis, MCS = Mental Component Score, NSAID = Non-Steroidal Anti Inflammatory Drug, PCS = Physical Component Score, PGA = Patient Global Assessment, PhGA = Physician Global Assessment, SF-36 = Short Form 36 Health Survey, VAS= Visual Analog Scale

Discussion

This study showed that T2T is applied to a limited extent in clinical practice although a dashboard with disease activity scores was available supporting both healthcare providers and patients. Disease activity was monitored at least once during a 1-year period in 84% of the patients with the ASDAS and in nearly all patients with the BASDAI. However, the available scores for disease activity did not appear to be used to drive re-evaluation nor treatment adaptation. In less than a quarter of the patients with HDA, ASDAS was re-evaluated within the recommended time period of 3 months, and treatment was adapted in a small proportion of patients with HDA measured at one or two consecutive occasions. Also, clinically important worsening in ASDAS and consequently obtaining an HDA state did not appear to be used for making treatment decisions as advised by experts from ASAS[9]. Analyses using the BASDAI instead of the ASDAS showed comparable results.

A T2T approach might not have been applied as the T2T recommendations have no official status, despite international agreement, were relatively new at the start of the study period, and were not yet justified by an randomized controlled trial (RCT). Recently, the first results of an RCT evaluating the effect of application of T2T in axial SpA towards predefined disease activity targets on health status, compared to routine care, were presented (Tight Control in SpA, TICOSPA, NCT03043846)[23]. Although the primary endpoint (statistically significant difference of ≥30% improvement in the ASAS Health Index between T2T and usual care group) was not met, outcome measures for disease activity, physical functioning and HR-QoL showed a general trend in favour of T2T with a comparable safety profile. T2T was also found to be favourable from a health economics perspective.

In clinical practice, monitoring of disease activity within pre-defined time periods can be hampered as healthcare providers and patients might not use an electronic monitoring tool due to lack of availability of such a system, lack of time, motivation or experience. The results of our study are in line with a 2015 UK physician survey that estimated that a limited proportion of healthcare providers use a T2T approach or routinely include specific assessments in patients with psoriatic arthritis (PsA)[24]. In addition, partial implementation of T2T recommendations is also still seen in patients with rheumatoid arthritis (RA) for whom applying T2T has been strongly being advised now for over 10 years[25]. The implementation of T2T in these patients was not universal, differed between specific recommendations and decreased over time[26]. Furthermore, a discrepancy between rheumatologists agreeing with EULAR/T2T recommendations for patients with RA and their actual performance in clinical practice was observed in an international study[27].

Interpretation of the limited extent to which T2T is applied remains speculative, as it is unknown whether the lack of implementation is intentional or unintentional. Patients or healthcare providers could decide to continue pharmacological treatment in patients with HDA for several reasons, for example, non-pharmacological treatment could have been initiated or intensified, irrespective of provided pharmacological treatment[1]. Treatment could also be guided

towards alternative treatment targets in patients who are unlikely to achieve ID/LDA, such as patients with severe irreversible damage[28]. Alternatively, healthcare providers and patients might expect that disease activity will decrease without treatment intensification as a result of natural disease fluctuations[29]. The latter was also seen in our study: approximately 20% of the patients with HDA at the first measurement had ID/LDA at a consecutive measurement without treatment modification. Furthermore, patients may be reluctant to adapt their current treatment, because of beliefs about potential ineffectiveness of alternative treatment options or worries about potential adverse side effects of a new treatment[30]. Finally, it is possible that the pharmacological treatment in some patients with HDA is decreased or (partially) discontinued instead of intensified because of non-response or adverse side effects[31]. In our study, >20% of the patients with ASDAS HDA without treatment intensification had a medication history of ≥3 bDMARDs as opposed to 10% in those patients with treatment intensification. We also saw that treatment was decreased or (partially) discontinued in 7% of the patients with ASDAS HDA at the first measurement for various reasons.

Implementation of T2T guidelines in practice remains challenging. The above illustrates that barriers to application of a T2T approach can be found at several levels, for example the structure of the local health care and perceptions and preferences of the patients and physicians[26]. As a next step, we would therefore recommend developing studies identifying such barriers, but also facilitators for successful application of T2T in axial SpA in practice, after which a multifaceted implementation strategy should be developed[32, 33].

An important limitation of our study is that data were collected in centers with an online EMR available, and results were not compared to centers without an online EMR available, which might affect the generalizability of the results. In addition, it is possible that patients had a visit that was not logged in SpA-Net as using this patient registry is voluntary for both patients and physicians. Furthermore, modifications in non-pharmacological treatments were not considered, however, but these are also an important treatment aspect in axial SpA.

In conclusion, T2T was applied to a limited extent in patients with axial SpA in daily clinical practice, in a setting where healthcare providers were supported by an electronic monitoring tool. Measured disease activity scores seemed not to be used in accordance with T2T recommendations as re-evaluation within recommended intervals and treatment modifications occurred only in a small proportion of patients with HDA.

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CHAPTER 5

Fatigue in patients with rheumatic and musculoskeletal diseases: A scoping review on definitions, measurement instruments, determinants, consequences and interventions

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RMD Open, 2023

Abstract

Objectives

To scope published reviews addressing fatigue in rheumatoid arthritis (RA), spondyloarthritis (SpA), osteoarthritis and fibromyalgia in areas relevant for clinical practice: 1) definition, 2) measurement instruments and diagnosis, 3) determinants, 4) consequences and 5) effectiveness of interventions.

Methods

A systematic literature search of reviews was performed in 5 bibliographical databases. A hierarchical data extraction was applied based on review type (Cochrane reviews (CRs), followed by non-Cochrane systematic reviews (SRs) and narrative reviews (NRs)) and year of publication. Extracted data were summarised in elaborated narrative syntheses. Results were discussed with a patient panel.

Results

One hundred thirty-four reviews were included (19 CRs, 44 SRs, 71 NRs). No agreed upon definition was reported for general fatigue, nor for types of fatigue. Twenty-five measurement instruments were found, all self-reported. Five instruments proposed a threshold for excessive fatigue. Pain, physical function, and depressive symptoms were the most frequently studied disease-related determinants of fatigue; female sex and stress the most frequent contextual determinants. Work performance, followed by impact on pain, physical activity and social roles were the most frequently studied consequences. Whenever quantified, associations between fatigue with determinants and consequences were on average small. For non-pharmacological interventions, if effect sizes were reported, these were negligible to small and for pharmacological interventions negligible to moderate. Patients recommended actions for research and practice.

Conclusion

Syntheses of reviews point to the complexity of fatigue. The extensive amount of evidence could be used to offer tailored management plans to patients in clinical practice and inform future research agendas.

Introduction

Over two-thirds of patients with RMDs experience severe or very severe fatigue and patients with RMDs are more affected by fatigue compared to the general population[1-4]. Many patients feel that fatigue surpasses pain as a source of disability and that this symptom is insufficiently addressed by healthcare providers[3].

In continuous efforts to improve quality of care for patients with rheumatic and musculoskeletal diseases (RMDs), the Dutch Arthritis Society organised panel discussions among patients with RMDs to gain insight into the knowledge gaps that should be addressed to improve daily care. Patients ranked 'fatigue and its treatment' as the area with the highest priority[5].

To further specify the knowledge gap related to managing fatigue in clinical practice, the patient panel formulated 15 research questions that were subsequently summarised in 5 research areas including: (i) the definitions of fatigue; (ii) measurement instruments to quantify and diagnose fatigue; (iii) determinants of fatigue; (iv) consequences of fatigue; and (v) the effect of interventions on fatigue (Supplementary file 5.1).

The number of peer-reviewed clinical studies addressing fatigue in RMDs is substantial and many studies have already been summarised in literature reviews. Notwithstanding, knowledge across various research areas remains fragmented, as studies/reviews frequently focus on one rheumatic condition or address a specific topic in a larger research area. As a result, the available knowledge from various areas is insufficiently integrated and fails to recognise differences and similarities related to fatigue across RMDs. This fragmentation also hampers translation of knowledge into the management of fatigue and hinders identification of potentially unaddressed research questions. It was therefore decided to perform a scoping review of all available reviews that addresses the 5 agreed upon research areas.

A scoping review is a relatively new approach for mapping the existing literature in a given field[6]. Scoping reviews can be performed to summarise and disseminate research findings, to identify research gaps, and to make recommendations for future research. Quality assessments of underlying studies are no part of scoping reviews, as they aim to map the availability of these studies but not their robustness or generalizability[6].

The objective of this study was to perform a scoping review of published literature reviews addressing the five pre-identified research areas on fatigue in patients with rheumatoid arthritis (RA), spondyloarthritis (SpA, including psoriatic arthritis (PsA)), osteoarthritis (OA) and fibromyalgia (FM).

Methods

This scoping review was performed according to the methodological framework for scoping reviews by Arksey and O'Malley[6]. The research protocol was registered in the Registry for

Scoping Reviews (OSF, https://osf.io/3dr7b/). This paper was written in compliance with the Preferred Reporting Items for Systematic reviews and Meta-Analyses extension for Scoping Reviews (PRISMA-ScR) Checklist[7].

Literature search

A systematic literature search was performed in December 2020 and updated in December 2021 in the following 5 electronic bibliographical databases: MEDLINE (PubMed), EMBASE, the Cochrane Library for Reviews, CINAHL and PsycINFO. The search string contained the following search terms: 1) 'review', 2) 'fatigue', 3) 'rheumatoid arthritis' or 'spondyloarthritis' or 'psoriatic arthritis' or 'osteoarthritis' or 'fibromyalgia'. These search terms were specified by including synonyms and by transforming all relevant search terms to be compatible with each database (Supplementary file 5.2). The search was restricted to English and Dutch language. Reference lists of included reviews were screened for additional eligible reviews.

Eligibility criteria

Reviews were eligible if they considered adult patients with RA, SpA, OA or FM (by clinical diagnosis or by fulfilling classification criteria), and reported a quantitative or narrative synthesis of studies addressing one of the 5 research areas (15 research questions, Supplementary file 5.1). No restrictions were applied for the year of publication or type of review, and thus included Cochrane reviews (CRs), as well as non-Cochrane systematic reviews (SRs) and narrative reviews (NRs). Also, for underlying studies within the reviews, no restrictions were formulated concerning their setting (e.g. population surveys, rheumatology clinic), study design (e.g. quantitative or qualitative; prospective or retrospective; observational or experimental study design) or fatigue being a primary or concomitant objective of the reviews.

Review selection

Records were imported into Rayyan software and duplicates were removed[8]. Two reviewers (EB and KH) independently screened all selected records based on titles and abstracts for eligibility (Supplementary file 5.3). Next, one reviewer (EB) screened the full text articles and decided whether the eligibility criteria were met. Arguments for exclusion were checked by the second reviewer (KH). Disagreement was resolved by consensus in the presence of a third reviewer (AvT).

Data extraction

Standardised data extraction forms were in line with the Cochrane Collaboration's recommendations for systematic reviews for each of the 5 research areas[9]. Extraction forms were piloted and adapted for the purpose of evaluating reviews (e.g. the number of underlying studies, availability and results of pooled estimates for associations or effect sizes). Data extraction was performed by one reviewer (EB) and was checked by the second reviewer (KH) for 50% of the reviews. The data extraction was performed in a hierarchical approach based on review type (CRs followed by SRs, followed by NRs) and year of publication (from most recent to least recent). For example, SRs and NRs were not considered if a CR on a similar research question was

more recently published. In addition, reviews were excluded when there was (partial) overlap in underlying studies with other reviews, in that case the most complete review was included.

Data synthesis and reporting

Extracted data of each review were reported in an elaborated narrative synthesis stratified per research area and for each RMD separately (Supplementary files 5.4-5.18).

To facilitate synthesis for the research areas 'determinants' and 'consequences', individual 'determinants' or 'consequences' were categorised using the International Classification of Functioning, Disability and Health (ICF) as guidance[10]. The formal ICF linking rules could not be strictly applied, because determinants that actually belonged to separate ICF categories were often grouped for the purpose of the included reviews. Therefore, determinants and consequences were classified into the main ICF components (Body functions combined with Body Structures, Activities, Participation, Contextual personal factors and Contextual environmental factors) while further keeping the terminology (of grouped determinants/consequences) as in the reviews. For some studies within the reviews, it was unclear whether the factor studied was a 'determinant' or 'consequence', especially when underlying studies had a cross-sectional design. Whenever insufficiently reported in the review, factors were classified as determinants.

For each determinant of fatigue, bubble plots were computed per RMD of interest to summarise the number of unique underlying studies across reviews (bubble size) together with the overall direction of the association (positive, negative, absent or inconsistent association with fatigue).

For interventions, findings were reported separately for non-pharmacological and pharmacological interventions. Non-pharmacological interventions were reported per intervention type and pharmacological interventions were reported per drug class. Whenever available, quantitative findings were reported as formulated in each review (e.g. characteristics of measurement instruments, strength of associations (weak, moderate or strong) or effect sizes (small, moderate or large)).

Patient and public involvement

Two meetings were organised to discuss the results of this study with the patient discussion panel on fatigue from the Dutch Arthritis Society. In preparation, all participants received summaries of (preliminary) findings. At the first meeting, the types of fatigue most frequently encountered within reviews were preliminarily classified and subsequently discussed with the patient panel (as that part of the data extraction was finished). In the second meeting, the final results were presented, and the patient panel helped interpreting our findings on the research questions and identifying new knowledge gaps.

Results

Overall, 134 reviews were included (19 CRs, 44 SRs and 71 NRs, Supplementary file 5.4). Of these, 54/134 (40%) reviews addressed fatigue as the primary objective, and 45/134 (34%) reviews considered fatigue in RA. Table 5.1 shows the total number of included reviews per different review type for each research area and RMD of interest. CRs only reported on non-pharmacological and pharmacological interventions, whereas SRs and NRs also addressed other research areas.

Definition of fatigue

Fatigue in RMDs was defined in 16 NRs. Across reviews, there was agreement that fatigue is a complex, highly subjective symptom, including various types with specific characteristics that can occur simultaneously or alternatingly in daily life[3, 11-14]. Fatigue can therefore be defined and expressed differently over time within one person, among persons with the same RMD or different RMDs. The reviews differentiate fatigue in several ways, including acute versus chronic fatigue, central versus peripheral and spinal fatigue, normal versus pathological fatigue, and various definitions have been provided for fatigue in general (Table 5.2) and different types of fatigue. However, no agreed upon definition for fatigue or (any of the) different types of fatigue were found for any RMD (Supplementary file 5.5). Figure 5.1 attempts to synthesise the types of fatigue identified in studies in RMDs. Many papers distinguish between physical and mental fatigue. Described subtypes for physical fatigue include asthenia, fatigability and muscle weakness, and for mental fatigue this includes weariness and cognitive fatigue (Figure 5.1).

Table 5.1 Included reviews covering one or more research areas and/or RMDs

Research areas	Cochrane reviews n=19	Systematic reviews n=44	Narrative reviews n=71
Definition of fatigue n=16*			
■ RA	-	-	4 (4)
■ SpA	-	-	2 (2)
■ OA	-	-	2 (2)
■ FM	-	-	4 (3)
■ Mixed RMDs	-	-	5 (5)
Measurement instruments for fatigue n=26*			
■ RA	-	2 (1)	7 (5)
■ SpA	-	2 (0)	7 (3)
■ OA	-	1 (0)	1 (1)
■ FM	-	1 (0)	5 (2)
■ Mixed RMDs	-	-	1 (1)

[continued on next page]

Table 5.1 *[continued]*

Research areas	Cochrane reviews n=19	Systematic reviews n=44	Narrative reviews n=71
Determinants of fatigue n=28*			
■ RA	-	4 (4)	9 (7)
■ SpA	-	1 (0)	6 (3)
■ OA	-	-	3 (2)
■ FM	-	-	6 (3)
■ Mixed RMDs	-	-	-
Consequences of fatigue n=21*			
■ RA	-	4 (3)	11 (7)
■ SpA	-	1 (0)	3 (1)
■ OA	-	-	3 (2)
■ FM	-	-	-
■ Mixed RMDs	-	-	-
Non-pharmacological interventions n=39			
■ RA	1 (1)	1 (0)	2 (2)
■ SpA	1 (1)	1 (0)	2 (1)
■ OA	-	2 (0)	1 (1)
■ FM	10 (5)	14 (5)	4 (2)
■ Mixed RMDs	-	-	-
Pharmacological interventions n=39			
■ RA	1 (1)	3 (1)	9 (3)
■ SpA	-	2 (0)	5 (1)
■ OA	-	-	-
■ FM	6 (1)	8 (1)	5 (0)
■ Mixed RMDs	-	-	-

Number of included reviews (number of reviews including fatigue in their primary objective)
*Reported sum of reviews is not equal to the individual number of reviews per research area and review type, because some reviews cover one or more research areas and/or RMDs
References of all included reviews can be found in Supplementary file 5.4
FM = Fibromyalgia, OA = Osteoarthritis, PsA = Psoriatic Arthritis, RA = Rheumatoid Arthritis, RMDs = Rheumatic and musculoskeletal diseases, SpA = Spondyloarthritis

Table 5.2. Definitions of general fatigue reported in the included reviews

Included reviews†	Year of publication	Review type	Population	Reported definitions of fatigue in the included reviews*
Seifert, *et al.*	2019	NR	RMDs	■ An overwhelming, debilitating, and sustained sense of exhaustion that decreases the ability to function and carry out daily activities.
Dupond, *et al.*	2011	NR	RMDs	■ Perceiving an inability and surrendering to it.
Stebbings, *et al.*	2010	NR	RA and OA	■ Extreme tiredness, typically resulting from mental or physical exertion or illness. ■ A subjective, unpleasant symptom which incorporates total body feelings, ranging from tiredness to extreme exhaustion, creating an unrelenting overall condition which interferes with an individual's ability to function to their normal capacity.
Marrelli, *et al.*	2018	NR	RA	■ A state of exhaustion and decreased strength accompanied by a feeling of weariness, sleepiness and irritability, with a cognitive component.
Balsamo, *et al.*	2014	NR	RA	■ The enduring sensation of weakness, lack of energy, tiredness or exhaustion.
Rosen, *et al.*	2016	NR	SpA (PsA)	■ An overwhelming, sustained sense of exhaustion and decreased capacity for physical and mental work.
Hackney, *et al.*	2019	NR	OA	■ An overwhelming, debilitating, and sustained exhaustion that decreases one's ability to carry out daily activities, including the ability to work effectively and to function at one's usual level in family or social roles.
Casale, *et al.*	2011	NR	FM	■ A transient phenomenon caused by physical activity and which lead to an inability to maintain the requisite or expected force. ■ An acute impairment in performances that includes both an increase in the perceived effort necessary to exert a desired force and an eventual inability to produce this force. ■ A condition related to an exercise-induced reduction in the ability to produce force, which determines whether or not the task can be maintained. ■ A state where one is drained of strength and energy: fatigued often to the point of exhaustion (task failure).

† Complete references are provided in Supplementary file 5.5, as well as definitions of different types of fatigue.
* Minor textual adaptations were made for consistency reasons.
FM = Fibromyalgia, OA = Osteoarthritis, PsA = Psoriatic Arthritis, RA = Rheumatoid Arthritis, RMDs = Rheumatic and musculoskeletal diseases, SpA = Spondyloarthritis

Measurement instruments for fatigue

Measurement instruments for fatigue and their characteristics were addressed in 26/134 (19%) of the included reviews (6 SRs and 20 NRs). The majority of the information was retrieved from one narrative review by Elera-Fitzcarrald et al. that describes instruments used to assess fatigue in patients with RMDs[15]. References of all included reviews for this research area are available in Supplementary file 5.4.

Across reviews, 3 disease-specific (2 for RA and 1 for RA, SpA, OA and FM) and 22 generic self-reported measurement instruments were described (Supplementary file 5.6). Of these, 10/25 (40%) instruments aimed to be used in research settings, 7 (28%) were validated for use in both clinical and research settings and for the remaining 8 (32%) instruments this was not reported in the reviews. More than half of the available instruments (13/25; 52%) were single questions assessing overall fatigue, while the other instruments were multi-dimensional, i.e. assessing one or more types of fatigue. Fatigue as a single item was sometimes part of patient-reported outcomes assessing other health domains, e.g. a question on fatigue is part of the Rheumatoid Arthritis Impact of Disease (RAID), the Bath Ankylosing Spondylitis Disease Activity Index (BASDAI), the Psoriatic Arthritis Impact of Disease (PsAID) and the Fibromyalgia Impact Questionnaire (FIQ)[16-19]. One NR reported that the most frequently used measurement instruments for assessing fatigue in RMDs were the Functional Assessment of Chronic Illness Therapy Fatigue (FACIT-F), Fatigue Severity Scale (FSS), Multidimensional assessment of fatigue (MAF) and fatigue on a Visual Analogue Scale (VAS Fatigue)[15].

For 5 instruments (5/25; 25%), validated cut-off values to diagnose or classify 'excessive fatigue' were available. Of note, this was the case for only 1 instrument (single item 0-10 rating scale) that was proposed for use in clinical practice. Both reliability (internal consistency and/or test-retest) and validity (content-, construct-, and/or criterion validity) were reported for 17/25 (68%) instruments, and were mostly rated as moderate to strong. Overall, all disease-specific instruments, several generic multidimensional questionnaires (i.e. Short Form 36 (SF-36) vitality subscale, Multidimensional Fatigue Inventory (MFI), Multidimensional Fatigue Symptom Inventory Short Form (MFSI), Functional Assessment of Chronic Illness Therapy Fatigue (FACIT-F), Checklist Individual Strength (CIS) fatigue, Profile of Fatigue (ProF), Fatigue Severity Inventory (FSI), Fatigue Severity Scale (FSS)) and the single item questions (Fatigue Numeric Rating Scales (Fatigue NRS)) to assess severity or impact of fatigue had sufficient construct validity and reliability. Comparative validity was not reported in reviews.

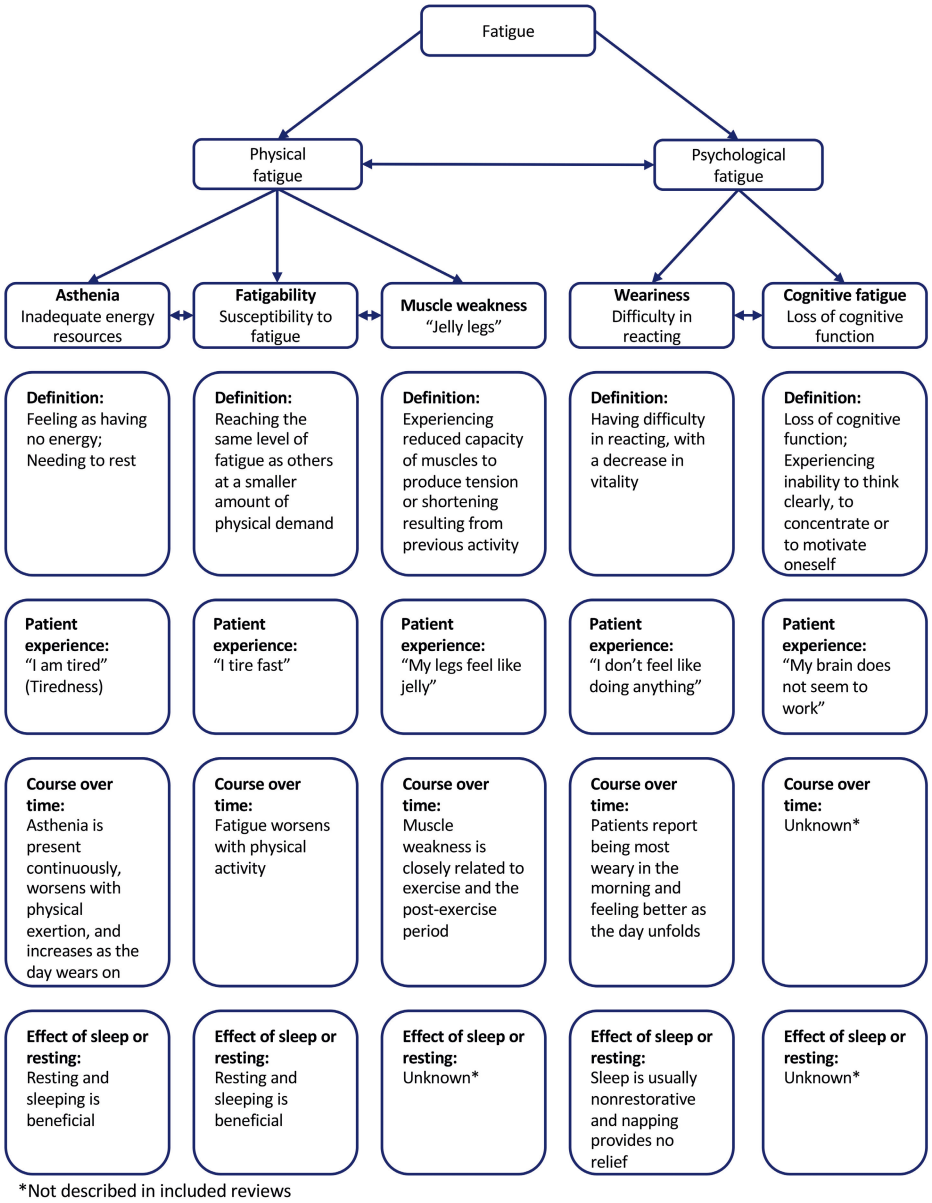

Figure 5.1 Schematic representation of the construct fatigue in RMDs based on included reviews

Determinants of fatigue

Determinants of fatigue in RMDs of interest were addressed in 28/134 reviews (21%; 5 SRs and 23 NRs, Table 5.1). Of these, 18/28 reviews (64%) addressed fatigue as their primary objective and 13/28 reviews (46%) concerned determinants of fatigue specifically in RA.

An overview of types of determinants per RMD of interest is available in Supplementary files 5.7-5.10. There was a broad range in the number of underlying studies across reviews for each determinant (range 1-130, median 3 and interquartile range 3 to 8, see Figure 5.2). Reviews sparsely reported relevant methodological aspects of underlying studies (e.g. design and setting; whether or not adjusted for confounders) and relevant aspects related to synthesis or findings (e.g. direction and strength of association; pooled effect) were often absent.

Clearly, determinants belonging to the ICF components 'disability and health' were more frequently studied than determinants belonging to the components 'contextual factors'. Across reviews, pain, sleep disturbances, physical function/disability, and depressive symptoms/anxiety were the most frequently studied health-related determinants of fatigue. Of note, pain was generally positively associated with fatigue in most reviews although some reviews in RA and OA reported inconsistent results. For disease activity, reviews in RA repeated generally positive findings while in SpA associations were inconsistent in all reviews. Whenever provided, strength of associations were generally small. A positive association between sleep disturbances and fatigue was reported in SpA, while both positive and inconsistent associations were reported for RA, OA and FM.

Female sex was consistently positively associated with (higher) fatigue in SpA, OA and FM, but inconsistent associations were found for RA. Inconsistent associations were reported for medication use in RA and OA.


A. Body function and structure
Vit D deficiency (1)
Joint damage (1)
Functional limitations (2)
Morning stiffness (3)
Muscle strength (4)
Comorbidities (4)
Low mental health (9)
Anxiety (16)
Sleep disturbances (31)
Tender and swollen joints (43)
Depression (49)
Disease activity (78)
Disease duration (81)
Pain (130)
B. Activities
Reduction sedentary time (1)
Physical capacity (5)
Physical activity (10)
Physical disability (31)
Low physical functioning (36)
C. Participation
Social functioning (5)
Reduced role functioning (6)
Interpersonal events (8)
D. Personal factors
Low emotional functioning (5)
Education level (5)
Marital status (5)
Obesity (6)
Positive beliefs (6)
Coping* (8)
Low self-efficacy (12)
Personality ‡ (16)
Stress (17)
Medication use ‡ (18)
Age (20)
Female sex (28)
E. Environmental factors
Seasonal variation † (1)
Positive or negative events (8)
Positive social support (12)
A
RHEUMATOID ARTHRITIS
All reviews reported positive associations
Reviews reported positive and absent or inconsistent associations
Reviews reported absent or inconsistent associations
Reviews reported negative and absent or inconsistent associations
All reviews reported negative associations
Unclear associations
A. Body function and structure
Vit D deficiency (1)
Low general health (1)
Low psychological health (1)
Sleep disturbances (1)
Stiffness (1)
Enthesopathy (1)
Pruritus (1)
Psoriasis (1)
Disease activity (1)
Comorbidities (2)
Depression (2)
Pain (12)
B. Activities
Physical disability (31)
Low physical functioning (36)
C. Participation
Social functioning (1)
D. Personal factors
Systemic treatment (1)
Alcohol consumption (1)
Low vitality (1)
Emotional and social aspects (1)
Reduced development level (1)
Demographic factors (1)
Smoking (2)
Female sex (2)
E. Environmental factors
Warm weather (2)
B
SPONDYLOARTHRITIS

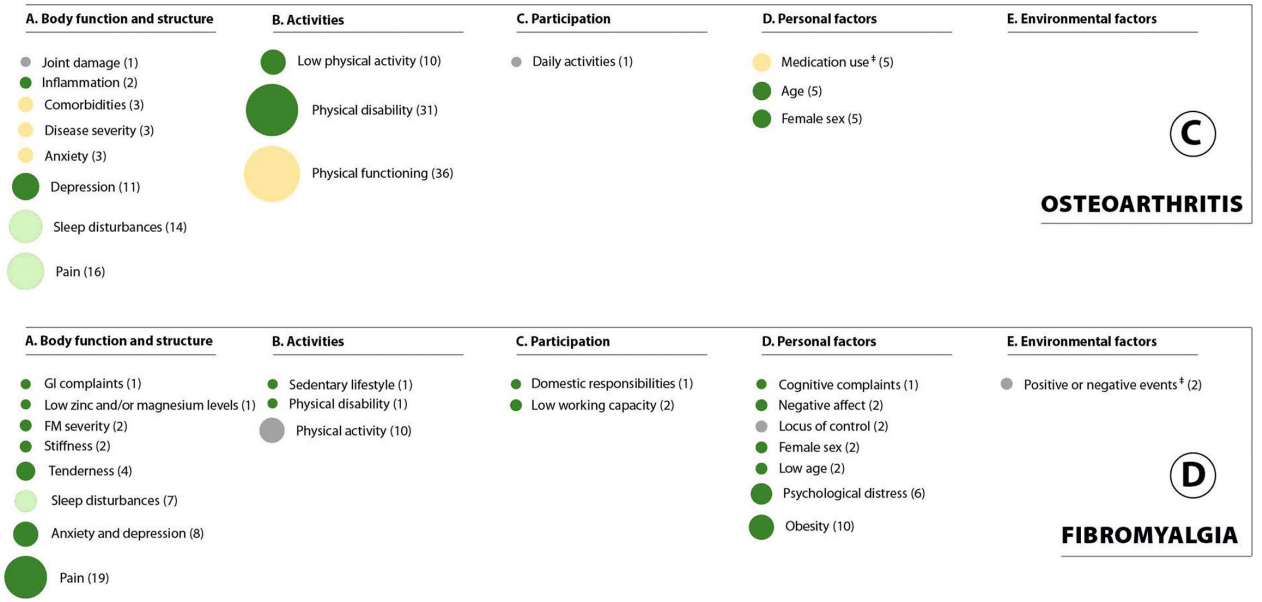

Figure 5.2. Identified determinants of fatigue categorised within the ICF-model

The overall direction of associations between determinants and fatigue across reviews were summarised and color-coded for (A) Rheumatoid arthritis, (B) Spondyloarthritis, (C) Osteoarthritis and (D) Fibromyalgia.

A positive association indicates that an increase in the factors contributes to more severe experiences of fatigue. These summaries are reported independent of strength (weak, moderate or strong) and statistical significance of the associations. The bubble size represents the number of underlying studies according to the reviews that studied these associations.

* In multivariable analyses, only worrying coping retained its significant association with fatigue.

† Higher fatigue during winter was suggested, but multivariable analyses were inconsistent.

‡ Variable summarizing a concept that includes ≥2 dimensions: for details, see Supplementary files 5.7-5.10.

Table 5.3 Consequences of fatigue reported by included reviews

ICF-model component			RA	SpA	OA	FM
Functional perspective	Body function and structure	Pain	X*		X*	
		Disease activity/severity	X*	X*		
		Fatigue	X†			
		Overall health / health related quality of life	X	X	X	
		Depression	X*	X*	X*	
		Sleep (disturbances)			X*	
	Activities	Physical functioning‡	X*†			
		Physical activity‡	X*†	X†	X*	
		Physical impairment / disability‡			X*	
		Sexual activities	X			
Contextual perspective	Participation	Work performance	X†	X	X	
		Social activities and household chores	X*		X	
		Role limitations (general)	X*			
		Daily self-care and socially relevant tasks	X			
	Personal factors	Stress	X*†			
		Parenting and family size	X†			
		Physical and mental or emotional well-being	X*			
		Coping	X*			
	Environmental factors	Social support	X*†			
		Partner relationships	X			
		Relational and socioeconomic variables	X*†			

* Also reported as determinants for fatigue by included reviews.
† Reported in at least one systematic review, excluding those that were unclear as to whether variable was considered a determinant or consequence.
‡ Conceptual difference between these consequences was not clear based on the reviews.
FM = Fibromyalgia, OA = Osteoarthritis, PsA = Psoriatic Arthritis, RA = Rheumatoid Arthritis, SpA = Spondyloarthritis

Consequences of fatigue

The consequences of fatigue on health outcomes were addressed in 21/134 reviews (16%, 5 SRs and 16 NRs) for RA, SpA and OA, but not for FM (Table 5.1). Of these, 12/21 reviews (57%) addressed fatigue as a primary objective. Of note, 15/21 reviews (71%) concerned consequences of fatigue specifically in RA.

Twenty-one types of consequences had been reported, among which 8 were studied in at least 1 SR and 15 types of consequences were exclusively addressed in NRs in one or more of the RMDs (Table 5.3). Overall, 14 types of consequences were also reported as determinants. Again, methodological aspects of underlying studies and numeric findings of statistical analyses were sparsely reported.

Across reviews, consistent associations were found between more fatigue and impairments of body functions (e.g. pain, disease activity and depression), limitations in the performance of activities and restrictions in the level of participation (e.g. social activities) (Supplementary files 5.11-5.13). In RA, work performance was the most frequently reported consequence of fatigue, including presenteeism, absenteeism and work productivity loss (2 SRs and 3 NRs). Consequences of fatigue on aspects belonging to the ICF components 'contextual factors' were only reported for RA (e.g. family size, social support and socioeconomic variables). Findings on the influence of fatigue on contextual factors in RA revealed that fatigue negatively influences experiences of stress, coping strategies and feelings of having adequate social support.

Effect of non-pharmacological interventions on fatigue

The effect of non-pharmacological interventions on fatigue in RMDs was addressed in 39/134 reviews (29%) (12 CRs, 18 SRs and 9 NRs, Table 5.1). Of these, 18 reviews (46%) addressed fatigue in their primary objective.

The 39 reviews summarised 75 interventions comprising exercise (n=28); psychotherapy and education (n=16); lifestyle behaviour (n=5); electrical nerve stimulation (n=10); complementary and alternative medicine (n=7); or other interventions (n=9) (e.g. nurse-led care or massages) (Supplementary files 5.14-5.17). Of these, 14/75 interventions were exclusively discussed in NRs. An overview of interventions for which the effects were reported in CRs is provided in Table 5.4. Across RMDs, non-pharmacological interventions had generally no or a small positive effect on fatigue compared to usual care (Supplementary files 5.18-5.20). The effectiveness of interventions on fatigue was inconsistent across RMDs, for example two CRs summarised that aerobic exercise compared to usual care has a small effect on fatigue in RA, but no effect in SpA[20, 21].

Effect of pharmacological interventions on fatigue

The effect of pharmacological interventions on fatigue in patients with RMDs was addressed in 39/134 reviews (29%, 7 CRs, 13 SRs and 19 NRs). Of these, 8 reviews (21%) included fatigue as the primary objective. No review on pharmacological interventions in OA reported effects on fatigue (Table 5.1). An overview of pharmacological interventions on fatigue in RA and FM for

which the effects were reported in CRs is provided in Table 5.5 and 5.6. No CRs addressed the effects of pharmacological interventions on fatigue in SpA or OA.

In RA, the effect of 12 biological DMARDs (bDMARDs), 2 targeted synthetic DMARDs (tsDMARDs) and a cannabinoid on fatigue were summarized in 1 CR, 3 SRs and 9 NRs (Supplementary file 5.18). In patients with active RA and moderate to high levels of fatigue, 1 CR and 1 SR reported that bDMARDs as a group have a small to moderate positive effect on fatigue compared to placebo or usual care[22,23]. Additionally, for tocilizumab, another SR reported clinically important improvements in fatigue compared to placebo[24]. Two bDMARDs (sarilumab and anakinra) and both tsDMARDs (baricitinib and tofacitinib) were exclusively discussed in NRs[25-28]. In several intervention studies reported in CR or SR, methotrexate was an active comparator, but effects in this treatment arm or compared to placebo were not synthesised. One SR reported that the cannabinoid nabilone has no superiority in reducing fatigue compared to placebo[29].

In SpA, the effect of NSAIDs, 1 csDMARD, 4 bDMARDs and 2 tsDMARDs on fatigue were reported in 2 SRs and 5 NRs (Supplementary file 5.19). Overall, 'improvements' (without effect size) of fatigue were reported in SRs and NRs for NSAIDs and bDMARDs in axial SpA and 1 csDMARD (methotrexate) in PsA. For tofacitinib in PsA, no improvement in fatigue was found according to 1 NR[30]. Effects on fatigue were quantified in 2 NRs only. One NR discussed a pooled analysis of 3 randomised controlled trials in which apremilast resulted in clinically important reductions of fatigue in 51% of patients with PsA[31]. One other NR reported that infliximab and etanercept reduced fatigue levels by more than 50% in studies among patients with axial SpA[32].

In FM, the effect of 12 anti-depressants, 1 anticonvulsant, 1 antipsychotic, 2 dietary supplements and 10 'other' pharmacological interventions, such as a dopaminergic agonist (pramipexole), a central stimulant (modafinil) or hypnotics (zopiclone and zolpidem), on fatigue were reported in 6 CRs, 8 SRs and 5 NRs (Supplementary file 5.20). Five CRs reported that almost all antidepressants have no or a small positive effect on fatigue compared to control interventions[33-37]. One CR cautioned about the very low quality of evidence for effect of antipsychotics on fatigue in FM[38]. One SR reported a significant reduction of fatigue for the dietary supplement Coenzyme Q10 compared to control[39]. A second dietary supplement (s-adenosylmethionine) and 9 'other' pharmacological interventions were exclusively discussed in NRs (Supplementary file 5.20)[40-43].

Table 5.4 Effect of non-pharmacological interventions on fatigue in patients with RMDs, as reported in Cochrane reviews

Cochrane review[†]	Year of publication	RMD	Type of intervention	Reported effect of intervention on fatigue[‡] (Reported quality of evidence)
			Physical exercise interventions	
Cramp, *et al.*	2013	RA	■ Physical exercise *vs* usual care (Pool based therapy, yoga, dynamic strength training, stationary cycling, low impact aerobics and Tai Chi)	**Small effect** (M)
Regnaux, *et al.*	2019	SpA	■ Exercise programs *vs* no intervention	**No effect** (VL) **Reduction** in fatigue (1 study) (VL)
			Resistance exercise therapy	
Busch, *et al.*	2013	FM	■ Resistance training *vs* usual care or flexibility exercise	**Large effects** (NR)
		FM	■ Resistance training *vs* aerobic training	**No effect** (NR)
			Whole body vibration (WBV) therapy	
Bidonde, *et al.*	2017	FM	■ WBV therapy plus mixed exercise *vs* placebo plus mixed exercise or other exercise	**Reduction** that met the threshold for **clinical relevance** (VL)
			Meditative movement therapies therapy (MMT) (e.g. Ai Chi, Tai Chi, Yoga awareness, Bat, Qi-Gong, Water yoga)	
Theadom, *et al.*	2015	FM	■ MMT *vs* usual care	**Advantageous** (VL)
			Mixed exercise training (two or more components of physical exercise)	
Bidonde, *et al.*	2019	FM	■ Mixed exercise training *vs* no exercise	More **improvement** post-intervention, but at long-term follow-up only 1/3 studies showed an effect (M)
		FM	■ Mixed exercise *vs* self-help programs, or cognitive-behavioral therapy, or biofeedback, or medication, or aerobic exercise only	**No effect** (VL)
		FM	■ Mixed exercise plus education *vs* education alone	**No effect** (VL)
		FM	■ Mixed exercise (aerobic + flexibility) *vs* mixed exercise (resistance + aerobic + flexibility)	**No effect** (VL)

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Table 5.4 *[continued]*

Cochrane review[†]	Year of publication	RMD	Type of intervention	Reported effect of intervention on fatigue[‡] (Reported quality of evidence)
		FM	■ Mixed exercise (calisthenics + aerobic + flexibility) *vs* mixed exercise (resistance + flexibility + posture exercise)	**No effect** (VL)
			Aerobics exercise (e.g. cycling, walking, regardless of frequency, duration, or intensity)	
Bidonde, *et al.*	2017	FM	■ Aerobics *vs* controls (treatment as usual, wait list control, daily activities)	N**o effect** (1 study) (VL) **Significant effect** (2 studies) at long-term follow-up (VL)
		FM	■ Aerobics (Nordic walking) vs aerobics (low-intensity training)	**No effect** (L)
		FM	■ Aerobics *vs* other non-exercise interventions	N**o effect** (L)
Busch, *et al.*	2007	FM	■ Aerobics at American College of Sport Medicine levels	**No effect** (VL)
			Aquatic exercise therapy	
Bidonde, *et al.*	2014	FM	■ Aquatic exercise *vs* controls (treatment as usual, balneotherapy or education)	**No effect** (NR)
		FM	■ Aquatic exercise *vs* land-based training	**No effect** (NR)
		FM	■ Aquatic exercise (Tai Chi) *vs* aquatic exercise (stretching)	**No effect** (NR)
		FM	■ Aquatic exercise in outdoor pool *vs* aquatic exercise in sea water (effects of salinity of water)	**No effect** (NR)
			Flexibility exercise therapy	
Kim, *et al.*	2019	FM	■ Flexibility exercise *vs* land-based aerobic exercise, untreated controls, resistance training, Tai Chi, or aquatic biodanza	**No effect** (VL)
			Psychosocial interventions	
Cramp, *et al.*	2013	RA	■ Psychosocial interventions *vs* usual care (including benefit finding, expressive writing, cognitive behavioural therapy, mindfulness, lifestyle management, energy conservation, self-management and group education)	**Small effect** (L)

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Table 5.4 *[continued]*

Cochrane review[†]	Year of publication	RMD	Type of intervention	Reported effect of intervention on fatigue[‡] (Reported quality of evidence)
			Mind and body therapy	
Theadom, *et al.*	2015	FM	■ Psychological therapies *vs* attention care or usual care	**No effect** (VL)
		FM	■ Relaxation-based therapies *vs* usual care	**No effect** (VL)
			Complementary interventions and alternative medicine	
Cramp, *et al.*	2013	RA	■ **Herbal medicine**: Andrographis paniculata *vs* placebo	**No effect** (L)
		RA	■ **Reflexology**: Reflexology *vs* a non-specific foot massage	**Greater mean reduction** (L)
			Acupuncture	
Deare, *et al.*	2013	FM	■ Real acupuncture *vs* non-acupuncture treatment	**Significant difference** (L)
		FM	■ Real acupuncture *vs* placebo or sham acupuncture	**No effect** (M)
		FM	■ Deep invasive needling with stimulation *vs* deep invasive needling without stimulation	**No effect** (NR)
			Electrical nerve stimulation interventions	
			Transcutaneous electrical nerve stimulation (TENS)	
Johnson, *et al.*	2017	FM	■ TENS *vs* placebo TENS, no treatment, or waiting list control	**Reduced** fatigue with movement, but **not** at rest (VL)
		FM	■ TENS added to exercise *vs* exercise alone (usual care)	**Clinically important improvements** (VL)
		FM	■ TENS *vs* other treatment	**Clinically important improvements** (VL)

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Table 5.4 *[continued]*

Cochrane review†	Year of publi-cation	RMD	Type of intervention	Reported effect of intervention on fatigue‡ (Reported quality of evidence)
			Lifestyle interventions	
Cramp, *et al.*	2013	RA	■ **Diet interventions**: Mediterranean diet *vs* Western diet	**Improvement** in intervention group* (L)
		RA	■ **Diet interventions** Omega-3 fatty acid supplementation	**Improvements** between baseline and follow-up (L)
		RA	■ **Providing health information**: Data tracker *vs* usual care	**Small improvements** between baseline and follow-up (L)

† Complete references are provided in Supplementary files 5.14-5.17, as well as results of non-Cochrane systematic reviews and narrative reviews
‡ Effect always refers to a reduction of fatigue compared to controls, unless otherwise indicated
* Between-arm comparisons were not reported
FM = Fibromyalgia, OA = Osteoarthritis, PsA = Psoriatic Arthritis, RA = Rheumatoid Arthritis, RMDs = Rheumatic and musculoskeletal diseases, SpA = Spondyloarthritis, vs = Versus, VL = Very Low, L = Low, M = Moderate, NR = Not Reported

Table 5.5. Effect of pharmacological interventions on fatigue in patients with rheumatoid arthritis, as reported in Cochrane reviews

Cochrane review†	Year of publication	Pharmacological interventions	Reported effect of intervention on fatigue‡ (Reported quality of evidence)
		Biological DMARDs (bDMARDs)	
Almeida, *et al.*	2016	■ bDMARDs *vs* placebo or usual care (Adalimumab, certolizumab, etanercept, golimumab, infliximab, abatacept, canakinumab*, rituximab, tocilizumab and an anti-interferon gamma monoclonal antibody*)	**Small to moderate improvement** in patients with active RA and moderate to high levels of fatigue (M)
		■ bDMARDs *vs* placebo or usual care (Abatacept, canakinumab*, rituximab, tocilizumab and an anti-interferon gamma monoclonal antibody*)	**Moderate effect** (M)
		■ **TNF inhibitors grouped:** TNF inhibitors *vs* placebo or usual care (Adalimumab, certolizumab, etanercept, golimumab, infliximab)	**Moderate effect** (M)

† Complete references are provided in Supplementary file 5.18, as well as results of non-Cochrane systematic reviews and narrative reviews.
‡ Effect always refers to a reduction of fatigue compared to controls.
* These drugs are not prescribed in patients with RA.
vs = Versus, VL = Very Low, L = Low, M = Moderate, NR = Not Reported
bDMARDs = Biological Disease-Modifying Antirheumatic Drugs, RA = Rheumatoid Arthritis, TNF = Tumour Necrosis Factor

Table 5.6 Effect of pharmacological interventions on fatigue in patients with fibromyalgia, as reported in Cochrane reviews

Cochrane review†	Year of publication	Pharmacological interventions	Reported effect of intervention on fatigue‡ (Reported quality of evidence)
		Anti-depressant class serotonin and noradrenaline reuptake inhibitors (SNRIs)	
Welsch, *et al.*	2018	■ **SNRIs grouped:** Duloxetine, milnacipran or desvenlafaxine *vs* placebo	Overall effect **not substantial** (L)
		Anti-depressant class selective serotonin reuptake inhibitors (SSRIs)	
Walitt, *et al.*	2015	■ Citalopram *vs* placebo	**Not statistically significantly superior** (VL)
		■ Fluoxetine *vs* melatonin	**Not statistically significantly superior** (VL)
		Anti-depressant class tricyclic antidepressants (TCAs)	
Tofferi, *et al.*	2004	■ Cyclobenzaprine*	**No improvement** (NR)

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Table 5.6 *[continued]*

Cochrane review†	Year of publication	Pharmacological interventions	Reported effect of intervention on fatigue‡ (Reported quality of evidence)
Welsch, *et al.*	2018	■ Mirtazapine *vs* placebo	**No statistically significant benefit** (L)
		Antipsychotics	
Walitt, *et al.*	2016	■ Quetiapine *vs* placebo	**Significant improvement** (VL)
		■ Quetiapine *vs* amitriptyline	**No statistically significant difference** (L)
		Cannabinoids	
Walitt, *et al.*	2016	■ Nabilone *vs* placebo or amitriptyline	**Did not convincingly relieve fatigue** (VL)
		Combinations of pharmacological interventions for fatigue	
Thorpe, *et al.*	2018	■ **TCA and SSRI:** Amitriptyline and fluoxetine alone and in combination *vs* placebo or monotherapy	**No statistically significant effect** (VL)
		■ **TCA:** Amitriptyline either alone or in combination with naproxen	Amitriptyline alone or in combination with naproxen: **significantly larger improvements** in VAS scores of sleep difficulty, fatigue, and morning tiredness (VL) Naproxen: **no statistically significant effect** (VL)
		■ **TCA:** Amitriptyline monotherapy *vs* combination therapy of amitriptyline and intravenous lidocaine.	**No statistically significant change** (VL)
		■ Anti-depressants combined with melatonin	Melatonin (low/high dose) with fluoxetine: **significant improvement** (VL) Melatonin (high dose) monotherapy: **no improvement** (VL)
		Comparative efficacy of pharmacological interventions for fatigue	
Welsch, *et al.*	2018	■ **SNRIs:** Duloxetine *vs* milnacipran	**No significant differences** (NR for subgroup analyses)

† Complete references are provided in Supplementary file 5.17, as well as results of non-Cochrane systematic reviews and narrative reviews.
‡ Effect always refers to a reduction of fatigue compared to controls.
***** Cyclobenzaprine is a muscle relaxant, structurally related to TCAs.
FM = Fibromyalgia, vs = Versus, VL = Very Low, L = Low, M = Moderate, NR = Not Reported

Patient panel discussion feedback

At the first meeting with the patient discussion panel, participants discussed the proposed schematic classification for types of fatigue and their descriptions (i.e. Figure 5.1), and consented to the final version. When discussing the full results in the second meeting, participants felt that the findings overall confirmed their experience in daily life. They were impressed by the large amount of available knowledge on fatigue, which contrasted with the limited attention paid to fatigue in daily clinical practice. In addition, participants pointed to factors related to fatigue that were not discussed in the included reviews, such as the effect of specific lifestyle interventions on fatigue (e.g. two patients participated in the lifestyle intervention 'plants for joints', of which findings were not yet available at time of our literature searches and therefore not included)[44]. Some participants felt that it was stigmatising that the majority of reviews of non-pharmacological interventions were performed in FM. Overall, the patient panel advised to translate the findings into points to be considered for clinical practice and to define a research agenda with specific attention for diagnosing and treating excessive fatigue in RMDs.

Discussion

A panel of patients with RMDs prioritised fatigue as the most important topic that should be addressed to improve daily clinical care. As a first step, this scoping review summarised systematic and non-systematic reviews on aspects of fatigue that are relevant for clinical practice, addressing 5 predefined research areas in 4 RMDs.

Although no consensus definition exists for fatigue in RMDs, the reviews were in agreement that patients with RMDs can experience several types of fatigue that can occur simultanously or alternatingly in patients' lives. Notwithstanding, no agreement exists on which types should be distinguished. It is therefore not suprising that measurement instruments summarised in reviews, even if multi-dimensional, differed largely on the number and type of dimensions adressed. Importantly, all instruments were patient-reported and only a small proportion of these instruments were specifically developed and/or validated for use in clinical care or included cut-off values to identify persons with excessive fatigue.

Numerous reviews showed that a large number of health-related and contextual factors were associated with fatigue as either a determinant or a consequence, but overall the strength of associations was small. Whenever quantified, pharmacological interventions had a small to moderate effect on fatigue in RA, but no to a small positive effect in FM. No SRs reported effect sizes of pharmacological interventions on fatigue in SpA but narrative summaries frequently reported improvements on fatigue following drug treatment. A large variety of non-pharmacological interventions (including cognitive behavioral therapy and dietary changes) had generally no to a small positive effect on fatigue across RMDs, with most reviews focusing specifically on FM.

Whenever reported, strength of associations and effects of interventions were overall weak or small, with the exception of some pharmacological interventions in RA that showed a

moderate effect size. Partly, this could be explained by methodological issues. First, fatigue was not always the primary objective of the review and therefore effects were not always quantified, even not in SRs. Also, in the underlying studies, fatigue was rarely the primary endpoint. Consequently, effects from intervention and association studies might be underestimated as study populations were often not selected on the presence of (a specific type or specified level of) fatigue, reducing potential for improvement and lacking power to adequately determine strength of associations. Finally, the synthesis and interpretation of aggregated data in reviews is likely complicated by the heterogeneity of study designs (e.g. head-to-head comparisons or placebo-controlled interventions) and measurement of fatigue.

Multiple variables were reported both as a potential determinant (i.e. predicting fatigue) ánd a potential consequence (i.e. predicted by fatigue). This notably includes variables such as pain, disease activity/severity, physical functioning and depression, as well as factors related to social functioning. Unfortunately, findings from studies reporting on associations with or consequences of fatigue often relied on bivariate correlations and the majority of included reviews did not explicitly report whether underlying studies involved cross-sectional and/or longitudinal analyses, nor whether they were adjusted for confounders, which precludes firm conclusions on the direction of causal relationships. Most likely however, fatigue in RMDs is determined by numerous multidirectional and/or circular pathways. As an example, whilst pain was positively correlated with fatigue in RA, SpA, OA and FM, there were reviews describing an indirect effect of sleep disturbances on fatigue by lowering pain thresholds in these RMDs, with some studies indicating that the effect of sleep disturbance on fatigue might even be fully mediated by pain. Similarly, it seems plausible that the effects of interventions on fatigue might – at least in part – be indirect and/or mediated by effects of these interventions on e.g. pain and physical or emotional functioning.

The patient panel questioned whether findings could be translated to clinical practice. Currently, patients may struggle to communicate their fatigue with their healthcare provider and as a result may feel misunderstood or isolated[2,13]. Our scoping review indicates fatigue is a complex symptom, and patients clearly recognize different types of fatigue. Using clinical reasoning, the information retrieved about type(s) of fatigue experienced, determinants and consequences can subsequently be used to compose a personalised treatment plan together with the patient. Such proposal might vary from spreading activities throughout the day to save energy, to increasing physical fitness, practicing mindfulness or focusing rather on patients' acceptance of fatigue. The European League Against Rheumatism (EULAR) recommendations for core competences of health professionals in rheumatology advise to stimulate patients' self-management for fatigue, and our review can also help to identify factors and treatment options to consider when discussing self-management[45].

An important aim of scoping reviews is to identify potential knowledge gaps and highlight areas that are in need of further inquiry. Our results underline the importance of establishing consensus on an overarching definition of fatigue and different types of fatigue in RMDs. An

operable construct that comprehensively captures the various experiences of fatigue among patients with RMDs could not only serve as a framework to identify or develop/adapt measurement instruments in alignment with types of fatigue, but could also support communication between patients and healthcare providers in clinical practice. Ideally, this should be developed in cooperation with patients, based on the available evidence. The schematic synthesis of fatigue proposed in this scoping review (Figure 5.1), verified and supported by a patient panel, illustrates a possible approach and potential starting point for such an endeavour. As for clinical trials, the EULAR / American College of Rheumatology (ACR) collaborative recommendations for reporting disease activity in clinical trials in RA, already advised to include fatigue when evaluating effectiveness of interventions[46]. Our findings suggest that a comprehensive understanding of fatigue would benefit from high quality studies which include fatigue as a specific research objective. Given the complex multidimensional nature of fatigue, the development of a conceptual framework for fatigue in RMDs would be beneficial. Conceptual models have previously been proposed for fatigue in RA and other inflammatory rheumatic diseases, but were primarily focused on pathogenesis[47,48]. Similar conceptual models to understand the experience of health could be proposed. Overall, as an essential next step to unravel and ultimately improve fatigue in RMDs, the development of an agreed research agenda on fatigue is warranted.

Our review has several limitations. First, in line with the methodology of scoping reviews, we did not perform quality assessments of the reviews. Clearly, NRs have higher risk of bias in the conclusions. Second, relevant determinants, consequences and interventions might have been missed when they have not (yet) been the objective of a published review. Third, reviews sparsely reported whether fatigue was assessed as one general construct or as one or more types of fatigue, which hampers the translation of these research results into clinical practice. Fourth, pathophysiological pathways of fatigue were no research area of this scoping review as we focused on relevant areas for clinical practice. The clinical value of potential (laboratory or imaging) biomarkers for various types of fatigue could be added to the research agenda.

Strengths of this scoping review are that it addresses areas that are typically relevant for clinical care. Furthermore, this project was initiated by patients and all results were discussed with a patient panel to include patients' interpretations, verifying that results are relatable from the patient perspective.

In conclusion, many reviews have been published on fatigue in RMDs, but fatigue was often addressed as a secondary objective in these studies. The extensive amount of evidence synthesised in this scoping review can be translated to clinical care in order to support clinical reasoning and to compose a tailored treatment plan for fatigue in an individual patient. More important, the findings should stimulate the development of a research agenda as a logical next step. That process should emphasize collaboration between research areas to efficiently develop more insights into and solutions for this complex symptom.

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CHAPTER 6

Development of a web-based decision aid for initiating biologic or targeted synthetic disease-modifying antirheumatic drugs (b/tsDMARDs) in axial spondyloarthritis

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RMD Open, 2023

Abstract

Objectives

To develop a web-based evidence-based decision aid to support shared-decision making in patients with axial spondyloarthritis (SpA) who face a treatment decision to initiate or switch a biologic or targeted synthetic Disease-Modyfying Antirheumatic Drug (b/tsDMARDs).

Methods

Through an iterative process, we systematically developed a decision aid based on evidence from the literature, explorative needs assessment interviews among patients and healthcare providers, and input from experts of the SpA working group of the Dutch Society for Rheumatology and professionals on patient information employed at the Dutch Arthritis Society. The usability, ease-of-use and feasibility of the pilot version were tested among stakeholders and feedback was used to adapt the decision aid. Finally, a multifaceted strategy was used to introduce the decision aid in clinical practice.

Results

The decision aid consists of 1) consultation support instructions in the context of disease control and treatment needs, 2) an overview of available treatment options for axial SpA, 3) detailed information on b/tsDMARDs and an interactive option grid that facilitates comparison of characteristics, and 4) a final check supporting patients to deliberate on the decision to initiate or switch a b/tsDMARD. Rheumatologists introduced the decision aid in several Dutch rheumatology settings and the Dutch Arthritis Society posted it on their website, social media and in their monthly newsletter.

Conclusion

We developed an evidence-based decision aid to support axial SpA patients who face a treatment decision to initiate or switch a b/tsDMARD and introduced this in clinical practice. Introduction.

Introduction

The principle of shared-decision making (SDM) is a key element for providing high quality of care[1]. SDM has been defined as the process of healthcare providers and patients jointly participating in making health decisions2. This is grounded in the paradigm that care should be based on the best evidence and should be respectful of, and responsive to, individual patient preferences, needs, and values[1]. Applying SDM requires that patients are fully informed on their medical situation and that they receive evidence-based information on the expected effect of treatment options on disease outcomes and their personal life[3]. Patients can be informed on these aspects by paper-based or electronic tools, such as patient information leaflets, health education materials and decision aids. The latter are evidence-based tools designed to support patients in making specific and deliberated choices among healthcare options and to support patients in communicating their considerations with healthcare providers[4]. According to the International Patient Decision Aids Standards (IPDAS) Collaboration, decision aids should specifically state the decision, inform patients about their treatment options and associated benefits and harms, enable comparing treatment options and support patients in identifying personal values[4,5]. Decision aids can help empower patients to make well-informed personal treatment decisions, thereby potentially increasing long-term satisfaction with the provided care[6].

A systematic Cochrane review concluded that patients who faced a treatment or screening decision and who used a decision aid, had more knowledge on their options, had increased accuracy of risk perceptions and experienced more agreement between informed values and care choices compared to usual care[7]. In addition, the proportion of patients who were passive in decision-making or who experienced a decisional conflict, related to feeling uninformed, decreased. Moreover, this Cochrane review suggested that the use of decision aids might have a positive effect on the communication between patients and healthcare providers.

For patients with axial spondyloarthritis (SpA), the overarching principles of the 2022 update of the Assessment of SpondyloArthritis international Society (ASAS)/European League Against Rheumatism (EULAR) recommendations for disease management state that treatment of patients should aim at the best care and must be based on a shared decision between patient and rheumatologists[8].

In patients with axial SpA and persistently high disease activity (despite conventional treatment), the decision-making process for initiating a biologic or targeted synthetic Disease-Modyfying Antirheumatic Drug (bDMARD or tsDMARD) has become more complex due to the availability of different drug classes that differ in mode of action, currently including five TNF-inhibitors, two IL-17 inhibitors and two JAK-inhibitors for patients with radiographic axial SpA[8,9]. These b/tsDMARDs have comparable effectiveness for axial manifestations, but differ in individual characteristics, such as the route of administration (subcutaneous, intravenous or oral), frequency of administration (daily, weekly, monthly or every few months), expected effect

on extra-musculoskeletal manifestations (uveitis, psoriasis, inflammatory bowel disease (IBD)) and potential adverse effects.

In patients who face a treatment decision on whether and which b/tsDMARD to initiate, the drug characteristics should be balanced to find the best fit with patients' personal values and preferences as they might require some changes in patients' lives. For example, patients may need to take time off during working hours to visit a clinic for intravenous drug administration instead of taking tablets daily at home. This balance should be made upon starting as well as upon switching a drug.

Previous studies have shown that patients with RA want to be informed about the characteristics of individual bDMARDs when deciding to initiate a drug[10-12]. A decision aid could therefore be useful to support these patients in the decision-making process.

In 2017, one high-quality web-based decision aid has been developed in the Dutch language to support SDM in patients with inflammatory arthritis who are about to initiate or switch a b/tsDMARD[13]. However, the decision aid was not specifically developed for the axial SpA patient population. Consequently, important information on the effectivity of the b/tsDMARDs on extra-musculoskeletal manifestations is missing. Furthermore, this decision aid has never been updated and recently approved treatment options are also lacking. The objective of this study is therefore to develop a new evidence-based and web-based decision aid, feasible for supporting SDM in patients with axial SpA who face a treatment decision to initiate or switch a b/tsDMARD and introduce this in clinical practice.

Methods

A steering group was assembled to refine the scope and setting, to guide the development process and to be responsible for the final decisions. The steering group consisted of a researcher (EB) and two rheumatologists with expertise in SpA. The development process was based on a Dutch guidance document of the Dutch Health Care Institute for the development of patient information and decision aids in accordance with quality standards, and on the internationally accepted process development model of the IPDAS collaboration[14,15]. The development process comprised five iterative phases: 1) establishing the scope and setting, 2) designing the content by assessment of needs and search of evidence to support these needs, 3) development of a pilot version, 4) pilot testing and 5) introduction in clinical practice and evaluation (Figure 6.1). Throughout the development process, we consulted patients with SpA, professionals on patient information employed at the Dutch Arthritis Society, and 18 expert rheumatologists from the working group SpA of the Dutch Society for Rheumatology. This paper was written in compliance with the Standards for Universal reporting of patient Decision Aid Evaluations (SUNDEA) checklist for decision aid evaluation studies16. This study was reviewed by the Medical Ethics Review Committee at Maastricht UMC+ and it was determined that the Medical Research Involving Human Subjects Act did not apply (2018–0627).

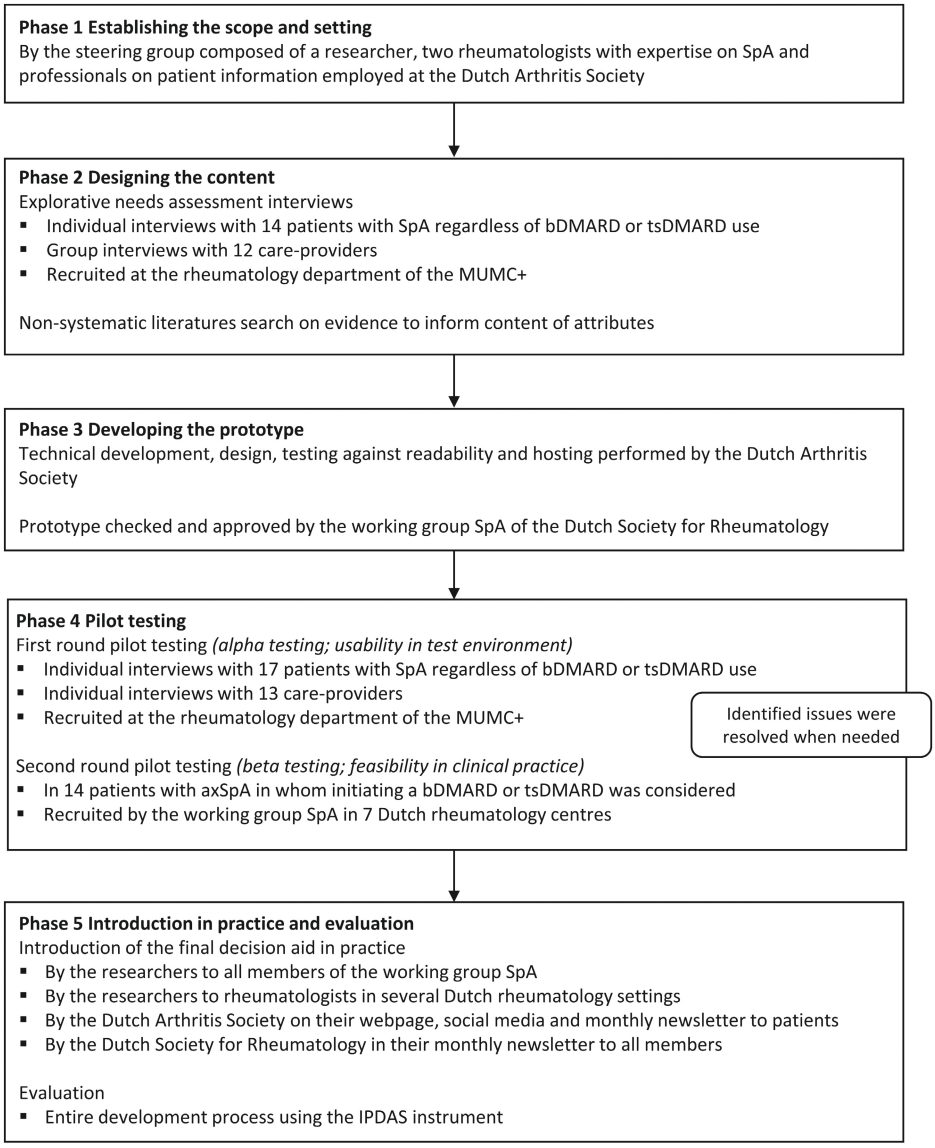

Figure 6.1 Phases of the development process for the decision aid for patients with axial SpA facing a treatment decision to initiate or switch a b/tsDMARD

axSpA = Axial Spondyloarthritis, bDMARD = biological Disease-modifying Antirheumatic Drug, IPDAS = International Patient Decision Aids Standards, MUMC+ = Maastricht University Medical Centre, SpA = Spondyloarthritis, tsDMARD = targeted synthetic Disease-modifying Antirheumatic Drug

Phase 1 Scope and setting

The scope of the decision aid was to develop a decision aid that supports SDM in patients with axial SpA who face a treatment decision to initiate or switch a b/tsDMARD. The intended setting was that the decision aid would be used by patients at home after their outpatient visit in which they discussed to initiate or switch a b/tsDMARD, as this would give patients sufficient time to reflect on their options. Patients would be informed by their rheumatologist on available drugs for their personal current medical situation and would receive a paper-based information card with personalized b/tsDMARDs options and with a link to the website of the decision aid. Subsequently, patients would discuss the results whether or not to initiate a b/tsDMARD and which drug is preferred (if applicable) during their next outpatient visit or telephone consultation. Alternatively, if preferred, this process could also take place during the outpatient visit together with the healthcare provider.

Phase 2 Designing the content

Explorative needs assessment interviews

The needs and wishes regarding the content and layout of a decision aid were identified in explorative interviews among patients and healthcare providers, including rheumatologists, rheumatology fellows and specialised rheumatology nurses employed at the local rheumatology department. Individual interviews were planned with ±15 patients with a clinical diagnosis of SpA who recently (≤2 weeks) discussed with their healthcare provider to initiate a b/tsDMARD, followed by group interviews among ±10 healthcare providers (see Supplementary file 6.1 for more details on the methodology)[17].

In preparation of the interview, a non-systematic literature search was performed in PubMed to identify relevant needs for SDM on initiating b/tsDMARDs in patients with SpA, RA or PsA. Keywords for this search included 'decision aid', 'treatment' and 'shared-decision making'. All interviews were performed by one trained and experienced interviewer. The interviews with patients started with a short explanation of patient centered care and the principles of SDM. Next, the available Dutch web-based decision aid on starting or switching DMARDs in persons with inflammatory arthritis was shown as an example of how such tools can support clinical decision making (available at http://www.reumamedicatiekeuzehulp.nl/home)[13]. Further, obtained knowledge from the literature review was used to guide the semi-structured interviews (see Supplementary file 6.2 for the interview guide). Interviews with healthcare providers were organised as a group interview. First, results from the previously performed patient interviews were presented and healthcare providers were asked to reflect on the relevance and feasibility of the discussed wishes. All interviews were analysed using the thematic structure of the interview guide. Finally, all needs and wishes were used for the development of the decision aid.

Literature search

Next, a non-systematic literature search was performed to retrieve data necessary to accommodate the needs and wishes identified from the explorative needs assessments. For individual characteristics of b/tsDMARDs, we checked the axial SpA treatment guidelines of the Dutch

Society for Rheumatology which includes elaborated evidence on the effectiveness and safety of drugs, the European public assessment reports on individual drugs of the European Medicines Agency and the Dutch pharmacotherapeutic database that encompasses independent information on drugs available in the Netherlands[18-21].

Phase 3 Development of a pilot version

Parallel to the development of our decision aid, a web-based information tool was launched by the Dutch Arthritis Society in collaboration with the Dutch Society for Rheumatology, which aimed to prepare patients with RA for making treatment decisions (available at https://reumanederland.nl/formulieren/keuzehulp/)22.

This tool comprises: 1) consultation support instructions in the context of disease control and treatment needs and 2) an overview of available treatment options for RA. The steering group assumed that the type of information within these parts were also relevant to support SDM in patients with axial SpA facing treatment decisions. For the development of the pilot version, we therefore adapted these two parts to align with the axial SpA situation (forming part 1 and 2 of our decision aid).

Next, two new parts (the actual decision aid, forming part 3 and 4) were developed, based on the results of the literature searches and the explorative needs assessments interviews: 1) detailed information on b/tsDMARDs followed by an interactive option grid that facilitates comparison of characteristics and 2) a final check supporting patients to deliberate on the decision to initiate or switch a b/tsDMARD (Box 6.1).

The Dutch Arthritis Society was responsible for the technical development, layout and hosting of the web-based decision aid. In addition, the functional health literacy levels were ensured by testing readability across literacy levels using the Common European Framework of Reference for Languages (CEFRL) language level B1, for which there is broad consensus that the majority of the population is able to read and understand the written information[23-25]. Furthermore, we developed a paper-based information card with personalized b/tsDMARDs options and with a link to the website of the decision aid, which could be handed out to patients during a clinical visit (Supplementary file 6.3). The content and look and feel of the decision aid, and the paper-based card were approved by experts from the working group SpA of the Dutch Society for Rheumatology.

Phase 4 Pilot testing

The pilot version of the decision aid was tested in two rounds. In the first round (alpha testing), we performed individual semi-structured interviews with patients and healthcare providers to evaluate its usability and ease-of-use and to check whether all agreed upon information and layout wishes were adequately incorporated in the pilot version (see Supplementary file 6.4 for more details on the methodology).

During the interviews, participants were asked to read the different parts of the decision aid and to reflect on the content, usability, comprehensibility, layout, readability and expected future use according to the concurrent thinking aloud-method. In-depth questions and clarification of comments were asked when needed following a short semi-structured interview guide (Supplementary file 6.5). After each individual interview with a patient, the research team evaluated whether data saturation was reached and if not, additional interviews were planned. Again, interviews were analysed using the thematic structure of the interview guide. Based on comments retrieved from the interviews, revisions were made.

In the second round (beta testing), we evaluated the feasibility of the final version in clinical practice in ±15 patients who face a treatment decision to initiate or switch a b/tsDMARD (see Supplementary file 6.6 for details on the methodology). Patients and healthcare providers were invited to use the decision aid in clinical practice and afterwards patients completed an online questionnaire on patients' socio-demographic characteristics and nine statements to be answered on a 1-5 Likert scale adapted from the Technology Acceptance Model and Telehealth Usability Questionnaire[26,27] (Supplementary file 6.7). When needed, results from this questionnaire were used to make final adjustments in the prototype.

Phase 5 Introduction in clinical practice and evaluation

A multifaceted strategy was devised to introduce the decision aid to healthcare providers and patients in Dutch rheumatology settings. The researchers assessed the quality of the final version of the decision aid using the IPDAS instrument[28].

Results

Phase 1 Scope and setting

The steering group decided that a web-based decision aid was preferred over a paper-based aid, as this is more easily accessible for healthcare providers and patients. However, the decision aid can be printed and used on paper for patients who prefer paper-based tools or have limited health literacy or digital skills. Furthermore, the decision aid should be published on the open to use website of the Dutch Arthritis Society, which is considered a comprehensive and credible source of information on rheumatic and musculoskeletal diseases and available treatment options (in Dutch: https://reumanederland.nl/).

Phase 2 Explorative needs assessments

Semi-structured explorative interviews were performed with 17 patients and 12 healthcare providers using an interview guide to identify needs and wishes regarding the content and layout of the decision aid (Table 6.1).

Table 6.1 Characteristics of participants in needs assessment interviews and pilot testing

	Explorative needs assessment	Pilot testing	
		Alpha testing	Beta testing
Healthcare providers	N = 12	N = 13	-
Rheumatologists	6	7	-
Rheumatology fellows	4	3	-
Specialised rheumatology nurse	2	3	-
Patients	N = 17	N = 14*	N = 14
Age, years (range)	53.5 (23-80)	53.3 (21-78)	47.8 (9.0)
Female, n (%)	9 (52.9)	5 (35.7)	9 (64.3%)
Disease duration, years**	13.8 (10.5)	16.2 (10.4)	§
Past and current use of b/tsDMARDs**, n (%)	14 (82.3%)	12 (85.6%)	§
Educational attainment, n (%)			
High	5 (29.4%)	10 (71.4%)	9 (64.3%)
Middle	7 (41.2%)	4 (28.6%)	2 (14.3%)
Low	4 (23.5%)	0 (0.0%)	2 (14.3%)
Unknown	0 (0.0%)	0 (0.0%)	1 (7.1%)
Living status, n (%)			
Living alone	3 (17.6%)	4 (28.6%)	1 (7.1%)
Living with partner without children	9 (52.9%)	7 (50.0%)	5 (35.7%)
Living with partner with children	2 (11.8%)	3 (21.4%)	7 (50.0%)
Living without partner with children	1 (5.9%)	0 (0.0%)	1 (7.1%)
Other	2 (11.8%)	0 (0.0%)	0 (0.0%)
Occupational status, n (%)			
Employed	4 (23.5%)	10 (71.4%)	12 (85.7%)
Retired	4 (23.5%)	2 (14.3%)	0.0 (0.0%)
Disabled for work	6 (35.3%)	2 (14.3%)	2 (14.3%)
Other	3 (17.6%)	0 (0.0%)	0 (0.0%)

Results are reported as mean (S.D.), unless reported otherwise
* Six patients who participated in the explorative need assessment interviews also participated in the alpha testing.
** This information was retrieved from patients' medical records
§ This information could not be retrieved as the online questionnaire was answered anonymously
b/tsDMARD = biologic or targeted synthetic Disease-modifying Antirheumatic Drug

Regarding information needs and wishes, both patients and healthcare providers suggested information they deemed necessary to know for making treatment decisions on initiating or switching b/tsDMARDs. Healthcare providers categorized their information needs and wishes between general information on b/tsDMARDs and information on specific characteristics of each b/tsDMARD (Box 6.1). Regarding layout needs and wishes, it was suggested by both patients and healthcare providers that the decision aid should be concise and clear and that its readability could be increased by using icons, dropdown menus and pop-up windows. Furthermore, the decision aid should be useable on a mobile device, should include support functions for patients with limited literacy and/or digital skills (e.g. reading-aloud and text magnification functions) and should be available in a print-format for patients who prefer paper-based tools. Finally, regarding emotional and support needs and wishes, healthcare providers and patients suggested to stimulate patients to reflect whether they felt sufficiently prepared to make an informed decision. Patients also a wished that the decision aid includes a textual reminder on the possibility to discuss treatment options with friends and family and that they could ask any remaining questions on emotional and support needs with their healthcare providers.

Phase 3 Development of a pilot version

The decision aid was developed as a one-page tool on the website of the Dutch Arthritis Society and is also readable and functional on mobile devices. On top of the page, the overall aim of the decision aid was stated and the parts and support functionalities on this page were briefly introduced (Box 6.1).

The first part, 'consultation support instructions in the context of disease control and treatment needs', informed patients on how to prepare for making treatment decision in the context of outpatient visits, such as gaining insight into what personal aspects matter most and advice to bring notes to outpatient visits.

The second part, 'an overview of available treatment options for axial SpA', informed patients on all available drugs for the treatment of axial SpA (i.e. NSAIDs, glucocorticosteroids, conventional synthetic DMARDs and b/tsDMARDs) and information on when these drugs are indicated.
The third part, 'detailed information on b/tsDMARDs and an interactive option grid that facilitates comparison of characteristics', informed patients on what they need to know prior to initiating a b/tsDMARD and includes an interactive option grid that facilitates comparing characteristics of these drugs. A maximum of five drugs can simultaneously be compared in the option grid.

The final part, 'a final check supporting patients to deliberate on the decision to initiate or switch a b/tsDMARD', supported patients in determining whether they had sufficient information to make a treatment decision. It was pointed out that remaining questions on treatment options or their personal worries and beliefs could be discussed with their healthcare provider and that patients can refrain from initiating or switching a b/tsDMARD on their request. Experts from the working group SpA suggested minor textual revisions on the content and layout of the pilot version.

Box 6.1 Summary of all parts of the decision aid

Part 1) Consultation support instructions in the context of disease control and treatment needs
1. Discuss how your disease affects your life
2. Formulate personal goals
3. Discuss whether your treatment matches with your personal goals
4. Discuss the disadvantages and advantages of your treatment options
5. Schedule a new appointment and discuss how you are going to monitor your disease
Part 2) Overview of available treatment options for axial SpA
1. NSAIDs
2. Glucocorticoids
3. DMARDs for patients with peripheral joint involvement
4. b/tsDMARDs
Part 3) Detailed information on b/tsDMARDs in axial SpA
1. Physical checks required prior to starting
2. Necessary regular checks required during use
3. Risk on infections
4. Storage of drugs at home
5. Requirement for and response to vaccination
6. Instructions to inform rheumatologist on (wished-for) pregnancy and breastfeeding
Information shown in an interactive option grid that facilitates comparison of characteristics:
1. Route of administration
2. Frequency of administration
3. Need for a step-up approach
4. Year of approval drug for axial SpA
5. Drug class (TNFi, IL17 or JAKi)
6. Expected time before effect can be experienced
7. Expected effect on axial joints
8. Expected effect on peripheral joints
9. Expected effect on enthesitis
10. Expected effect on psoriasis
11. Expected effect on ulcerative colitis and Crohn's disease
12. Expected effect on anterior uveitis
13. Most frequent adverse events

[continued on next page]

Box 6.1 *[continued]*

14. Drug safety in pregnancy and breastfeeding
15. Web link to lay information on medication

Part 4) A final check supporting patients to deliberate on the decision to initiate or switch a b/tsDMARD

1. Print or save the information in the option grid
2. Discuss you preferences on initiating or switching a b/tsDMARD with your rheumatologist
3. Be aware that you do not have to start a (new) drug at this moment
4. Consider whether you have sufficient information of make an informed decision
5. Discuss any remaining any questions or worries with your rheumatologist

axSpA =Axial Spondyloarthritis, b/tsDMARD = biological or targeted synthetic Disease-Modifying Antirheumatic Drug, IL17i = Interleukin 17 inhibitor, JAKi = Janus Kinase inhibitor, NSAIDs = Non-steroidal anti-inflammatory drugs, TNFi = Tumour Necrosis Factor inhibitor

Phase 4 Pilot testing

Alpha testing

For the alpha testing, individual semi-structured interviews were performed with 14 patients and 13 healthcare providers (Table 6.1). Eight out of 14 patients (57.1%)) who participated in the explorative needs assessment interviews also participated in the alpha testing. Overall, participants confirmed that all parts of the decision aid were useful for making treatment decisions on initiating a b/tsDMARD, especially the option grid enabled them to compare treatment options in a structured manner. Based on results from the alpha testing, minor modifications were made in the content and layout of the decision aid, including rephrasing of sentences and use of icons (see Supplementary file 6.8 for the received comments during alpha testing phase and performed actions by the steering group and professionals from the Dutch Arthritis Society and Supplementary file 6.9 for the final version of the decision aid).

Beta testing

For the beta testing, we assessed the feasibility of the decision aid in 14 patients recruited from seven rheumatology centres in the Netherlands (Table 6.1). All patients agreed they felt motivated to use the decision aid. Also, there was broad agreement that the decision aid was feasible to use in clinical practice (Figure 6.2). Notwithstanding, one third of the patients were neutral on the additional value of the decision aid on making treatment decisions and on recommending the decision aid to other patients. Two patients found that the decision aid was not easy-to-use nor that the duration of the decision aid was acceptable. However, the steering group and the Dutch Arthritis Society jointly decided to refrain from any further adjustments.

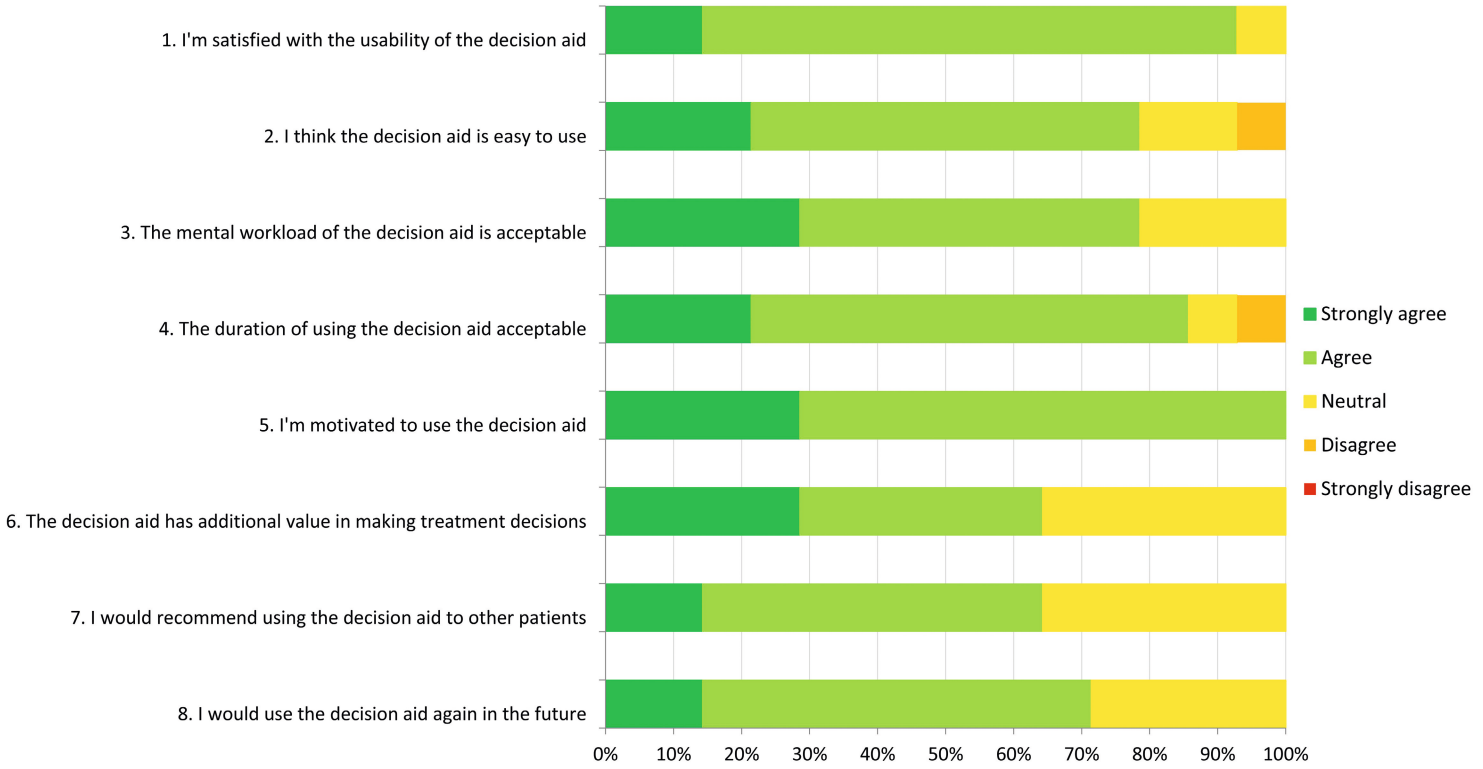

Figure 6.2 Feasibility testing (beta testing) of the decision aid in 14 patients in clinical practice

Phase 5 Introduction in clinical practice and evaluation

For the multifaceted strategy, the decision aid was introduced by the researchers to rheumatologists in several hospitals and to all members of the working group SpA. In addition, the Dutch Arthritis Society repeatedly promoted the decision aid to patients and healthcare providers on their website, social media and in their monthly newsletter. The paper-based information card with personalized b/tsDMARDs options can be requested free of charge at the Dutch Arthritis Society to continuously facilitate the use of the decision aid in clinical practice. In the future, the decision aid will be further promoted whenever possible.

The final version of the decision aid met 32 out of 38 (84.2%) items of the IPDAS quality instrument (Supplementary file 6.10). The remaining items were not explicitly stated in the decision aid because of lack of evidence or because of fear of abundant information, which might hinder the usability of the decision aid. The quality of the decision aid was officially approved by the board of the Dutch Society for Rheumatology.

Discussion

We described the development of an evidence-based decision aid that is feasible to support SDM in patients with axial SpA who face a treatment decision to initiate or switch a b/tsDMARD and its introduction in clinical practice. Patients can use this tool at home for retrieving more information, which will enable them to discuss their preferences for the decision with their rheumatologist. The systematic development process consisted of state of the art consecutive phases, including explorative needs assessment interviews, development of a prototype, and usability, ease-of-use and feasibility testing among patients and healthcare providers. Experts on axial SpA and professionals on patient information from the Dutch Arthritis Society were involved throughout all phases of the development process. The final version of the developed decision aid provides consultation support instructions in the context of disease control and treatment needs, informs on all available treatment options for axial SpA, provides detailed information on b/tsDMARDs, facilitates comparison of characteristics, and supports patients to deliberate on the decision to initiate or switch a b/tsDMARD. The pilot testing phases revealed that the usability, ease-of-use and feasibility of the decision aid were acceptable. The final decision aid was introduced to patients and healthcare providers in several Dutch rheumatology settings.

During several phases of the development process, both healthcare providers and patients mentioned that the SDM process in absence of a decision aid is mainly focussed on deciding whether or not to initiate a (new) b/tsDMARD, and to a lesser extent on which b/tsDMARD is preferred in the scenario in which two or more drugs are available. In daily practice, the decision on which b/tsDMARD is preferred depends not only on patient's clinical situation, but also on healthcare providers' knowledge, experiences and habits related to prescribing b/tsDMARDs, as well as preferential prescription policies within a rheumatology setting[29]. During the prototype development phase, we encountered challenges in realizing some information needs from

patients. For example, patients wished that the proposed effect of b/tsDMARDs on disease manifestations in the option grid could be tailored towards their personal medical situation, such as their b/tsDMARD history. However, this is challenging as failing a first b/tsDMARD might affect the proposed effectivity of a second b/tsDMARD compared to b/tsDMARD naïve patients[8].

We also refrained from the IPDAS recommendation to present the effectiveness of b/tsDMARDs as natural frequencies as there is limited evidence for some drugs[28]. Instead, we used simultaneously descriptive terminology and icons to report the effectiveness of these treatment options in the option grid (i.e. positive effect but more evidence is needed (icon: +), positive effect (icon: ++) and strong positive effect (icon +++). Both healthcare providers and patients found this way of presenting effectiveness of b/tsDMARDs in the option grid useful.

The overall impact of the decision aid on patient and disease outcomes does not only depend on patient' knowledge retrieved from the decision aid, but also on their skills and power[30]. For example, patients should have adequate health literacy and decision-making skills, such as applying health information and eliciting one's own preferences[30]. In addition, patients need power to believe in their capacity to influence the decision-making process, such as believing that they have permission to participate and having confidence in the value of their own abilities[30].

This study has some limitations. A first limitation is that, due to the COVID-19 pandemic, some patients who participated in the explorative needs assessment interviews refused participation in the pilot testing. This could explain the inclusion of more higher educated patients and patients with a job, which may not be representative for the total axial SpA population. Also, we could not evaluate whether their envisioned information and design needs were adequately incorporated in the decision aid. Second, selection bias might also have occurred by inviting patients for the feasibility testing phase via posts on social media, the website of the Dutch Arthritis Society and the monthly newsletter, as this requires sufficient digital skills of patients. Therefore, our findings on the usability, ease-of-use and feasibility of the decision aid might not be generalizable to patients who attained lower education, who are not employed or who have lower health literacy or digital skills. However, we consulted professionals on patient information throughout the development process to ensure the ease-of-use of the decision aid by all patients.

This study also has notable strengths. First, we involved patients and healthcare providers in nearly all phases of the development process to enhance broad acceptance and use of the developed tool in clinical practice. Second, the web-based design facilitates that the decision aid is accessible anytime and anywhere on a well-known website for patients with rheumatic diseases, which is also readable and functional on mobile devices. Besides, the decision aid can be printed and used on paper for patients who prefer paper-based tools or have limited health literacy or digital skills. As a result, the decision aid can be used by patients themselves at home, as well as together with healthcare providers during outpatient visits. Third, the overall quality of the decision aid is endorsed by national recognized accreditation of the Dutch Society for

Rheumatology, which confirms the correctness of the presented information. Fourth, we were able to evaluate the decision aids' usability and ease-of-use as well as its feasibility, of which findings have optimized the tool for use in clinical practice.

In conclusion, we developed an evidence-based decision aid to support patients who face a treatment decision to initiate or switch a b/tsDMARD and introduced this in clinical practice. Future studies should evaluate the overall impact of the decision aid on health outcomes of patients as well as improving the patient's experiences with the decision making process.

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CHAPTER 7

Validation and implementation of a patient reported experience measure for patients with rheumatoid arthritis and spondyloarthritis in the Netherlands

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Clin Rheumatol, 2020;39(10):2889-97
doi:10.1007/s10067-020-05076-6

Abstract

Objectives

To test the psychometric properties of the United Kingdom's Commissioning for Quality in Rheumatoid Arthritis Patient Reported Experience Measure (CQRA-PREM) in patients with spondyloarthritis (SpA) and rheumatoid arthritis (RA) and to implement this questionnaire in daily practice in the Netherlands.

Methods

After a forward-backward translation procedure into Dutch, the CQRA-PREM was tested in two quality registries in daily practice. Face validity was assessed with focus group interviews. Feasibility was evaluated through completion times and interpretability of domain scores through floor- and ceiling effects. Internal consistency (Cronbach's α coefficients) and homogeneity (corrected item-total correlations) were determined. Divergent validity was assessed by Spearman-rank correlation coefficients (r_s) between the average scores of domains and outcome measures. The CQRA-PREM was implemented in daily practice and the results were used in quality improvement cycles.

Results

Face validity of the CQRA-PREM was good. The CQRA-PREM was completed by 282 patients with SpA and 376 with RA. Median time to complete the CQRA-PREM was 4.7 minutes. Ceiling effects were found in three out of seven domains. Internal consistency of nearly all domains was considered good ($0.65 \leq \alpha \leq 0.95$). Thresholds for homogeneity were exceeded within three domains ($r_p > 0.7$), suggesting item redundancy. Divergent validity showed that nearly all domains of the CQRA-PREM were at most weakly correlated with outcomes measures ($-0.3 \leq r_s \leq 0.3$). The CQRA-PREM could identify areas of improvement for providing patient-centered care.

Conclusion

The CQRA-PREM has acceptable psychometric properties and has shown to be a useful tool in evaluating quality of care from the patients' perspective in the Netherlands.

Introduction

Evaluating the quality of care provided is helpful to reveal areas of improvement of care, identify best practices and stimulate development and implementation of care innovations. Health care services should also be transparent with respect to care provided, as decision makers, society and patients have the right to know about the quality of the services available to them[1]. The Institute of Medicine (IOM) identifies six pillars for evaluating quality of care in the current health care system: care that is provided should be safe, effective, patient-centered, timely, efficient and equitable[2]. Patient-centered care is gaining more attention in the last decade and has become a key part of audits of care organizations[3]. Patient-centered care is defined by the IOM as care that is respectful of, and responsive to, individual patient preferences, needs and values, and ensures that patient values guide all clinical decisions[2]. It is organized around the health needs and expectations of patients rather than around diseases.

There are several advantages of applying patient-centered care in daily practice. A literature overview showed that patient-centered care in patients with rheumatoid arthritis (RA) improved clinical safety and effectiveness[4]. Another study showed that better patient care experiences were associated with higher levels of adherence to treatment[5]. In addition, a patient-centered approach by family physicians and general internists in primary care was associated with decreased utilization of health care services and lower annual medical charges[6]. Therefore, it is important that patients should be asked about their experienced care and improve this where necessary.

Patients' perspectives on care provided within a certain time period can be evaluated with patient reported experience measures (PREMs), which focus on aspects of care that matter to patients and thereby identify areas of improvement for health care services. PREMs assess patients' experiences relating to the structure and/or process of care provided and might include questions relating to outcomes of care provided. PREMs can assess quality of care for the generic population or for a disease-specific population. Disease-specific PREMs are preferred for assessing quality of care provided as generic PREMs might not cover aspects of care that are specific and weighted towards a particular condition[7].

Currently, there are two measures available for assessing patient experiences with rheumatic care in the Netherlands: the Consumer Quality Index for patients with Rheumatoid Arthritis (CQ Index RA) and the Quality of Care Through the Patients Eye for all Rheumatic Patients (QUOTE – Rheumatic Patients)[8,9]. Both questionnaires are generic measures for assessing the quality of care provided in all health care services available to patients with RA and include the importance patients award to each aspect of quality of care.

However, both questionnaires have several limitations. First, the CQ Index RA and QUOTE – Rheumatic Patients contain a large number of questions (115 and 155 questions, respectively), which might be too time-consuming. Second, the CQ Index RA is disease-specific for RA and

therefore not applicable to other rheumatic diseases. Third, both measures are generic for health care services and are not specifically developed for rheumatology services.

In the United Kingdom (UK), a PREM has been developed by the Commissioning for Quality in Rheumatoid Arthritis (CQRA-PREM) to evaluate patients' perspectives on care provided in rheumatology units in the UK National Health Service (NHS)[10]. This questionnaire has been developed and validated in RA, modified and validated in other rheumatic conditions and is in use since 2015[10,11]. The CQRA-PREM includes 23 questions in seven domains aligned to the National Health Service Patient Experience Framework (NPEF) for patient-centered care and one question for evaluating the overall experience of the care provided[10]. The framework of the CQRA-PREM represents the most salient issues in patients' experiences with hospital care for RA patients and is widely used for assessing patients' experiences with care provided in several rheumatology units[12-14]. The NPEF domains can be used to identify specific areas of improvement from the patients' perspective within care departments. The implementation of the CQRA-PREM in rheumatology units was found to be effective in this regard[10].

Currently, a feasible PREM that is applicable to different rheumatic diseases in the setting of the rheumatology unit is lacking in the Netherlands. The primary aim of our study was to test the psychometric properties of the CQRA-PREM by performing qualitative and quantitative analyses in Dutch patients with SpA and RA. A secondary aim was to implement the CQRA-PREM in daily practice in the Netherlands. The results of the questionnaire were evaluated in quality improvement cycles for patient-centeredness of care.

Methods

PREM translation

The CQRA-PREM is categorized into seven NPEF domains for patient-centered care (one to five items per domain. Answers are given on a 5-point Likert scale ranging from "Strongly disagree" to "Strongly agree" (Supplementary files 1 and 2) [15]. Detailed information on the development and validation of the CQRA-PREM can be found elsewhere[10].

The UK version of the CQRA-PREM was independently translated into Dutch by two native Dutch-speaking researchers fluent in English (one rheumatologist and one health care scientist). Discrepancies were discussed and a consensus version was generated by both forward translators. The consensus version was back-translated by another bilingual Dutch researcher (a methodologist) with no prior knowledge of the questionnaire. A final version was developed by all three translators and was checked by an additional Dutch researcher unfamiliar with the original questionnaire (a rheumatologist).

Face validity

Face validity of the CQRA-PREM was studied by performing semi-structured focus group interviews with patients. Aspects of patient-centered care that were important to patients and their

current experiences with patient-centered care were assessed. A sample of adult patients from the rheumatology outpatient clinic of the Maastricht University Medical Center (MUMC) was invited to participate. Interviews were planned with approximately 5 patients per group, until data saturation was reached. Face validity was assessed by comparing aspects of care that were important to patients with domains of the CQRA-PREM.

Field testing

The psychometric properties of the CQRA-PREM were tested in two ongoing, prospective, disease-specific real-life quality registries in daily practice for patients with SpA and RA in the Netherlands, SpA-Net and DREAM-RA respectively, in two medical centers (MUMC and Medisch Spectrum Twente) in different geographical areas in the Netherlands[16,17]. Patients in these registries have a clinical diagnosis of SpA or RA and were consecutively included by their rheumatologist. In both registries, outcome measures, results of clinical examinations and laboratory investigations are routinely collected at every outpatient visit through a web-based data collection and quality management application (www.mijnreumacentrum.nl). Outcome measures consist of validated measures of disease activity, physical function and overall health status.

In SpA-Net, disease activity is measured by the Bath Ankylosing Spondylitis Disease Activity Index (BASDAI) and Ankylosing Spondylitis Disease Activity Score with C-Reactive Protein (ASDAS)[18,19], physical functioning by the Bath Ankylosing Spondylitis Functional Index (BASFI), Health Assessment Questionnaire – Spondyloarthritis (HAQ-S)[20,21] and disease impact by the Assessment of SpondyloArthritis international Society Health Index score (ASAS-HI)[22]. In DREAM-RA, disease activity is measured with the Disease Activity Score for 28 joints with Erythrocyte Sedimentation Rate (DAS28)[23] and physical functioning with the Health Assessment Questionnaire (HAQ)[24]. In both SpA-Net and DREAM-RA, overall health status is assessed with the self-report Health Survey Short Form (SF-36), resulting in physical component summary (PCS) and mental component summary (MCS) scores[25].

Starting from December 2016, patients from the two medical centers participating in SpA-Net and DREAM-RA were invited to annually complete the CQRA-PREM upon logging in to the application. Questionnaires were only saved if they were fully completed. Patients were informed that individual results are not visible for physicians or nurses. In the current cross-sectional analysis, the most recently completed CQRA-PREM from each patient was included for analyses. Results from outcome measures were included if they were completed within 14 days before or after completing the CQRA-PREM. For measures completed more than once within the 14-day timeframe, the measurement closest in time to the CQRA-PREM administration was selected.

Implementation and quality improvement

After translation and validation, the CQRA-PREM was implemented in daily practice. Through repeated Plan-Do-Check-Act (PDCA) quality improvement cycles, the results from the CQRA-PREM representing the patients' perspective on quality of provided care were evaluated at several occasions with rheumatologists and rheumatology nurses from both medical centres.

This was followed by group discussions to identify areas for improvement. Several action plans were formulated and executed in clinical practice, where possible.

Statistical analyses

Descriptive statistics were used to describe characteristics from participants of the focus group interviews, from patients who completed the CQRA-PREM in the patient registries and to describe the relative frequencies of scores in the CQRA-PREM for patients with SpA or RA. All focus group interviews were audiotaped and transcribed verbatim. In NVIVO V.11, the editing analysis style was used to analyze all transcripts by structurally classifying meaningful quotes into themes and subthemes. Finally, aspects of care that were important for patients were summarized and results were interpreted. Details about the patient inclusion procedure and data analyses have been described elsewhere[17].

In addition to face validity, the following elements of the COSMIN (Consensus based Standards for the selection of health status Measurement Instruments) checklist for evaluating the methodological quality of studies on measurement properties were examined: feasibility, interpretability and internal consistency[26]. Furthermore, homogeneity and divergent validity were also tested.

Feasibility of the CQRA-PREM was determined by calculating the median (interquartile range, (IQR)) time patients needed to complete the questionnaire. Interpretability of the CQRA-PREM was evaluated by testing floor- and ceiling effects in the average scores of the domains Needs and preferences, Coordination of care, Information about care, Daily living and physical comfort and Emotional support, thereby considering the categorical 5-point Likert scores as linear. Floor and ceiling effects were considered to be present if 15% or more of the patients had the lowest or highest possible average domain score[27].

Internal consistency of a single assessment of the CQRA-PREM was studied within domains containing more than two questions with correlation analyses (Cronbach's α coefficients) and was considered good if $0.70 \leq \alpha \leq 0.95$[28]. Homogeneity within domains containing more than two questions was studied with corrected item-total correlations (r_p) to identify questions with very weak or very strong correlations within the respective domain and was considered good if $0.3 \leq (r_p) \leq 0.70$[29].

Divergent validity was studied through non-parametric Spearman rank correlation coefficients (r_s) with average scores of domains and outcome measures for disease activity, daily functioning, health status and quality of life. Since PREMs are assumed to capture something different from the patient's condition or outcomes of treatment alone, and in accordance with studies evaluating PREMs in other medical conditions[30], correlations with patient-reported outcomes and clinical outcomes were hypothesized to be weak at most ($-0.30 \leq r_s \leq 0.30$), indicating that the measures evaluate relatively distinct constructs[31].

All analyses, except for face-validity, were repeated in patients stratified for the use of biological Disease-Modifying Antirheumatic Drugs (bDMARDs) at the time of completing of the CQRA-PREM. Statistical analyses were performed using IBM SPSS Statistics 24.

Results

The CQRA-PREM was completed by 282 patients with SpA and 376 patients with RA. The average age and the relative number of female patients with SpA were lower compared to patients with RA (52.7 (SD = 12.3) versus 61.5 (SD = 11.9) years and 47.9% versus 64.9% female patients, respectively (Table 7.1). The median disease duration was 8.6 (min 0.0 - max 66.5) years for patients with SpA and 7.7 (min 0.0 - max 44.0) years for patients with RA. Use of bDMARDs was 55.0% in patients with SpA and 29.8% in patients with RA. On average, disease activity was high for patients with SpA but low for patients with RA.

Both study populations experienced on average mild difficulties in physical functioning (mean HAQ-S = 0.8 (SpA) and mean HAQ = 0.8 (RA)). The overall health status related to physical health and mental health was comparable in patients with SpA and patients with RA (mean SF-36 PCS = 39.9 in SpA and mean SF-36 PCS = 40.9 in RA, and mean SF-36 MCS = 48.7 in SpA and mean SF-36 MCS = 50.5 in RA).

The distribution of the scores on the CQRA-PREM was skewed towards positive, indicating that patients have positive experiences with care, and is shown separately for patients with SpA and RA in Supplementary files 1 and 2.

Face validity

Semi-structured focus group interviews were performed to assess the face validity of the CQRA-PREM. Four focus group interviews were performed with 16 patients (3-5 patients per interview), after which information saturation was reached. Median age of the participants was 62.6 (41-78) years, median symptom duration 17.5 (1-66) years and 6 (37.5%) were male. The patients identified the following eight aspects as important for providing patient-centred care: 1) feeling heard by healthcare providers, 2) being involved in shared decision-making, 3) being able to visit the same healthcare provider over time, 4) being able to contact healthcare providers when needed, 5) feeling satisfied with the quality of answers, 6) being easily referred to other specialists when needed, 7) having the feeling that there is enough time during appointments and 8) having appointments on time. Nearly all these aspects are covered by the CQRA-PREM, except having appointments on time.

Psychometric properties

The median time to complete the CQRA-PREM was 4.7 minutes (IQR = 2.4) in the total population (4.7 minutes (IQR = 2.7) in SpA-Net and 4.6 minutes (IQR = 2.3) in DREAM-RA). Interpretability assessed by floor and ceiling effects in average scores of domains showed ceiling effects (≥15%) in the domains Needs and preferences for both patients with SpA and RA and in the

domains Daily living and physical comfort and Emotional support for patients with RA (Table 7.2). Internal consistency of all domains was considered good for patients with SpA or RA, except for the domain Daily living and physical comfort in patients with RA ($\alpha = 0.65$) (Table 7.2). Homogeneity was considered good for each question in the domains Information, education and self-care and Daily living and physical comfort for both patients with SpA or RA ($0.3 \leq (r_p) \leq 0.7$). However, thresholds for homogeneity were exceeded ($r_p > 0.7$) by two or more questions within the remaining domains for patients with SpA or RA (Table 7.2 and Supplementary file 7.3). The divergent validity showed that, as expected, nearly all domains of the CQRA-PREM were at most weakly correlated with patient reported outcomes ($-0.30 \leq r_s \leq 0.30$) (Table 7.3).

Table 7.1 Demographic characteristics and outcomes measures of patients in SpA-Net and DREAM-RA

	SpA-Net (n=282)	**DREAM-RA** (n=376)
Age, years	52.7 (12.3)	61.5 (11.9)
Female, n (%)	135 (47.9)	244 (64.9)
Symptom duration, years, median (min-max)	12.9 (0.6-67.5)	NA
Disease duration, years, median (min-max)	8.6 (0.0-66.5)	7.7 (0.0-44.0)
bDMARD use, n (%)	155 (55.0%)	112 (29.8%)
Disease activity		
BASDAI [0-10]	4.3 (2.2)	-
ASDAS [0-∞]	2.2 (0.9)	-
DAS28 [0-∞]	-	2.3 (1.2)
Physical function		
HAQ(-S) [0-3]	0.8 (0.6)	0.8 (0.7)
BASFI [0-10]	3.2 (2.4)	-
ASAS-HI [0-19]	5.7 (3.5)	-
Overall health status		
SF-36 PCS [0-100]	39.9 (10.4)	40.9 (9.6)
SF-36 MCS [0-100]	48.7 (11.2)	50.5 (10.8)

Values expressed as mean (SD), unless otherwise indicated.
ASAS-HI = Assessment of SpondyloArthritis international Society Health Index, ASDAS = Ankylosing Spondylitis Disease Activity Score, BASDAI = Bath Ankylosing Spondylitis Disease Activity Index, BASFI = Bath Ankylosing Spondylitis Functional Index, bDMARD = biological Disease-Modifying Antitrheumatic Drug, DAS28 = Disease Activity Score for 28 joints, HAQ(-S) = Health Assessment Questionnaire (for Spondyloarthritis), MCS = Mental Component Score, NA = Not Available, PCS = Physical Component Score, SF-36 = Short Form 36 Health Survey

Patient demographic characteristics and outcome measures were comparable between patients with or without bDMARDs use (Supplementary file 7.4), however, the median disease duration was higher in bDMARD users compared non-bDMARD users, both in RA and SpA. The median time to complete the CQRA-PREM did not differ between both subgroups (data not shown). Scores for interpretability and internal consistency were comparable between bDMARD and non-bDMARD users.

Table 7.2 Interpretability, internal consistency and homogeneity of the CQRA-PREM in patients with SpA or RA

		Interpretability				Internal consistency (Cronbach's α)		Homogeneity (r_p) [range]	
PREM domains	**N questions**	**SpA-Net**		**DREAM-RA**		**SpA-Net**	**DREAM-RA**	**SpA-Net**	**DREAM-RA**
		Floor effect	Ceiling effect	Floor effect	Ceiling effect				
1. Needs and preferences	5	0.4%	26.2%	0.0%	27.4%	0.90	0.93	0.69 – 0.82	0.71 – 0.85
2. Coordination of care and communication	4	0.4%	11.7%	1.1%	13.6%	0.87	0.91	0.65 – 0.78	0.71 – 0.87
3. Information, education and self-care	4	0.0%	8.5%	0.0%	7.4%	0.72	0.75	0.37 – 0.63	0.41 – 0.67
4. Daily living and physical comfort*	2	0.0%	14.9%	0.5%	18.4%	0.70	0.65	0.54	0.48
5. Emotional support*	2	0.0%	13.1%	0.5%	16.5%	0.84	0.91	0.73	0.83
6.Family and friends**	1	NA	NA	NA	NA	NA	NA	NA	NA
7. Access to care**	1	NA	NA	NA	NA	NA	NA	NA	NA

* No corrected item-total correlations range available as domain consists of 2 questions, ** No scores available as domain consists of 1 question
NA = Not Applicable

However, homogeneity differed between patients with and without bDMARDs in both SpA and RA (Supplementary files 7.5 and 7.6). Scores for divergent validity were also comparable between bDMARD and non-bDMARD users, except for the domains Access to care and Overall experience with care with all outcome measures in patients with SpA (Supplementary files 7 and 8). In both patients with RA and SpA without bDMARDs use, the correlations between these two domains and all outcome measures were in general higher compared to patients with bDMARD use, however, at most weakly correlated.

Implementation

In the PDCA-cycles, the CQRA-PREM identified the domain Information, education and self-care as an important area of improvement for patients with SpA and RA. Several adjustments in care were made to improve this domain. For example, every new patient with SpA or RA now receives a business card with contact information from his/her treating rheumatologist and is referred to a rheumatology nurse for education. The rheumatology nurse brings under attention the possibility of following a self-management course and supports the patient who is starting a disease-modifying antirheumatic drug. In addition, the awareness about patient organizations, patient groups and self-management programs was further increased by providing leaflets and projecting this on screens in the waiting room.

Discussion

In this study, we demonstrated that the CQRA-PREM has valid psychometric properties in patients with SpA and RA in clinical practice. In addition, we showed that the CQRA-PREM is a useful tool for assessing the patient-centeredness of care provided, and that it is able to identify areas of improvement in a Dutch rheumatology setting.

The CQRA-PREM showed good face validity as aspects that were rated as important to Dutch patients were similar to those raised by patients in the UK. The CQRA-PREM also covers all indicators from the Dutch QUOTE-Rheumatic patients[9]. However, the CQ-Index RA includes one domain specifically related to experiences with provided information about medication, which is missing in the CQRA-PREM. On the other hand, the CQRA-PREM includes two domains, Friends and family and Information, education and self-care, that are not addressed in both the CQ-Index RA and QUOTE – Rheumatic patients.

Feasibility of the CQRA-PREM was considered acceptable with a median completion time of 4.7 minutes. The homogeneity of the CQRA-PREM showed exceeded thresholds in three domains. This suggests that some questions are redundant within domains. However, our results for internal consistency did not differ from the original development study, both in RA patients (α=0.65 to α=0.93 (DREAM-RA) versus α=0.61 to α=0.90) and in SpA patients (α=0.70 to α=0.90 (SpA-Net) versus α=0.76 to α=0.91)[10]. Interpretability of the CQRA-PREM showed ceiling effects for the domains Needs and preferences, Daily living and physical comfort and Emotional support, which implies that the interpretability of the CQRA-PREM is not valid enough.

Table 7.3 Divergent validity of the CQRA-PREM in patients with SpA or RA

	Disease activity			Daily functioning			Overall health status	Generic health-related quality of life			
	SpA		RA	SpA		RA	SpA	SpA		RA	
Spearman's correlation coefficient (r_s)	BASDAI	ASDAS	DAS28	BASFI	HAQ-S	HAQ	ASAS HI	SF-36 PCS	SF-36 MCS	SF-36 PCS	SF-36 MCS
	n = 240	n = 186	n = 257	n = 200	n = 232	n = 342	n = 197	n = 260	n = 260	n = 349	n = 349
1. Needs and preferences	-0.18**	-0.16*	-0.08	-0.12	-0.10	-0.05	0.20**	0.12	0.14**	0.00	0.14
2.Coordination of care and communication	-0.09*	-0.11	-0.11	-0.11	-0.09	-0.05	-0.14*	0.09	0.07	0.10	0.04
3.Information, education and self-care	-0.05	-0.02	-0.10	-0.08	-0.01	-0.06	-0.09*	0.06	0.10*	0.07	0.17*
4. Daily living and physical comfort	-0.48**	-0.42**	-0.35**	-0.34**	-0.35**	-0.32**	-0.44**	0.40**	0.28**	0.34**	0.28**
5. Emotional support	-0.09*	-0.11	-0.25	-0.20**	-0.17**	-0.20*	-0.18	0.16**	0.10*	0.14	0.14
6. Family and friends	-0.14*	-0.18*	0.03	-0.08	-0.06	-0.01	-0.09	0.03	0.11	-0.05	0.06
7. Access to care	-0.19**	-0.25**	-0.09	-0.17*	-0.16*	-0.10	-0.22**	0.14*	0.13*	0.09	0.13*
8. Overall experience of care	-0.21**	-0.22**	-0.14	-0.24*	-0.19**	-0.11	-0.18*	0.17*	0.08	0.13	0.20**

* Spearman rank correlation is significant at 0.05 level ** Spearman rank correlation is significant at 0.01 level
ASAS-HI = Assessment of SpondyloArthritis international Society Health Index, ASDAS = Ankylosing Spondylitis Disease Activity Score, BASDAI = Bath Ankylosing Spondylitis Disease Activity Index, BASFI = Bath Ankylosing Spondylitis Functional Index, DAS28 = Disease Activity Score for 28 joints, HAQ(-S) = Health Assessment Questionnaire (for Spondyloarthritis), MCS = Mental Component Score, NA = Not Available, PCS = Physical Component Score, RA = Rheumatoid Arthritis, SF-36 = Short Form 36 Health Survey, SpA = Spondyloarthritis

However, these results could reflect true patient experiences and thus satisfaction with care provided or social desirability bias could have occurred, despite the fact that patients were made aware that results were not visible for physicians and nurses[29]. Moreover, ceiling effects are common in patient experiences measures, in contrast with scores for outcome measures[32].

Subgroup analyses were performed in patients with or without bDMARD use at the time of completing the PREM, as hypothetically these patients might have different experiences with provided care. Our study showed that results for feasibility, interpretability, internal consistency and nearly all analyses for divergent validity were comparable between these groups. Despite that scores for homogeneity differed slightly between these groups, the overall validity of the CQRA-PREM was acceptable in both subgroups.

The Dutch version of the CQRA-PREM was field tested in two patient registries and therefore patients might provide higher scores for question 2d (I feel that the people I see at the clinic are fully up to date with my current situation), which could result in selection bias. However, it is expected that this has a minimal effect on the validity of the domain Information, education and self-care, because it is not solely related to this information, but also to having received information on time and receiving enough information to make decisions. Results for the domain Coordination and communication are not biased by field testing in the patient registers, because patients cannot directly contact their healthcare providers through our registries as there is no email functionality in the system. We therefore believe that field testing in patient registries has resulted in only limited selection bias and that the CQRA-PREM can also be used in patients in standard care.

Evaluating the quality of care with PREMs, in addition to Patient Reported Outcome Measures (PROMs), is important as they measure different aspects of quality of care. PREMs assess patients' perspectives on the structure and process of provided care, while PROMs specifically assess patients' perspectives on the outcomes of provided care. Besides that, patients' perspectives on the quality of provided care might differ from the perspective of health care professionals. As we did in our study, PREMs can be used by healthcare providers to reflect on their own and their team's performance, indicate specific areas of improvement at clinical and organizational levels and can be used for evaluating the impact of introduced changes within organizations. Patients benefit from PREMs as it helps them by choosing high quality healthcare providers when results for quality of care are made transparent for the public.

This study has several limitations. First, no cognitive debriefing with native Dutch speaking patients and no cross-cultural validity were performed. However, besides the three translators, one additional native speaker was included to check the final Dutch version for linguistic and cultural accuracy. Second, no factor analyses were performed to support that the allocation of questions into domains is similar in the Dutch version as in the original CQRA-PREM. However, all translators agreed that each domain of the NPEF is represented by the allocated questions in the Dutch version of the questionnaire. Third, the psychometric properties test-retest reli-

ability, sensitivity-to-change over time and convergent validity could not be examined in this study. These aspects could be evaluated in further studies, as well the ability of the CQRA-PREM to discriminate between rheumatology units who have more or less attention for providing patient-centered care. Fourth, we acknowledge that selection bias could have occurred due to the registries' web-based design as patients with low health literacy and/or computer skills might have been excluded from this study. Fifth, the CQRA-PREM did not include a free text field for additional remarks from patients, who wanted to elaborate on their results or offer possible solutions for aspects that could be improved in their experiences. Although analyzing these additional remarks in a mixed-method approach might be time consuming, it could provide valuable information for the rheumatic care services.

A strength of our study is that the translation and validation of the CQRA-PREM was combined with focus group interviews to test face validity and with implementation of the measure in daily practice with which, through PDCA-cycles, areas for improvement were identified and acted upon. A second strength of this study is that the CQRA-PREM was tested in two real-life registries for SpA and RA in the Netherlands. We were able to validate the questionnaire in daily practice and study divergent validity with recorded outcome measures for disease activity, physical functioning, and overall health status.

In conclusion, the CQRA-PREM has acceptable psychometric properties for assessing quality of care provided in daily practice from the perspective of patients with SpA or RA in the Netherlands. Scores for quality of care provided are not substantially affected by outcome measures for disease activity, physical functioning and overall health status. The CQRA-PREM has shown to be a useful tool in PDCA quality improvement cycles and can be used to optimize patient-centered care in rheumatic health care services as recommended by the IOM.

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CHAPTER 8

Summary and general discussion

With this thesis, we aimed to improve the quality of healthcare for patients with rheumatic and musculoskeletal disease (RMDs). When we initiated this thesis, some improvements and innovations were necessary to optimize these aspects in clinical practice. We therefore responded to encountered challenges in clinical practice related to monitoring of outcomes and providing patient-centered care. These challenges are not specific for rheumatology, but apply to all disciplines when considering the role and position of medical specialists in the near future. The Dutch Federation of Medical Specialists (FMS) formulated the aspiration that by 2025 Dutch medical specialist healthcare is among the most innovative, efficient and best-quality healthcare worldwide[1]. In this final chapter, the main findings of all studies part of this thesis are summarized, followed by a discussion of the main results with respect to used methodology and the implementations of results into clinical practice. These studies resulted in new insights into an existing body of evidence, but also identified knowledge gaps and prompted new research questions.

Summary of main findings

In **chapter 2** of this thesis, we described the need for a web-based tool for systematic monitoring of patients with SpA in clinical practice in the Netherlands and our efforts to develop and implement such a system, called SpA-Net. This tool follows the patient journey in daily practice and summarizes all relevant aspects for clinical decision making, including comorbidities, prescribed medication, adverse events and patient- and physician-reported outcome measures for disease activity, physical functioning and overall health status. For the design and content of SpA-Net, we consulted rheumatologists (including experts in the field of SpA), nurses and experienced patient research partners. The technical development and infrastructure were performed by an external firm specialised in the development of software for collecting and monitoring clinical and patient-reported outcomes. After the initial development phase, SpA-Net was evaluated during multiple rounds of internal and external testing with all stakeholders after which encountered errors were solved and the last version was optimized. Finally, in 2016, we used a multifaceted strategy to successfully implement SpA-Net as an electronic medical record (EMR) as part of the standard workflow in five rheumatology centres in the Netherlands. In 2017, its usability and acceptability was evaluated and confirmed by both patients and healthcare providers (HCPs) and barriers against use were identified. Since its launch more than 1300 patients with SpA have been enrolled.

In **chapter 3**, we described the need for a composite score to assess disease activity in patients with peripheral SpA in clinical practice. We therefore evaluated the performance of the Disease Activity Index for Psoriatic Arthritis (DAPSA), the Psoriatic Arthritis Disease Activity Score (PASDAS) and ASDAS in patients with peripheral SpA. We assessed the concurrent validity, discrimination across available thresholds of disease activity and the concordance in classification of patients in DAPSA, PASDAS, and ASDAS disease activity states. Our findings showed that the concurrent validity and discrimination across thresholds of disease activity for the DAPSA, PASDAS and ASDAS were acceptable in patients with peripheral SpA with, on average, low degree of peripheral joint involvement. Classifying patients in the pre-defined disease

activity states of the composite scores showed remarkable discordance in the high disease activity states (DAPSA 22%, PASDAS 56% and ASDAS 48%). In patients with and without psoriasis some differences in the performance of the measures were found, however this might be caused by the small proportion of patients without psoriasis included in this study. Of interest, the performance of the ASDAS was comparable in patients with axial SpA and peripheral SpA.

In **chapter 4**, we evaluated the extent to which extent treat-to-target (T2T) recommendations (i.e. frequency of measurement, target-based treatment intensification) were applied in clinical practice in a setting where HCPs were supported by SpA-Net. During a 1-year study period, disease activity was assessed at least once with the Ankylosing Spondylitis Disease activity Score (ASDAS) in 185 out of 219 patients (84%). The frequency of measurement varied from 0 (34 patients) to 6 (1 patient), while the majority (158 patients, 73%) had 1 or 2 measurements during the 1-year follow-up. At the first measurement, 114 (62%) did not meet low disease activity. Interestingly, in only 26 (23%) of these patients, disease activity was re-evaluated within the recommended 3 months and after 12 months, still in 31 (27%) of the patients, disease activity was not re-evaluated. We also investigated whether treatment adaptation occurred based on the ASDAS state. In 19 out of 114 (17%) patients with high disease activity, treatment was changed within 6 weeks after ASDAS measurement. At re-evaluation after 3 months in those with persistent high disease activity, only 2 more treatment adaptations occurred. From this study, we can conclude that, even with access to a web-based tool for monitoring patients and supporting HCPs, T2T is applied to only a limited extent in daily practice in patients with axial SpA. The scores seemed not to be driving re-evaluation nor treatment adaptation.

In **chapter 5**, we aimed to further specify the knowledge gap related to managing fatigue, a major concern for patients with RMDs in clinical practice. A patient panel formulated 15 research questions that were subsequently summarised in five research areas including: (i) the definitions of fatigue; (ii) measurement instruments to quantify and diagnose fatigue; (iii) determinants of fatigue; (iv) consequences of fatigue; and (v) the effect of interventions on fatigue. We performed a scoping review of published literature reviews addressing the five pre-identified research areas on fatigue in patients with rheumatoid arthritis (RA), SpA, osteoarthritis and fibromyalgia. Overall, 134 reviews were included (19 Cochrane reviews, 44 non-Cochrane systematic reviews and 71 narrative reviews). Of these, 34% of the reviews considered fatigue in RA and only 4% of the reviews considered fatigue in osteoarthritis. Although no consensus definition exists for fatigue in RMDs, the reviews were in agreement that patients with RMDs can experience several types of fatigue that can occur simultanously or alternatingly in patients' lives.
Numerous unidimensional nor multidimensional patient-reported measurement instruments to assess fatigue were summarized in reviews. It was noted that only a small proportion of these instruments were developed and/or validated for use in clinical care and include cut-off values to identify persons with excessive fatigue. Further, a large number of health-related and contextual factors were identifed to be associated with fatigue as either a determinant or a consequence, but overall the strength of assocations was small, pointing to the complexity of fatigue. Regarding interventions, pharmacological interventions had a small to moderate

effect on fatigue in RA, improved fatigue in SpA (no effect sizes available), but had no to a small positive effect on fatigue in fibromyalgia. Non-pharmacological interventions had generally no to a small positive effect on fatigue across RMDs.

In **chapter 6**, we deliberated on the need to fully inform patients on their current medical situation and on the expected effect of treatment options on disease outcomes and their personal lives. In this chapter, we developed an evidence-based decision aid to support patients who face a treatment decision to initiate or switch a b/tsDMARD and introduced this in clinical practice. The development process was based on a Dutch guidance document of the Dutch Health Care Institute for the development of patient information and decision aids in accordance with quality standards, and on the internationally accepted process development model of the International Patient Decision Aid Standards (IPDAS) collaboration[2,3]. The systematic development process consisted of state of the art consecutive phases, including explorative needs assessment interviews, development of a prototype, and usability and feasibility testing among patients and healthcare providers. Experts on axial SpA and professionals on patient information from the Dutch Arthritis Society were involved throughout all phases of the development process. The final version of the decision aid provides consultation support instructions in the context of disease control and treatment needs, informs on all available treatment options for axial SpA, provides detailed information on b/tsDMARDs, facilitates comparison of characteristics, and supports patients to deliberate on the decision to initiate or switch a b/tsDMARD. The pilot testing phases revealed that the usability and feasibility of the decision aid were acceptable. The final decision aid was introduced to patients and healthcare providers in several Dutch rheumatology settings.

In **chapter 7**, we described the need for a Dutch patient-reported experience measure (PREM) to assess the patient perspective on the structure and processes of healthcare in rheumatology settings in the Netherlands. The English Commissioning for Quality in Rheumatoid Arthritis PREM (CQRA-PREM) was found to be useful for this purpose in patients with RA and other rheumatic conditions[4,5]. We drafted a Dutch version of the CQRA-PREM using a forward-background translation procedure and tested its face-validity during focus group interviews with patients with RMDs. The Dutch version of the CQRA-PREM was piloted by patients with SpA and RA in clinical practice using SpA-Net and DREAM-RA, respectively. Ceiling effects were found in three out of seven domains, internal consistency of nearly all domains was considered good ($0.65 \leq$ Cronbach's α coefficients), thresholds for homogeneity were exceeded within three domains (corrected item-total correlations >0.7) suggesting item redundancy and divergent validity showed that nearly all domains of the CQRA-PREM were at most weakly correlated with outcomes measures ($-0.3 \leq$ spearman's rank correlation coefficients ≤ 0.3). It was concluded that the performance of the Dutch version of the CQRA-PREM has acceptable measurement properties for evaluating quality of healthcare from the patients' perspective in the Netherlands.

Next, the CQRA-PREM was implemented in clinical practice in two rheumatology settings and results were evaluated through repeated Plan-Do-Check-Act (PDCA) quality improvement

cycles. During these cycles, the results from the CQRA-PREM were evaluated at several occasions with rheumatologists and rheumatology nurses from both medical centres after which action plans were formulated and executed in clinical practice to improve the structure and processes of healthcare where possible. For example, every new patient with SpA or RA now receives a business card with contact information from his/her treating rheumatologist and is referred to a rheumatology nurse for education. Also, the awareness about patient organizations, patient groups and self-management programs was further increased by providing leaflets and projecting information on screens in the waiting room. We concluded that the Dutch version of the CQRA-PREM is a useful tool for assessing patient experiences with healthcare in Dutch rheumatology settings.

Discussion main results

Monitoring of disease outcomes in practice

Monitoring of disease outcomes is essential for providing patient-centered care, as recorded results support HCPs in making optimal healthcare decisions. To this end, we developed and implemented an integrated web-based tool that facilitates regular and personalized (tele)monitoring of disease outcomes by both patients and HCPs in remote and outpatient settings, called SpA-Net (**chapter 2**).

Monitoring of disease outcomes in SpA-Net is useful for clinical practice as a recorded up-to-date complete overview of all relevant health and disease aspects can support HCPs and patients with clinical decision making, which in turn can result in better outcomes of care[6,7]. In addition, monitoring of disease outcomes using PROMs can support patients in understanding their disease and can stimulate engaging in their own healthcare[8]. In response, this might improve communication with their HCPs which enhances SDM and improves treatment adherence[9].

Besides, longitudinal observational data on relevant health outcomes in daily practice can be useful for research purposes, as these data come from a large heterogeneous real world patient population without focusing on specific interventions, which has better external validity compared to data collected in randomized control trials (RCTs). SpA-Net also enabled us to run a pragmatic multicentre RCT evaluating whether telemonitoring combined with patient-initiated follow-up can reduce the number of outpatient consultations compared to routine care in patients with SpA[10]. Such self-monitoring strategy with the use of SpA-Net can potentially lower the number of follow-up outpatient visits, which can optimize use of time and resources in clinical practice[11].

In SpA-Net, the effectiveness and safety of drugs are securely monitored for the total SpA population, including elderly and those with comorbidities. SpA-Net is also linked to the Dutch pharmacovigilance centre (Lareb) for reporting (serious) adverse events on medication[12]. Furthermore, the data collected in SpA-Net have been used to provide accountability towards external stakeholders who have the right to be informed on the quality of provided healthcare, such as

patients, policy makers and society. Finally, the collected data can be used to minimize any unwarranted variation in healthcare utilisation between practices by being transparent on benchmarking results at quality of healthcare assessment meetings[13].

Encountered challenges for monitoring in clinical practice

We demonstrated that an integrated tool for monitoring of disease outcomes can be developed and implemented, however it appeared to be challenging to use this tool as intended in daily clinical practice. Some hurdles were encountered on the level of patients, HCPs and the organisation.

At the level of the patient, it was observed that patients frequently lost their login credentials and often forgot to complete electronic patient-reported outcome measures (ePROMs) prior to an outpatient visit. We were partly able to tackle this by appointing a (specialized) nurse who proactively contacted patients who failed to complete ePROMs prior to their visit. In addition, touch-screen tablets became available in the hospital's waiting room and patients with low health literacy and digital skills were offered support when needed. Another hurdle was that some patients lost their motivation to use SpA-Net over time. High attrition rates can be observed when patients have to repeatedly complete the same questionnaires[14]. After exploring users' reasons for these high attrition rates, we made some minor adaptations in its content and design over the years. This was possible as SpA-Net was conceptualized as a dynamic system. For example, the graphs displayed were rearranged on request of patients, new PROMs were added and a few others were removed if they were no longer considered of value. In addition, we reduced the patient burden by prolonging the intervals at which some PROMs need to be completed. An alternative solution for high attribution rates could have been to use computerized adaptive testing methods to reduce the number of questions, such as offered by the Patient-Reported Outcomes Measurement Information System[15].

We also saw reluctance of some HCPs to use SpA-Net in clinical practice. Resistance from HCPs to change their (clinical) behaviour, including the implementation of new (digital) tools, is a common phenomenon as they might experience cognitive, motivational or attitudinal barriers[16]. We tried to tackle this resistance by intensively engaging end-users during all phases of development process. Furthermore, all rheumatologists and (specialized) nurses from participating centres were (repeatedly) trained to use SpA-Net in clinical practice and a standard operating procedure was provided for optimal record keeping. However, some were still not successful in incorporating SpA-Net in their workflow, because of to lack of interest, time, or technical skills or because of privacy or security concerns.

An important hurdle at the organisational level was the lack of integration of SpA-Net with the local hospital's EMR, which could potentially further reduce the administrative burden of HCPs by avoiding double registration. This hurdle also hindered the rollout of SpA-Net to other centres. Finally, the annual licence costs were a financial barrier for some hospitals to participate.

Evaluation of adherence to a management approach

Data from clinical care are useful sources for evaluating the adherence to recommended treatment approaches in practice. We evaluated to what extent disease activity was monitored and whether recorded scores were used to drive re-evaluation and treatment intensification in patients with axial SpA during a one 1-year study period, as recommended by the T2T management strategy (**chapter 3**)[17,18]. This study showed that disease activity scores appear not to drive the frequency of re-evaluation nor treatment adaptation when the predefined target of inactive disease or low disease activity was not achieved. These findings are in line with studies performed in patients with PsA or RA for whom applying T2T has been strongly advised now for over 10 years[19-21].

In this study, we did not evaluate the rheumatologists' and patients' reasons for being reluctant to act upon monitored disease activity scores. These reasons for not re-evaluating disease activity within recommended periods and treating to target will likely go beyond encountered challenges for monitoring in clinical practice[22]. We can therefore only speculate on rheumatologists and patients reasons for these results.

First, trial evidence for T2T was lacking prior to the start of the study period. To date, we do have trial evidence, however, the first RCT on the efficacy of T2T in patients with axial SpA, the Tight Control in SpA (TICOSPA) trial, turned out to be a negative trial, as treating patients towards ASDAS inactive disease or low disease activity was not significantly superior to usual care in achieving an improvement of ≥30% in the Assessment of SpondyloArthritis International Society Health Index (ASAS-HI), the primary endpoint[23]. Also, while the T2T strategy compared to care as usual showed some additional efficacy on disease activity, effects on radiographic damage were not studied in this short term study.

Although effectiveness of T2T in axial SpA remains undetermined, some results of the secondary analyses argue in favour of a T2T strategy[18]. Of interest, T2T was beneficial from a health economics perspective, mainly because of cost-saving related to lower sickness absence in the intervention arm.

Second, HCPs might be reluctant to adapt treatment in patients with ASDAS high disease activity, as they may experience uncertainty whether the scores truly reflect disease activity or whether these are attributable to comorbid disease (for example fibromyalgia). Also, the presence and activity of extra-musculoskeletal manifestations (e.g. psoriasis, inflammatory bowel disease) are not taken into account in the ASDAS, which may influence treatment decisions[24].

Finally, patients might also be reluctant to adapt their treatment as they might have worries about potential ineffectiveness of alternative treatment options or adverse side effects of a new drug[25]. Needless to say, patients should be equal partners and should be given the opportunity to be actively involved when making treatment decisions.

Future studies should explore all barriers and facilitators of T2T for successful monitoring of disease outcomes and acting upon these results in clinical practice. A first step should be performing a systematic literature review summarizing available knowledge on the barriers and facilitators for each element of the T2T approach, i.e. defining the target, selecting the preferred outcome measure for assessing this target, the frequency of monitoring, adapting the treatment and the overall SDM process for applying T2T. Next, qualitative interviews with stakeholders should be performed to check the completeness and correctness of the literature evidence and to explore solutions for these barriers in the structure and processes of care within rheumatology centres. This new obtained knowledge can be used to draft a multifaceted implementation strategy for successfully implementing T2T in clinical practice, or, if necessary, adapting the T2T recommendations.

Outcome measures for disease activity in peripheral SpA

It is self-evident that health outcomes should be assessed with trustworthy measurement instruments to prevent over- or under treatment of patients in clinical care and for making reliable conclusions in research settings.

For peripheral SpA, composite measurement instruments to comprehensively assess disease activity in clinical practice were lacking. We therefore assessed the performance of three instruments to assess disease activity SpA, the DAPSA, PASDAS and ASDAS, in patients with peripheral SpA and compared their performances in patients with and without psoriasis (**chapter 4**).

The process of evaluating the performance of measurement instruments can be guided by the systematic Outcome Measures in Rheumatology (OMERACT) instrument selection methodology[26]. This methodology describes a set of standards which, when met, answers whether there is enough evidence to support the use of an instrument in a specific setting, such as in RCTs, observational studies or clinical practice. The OMERACT methodology consists of three pillars: 1) *truth* (face/content validity and construct validity), 2) *discrimination* (reliability and discrimination between groups of interest), and 3) *feasibility* (applicability)[26]. For our study in patients with peripheral SpA, we evaluated aspects of the OMERACT pillar *truth* by means of face validity, concurrent validity (a type of criterion validity) and of the pillar *discrimination* by means of discrimination across thresholds of disease activity and concordance in classification in disease states.

Of interest, when applying each instrument's thresholds of meaning, there was substantial discordance in the proportion of patients classified into the two highest disease activity states, which was 22% of patients for the DAPSA, 56% for the PASDAS, and 48% for the ASDAS. These differences might be explained by the mathematical contribution of individual components of disease activity to the overall score of each instrument. In this line, it would be of interest to understand the contribution of the involvement of peripheral joints to the instruments' score, as the way peripheral joints are accounted for varies greatly between scores.

Alternatively, the discordance could also be an indication that the existing thresholds of disease activity states of the DAPSA and PASDAS for patients with psoriatic arthritis and of the ASDAS for axial SpA were not applicable to patients with peripheral SpA. This might be a result of the used external criteria that were considered to be representative of various diseases activity states. For example, the external criteria used for defining DAPSA thresholds include outcome measures reflecting peripheral involvement (such as the swollen and tender joint count), while the external criteria used for defining ASDAS thresholds reflect axial involvement (such as Bath Ankylosing Spondylitis Disease Activity Index (BASDAI) and ASAS partial remission criterion)[27,28]. It is therefore needed to redefine thresholds of the DAPSA, PASDAS and ASDAS using the same external criteria specifically relevant for peripheral SpA.

The OMERACT pillar *discrimination* also captures test-retest reliability, responsiveness (also called longitudinal construct validity), clinical trial discrimination and thresholds of meaning (i.e. minimal importance difference)[26]. Some of these measurement properties have been studied for the DAPSA, PASDAS and ASDAS in clinical trial settings and specific patient populations, but their performance could not be evaluated in our study due to lack of data.

The third OMERACT pillar *feasibility* states that the advantages and disadvantages of each instrument should be considered when selecting the preferred outcome measure. With respect to our study, we can conclude that the ASDAS has several practical advantages compared to the DAPSA and PASDAS. For example, its calculation is much faster as this does not require full joint examination. In addition, the ASDAS can be used for remote monitoring of disease activity as its components, including measuring C-reactive protein levels, are assessor independent. On the other hand, the DAPSA has a practical advantage over the PASDAS and ASDAS, as the calculations of these instruments are complex and require a calculator or online tool.

In a response to our study, Laura Coates and William Tillett wrote an editorial in which they reflected on how disease activity can be measured in patients with peripheral SpA[29]. They addressed the heterogeneous nature of the disease manifestations in peripheral SpA as one of the widely recognized challenges for assessing disease activity in these patients. The question arises whether the same measurement instrument should be used to assess disease activity in all subtypes of peripheral SpA or whether the preferred outcome measure depends on the present disease manifestations[30]. For example, the tender and swollen joint counts weigh relatively more to the overall score in the calculation of the DAPSA, which may lack face validity in patients with predominantly oligoarticular disease. Comparably, the ASDAS includes one question on back pain, which may lack face validity in patients peripheral SpA without axial involvement. In addition, concerns about the usefulness of the DAPSA and ASDAS as measures of disease activity for patients with PsA have been expressed, as these scores assess joint disease, but do not take into account other aspects of disease activity, such as the degree of skin involvement (psoriasis) which is also important to patients and may have treatment implications[31].

Our study on the performance of the DAPSA, PASDAS and ASDAS in peripheral SpA is a valuable first step forward towards finding a trustworthy composite score for assessing disease activity in peripheral SpA in clinical practice. However, more research is needed whether to select one measurement instrument or to develop a new instrument. A next step would be to study the remaining aspects of the OMERACT pillar discrimination for the DAPSA, PASDAS and ASDAS, including test-retest reliability, responsiveness and thresholds of meaning (i.e. minimal importance difference). Our results also warrant further studies for determining both patient and rheumatologist anchor statements around disease activity states.

Challenges related to providing patient-centered care

A key principle of patient-centered care is that HCPs and patients act towards healthcare aspects that matter to both of them[32]. Patients should therefore not only be actively engaged in their clinical care, but also in scientific research[33]. Patients can undertake several roles beyond those of traditional study participants, including being involved as consulting partners on study designs, as collaboration partners for raising funds or as partners for the dissemination of knowledge[34]. Such patient engagement can potentially increase the quality of research and ultimately improve healthcare services by preventing a mismatch between patients' preferences and the scientific focus[35,36]. Research agendas should therefore reflect patients' healthcare needs and preferences.

To this end, the Dutch Arthritis Society has organized panel discussions with patients with RMDs to draft a research agenda for reducing experienced hurdles on managing their rheumatic disease in daily life[37]. This patient discussion panel prioritised 'fatigue and its treatment' as the most important knowledge gap that should be addressed to improve daily clinical care. As a first step to act towards this prioritized research area, we performed an elaborated reviews of reviews on aspects of fatigue that are relevant for clinical practice for patients with RA, SpA, osteoarthritis and fibromyalgia (**chapter 5**).
The extensive amount of evidence synthesised in this scoping review reflects all current knowledge on fatigue in RMDs and reveals important knowledge gaps and research areas that are in need for further inquiry. An important insight is that numerous studies and reviews addressed fatigue in RMDs, but it is challenging to translate these results into clinical practice. A logical next step for unravelling and ultimately improving fatigue in RMDs would therefore be to develop an agreed upon research agenda on fatigue in RMDs in cooperation with patients to rank the importance of research areas from their perspective. This research agenda should also merge research areas to efficiently develop more insights into and solutions for this complex symptom.

A first step of the task force should be obtaining consensus on the overarching definitions of (types of) fatigue and composing a conceptual framework for (types of) fatigue in RMDs based on patient experiences and available evidence. This framework should be the starting point for the development or selection of validated measurement instruments that align with all identified types of fatigue. Next, the minimal clinical important differences (MCID) and cut-off values to diagnose or classify 'excessive fatigue' should be determined for these measurement

instruments. Ultimately, all newly obtained knowledge should be incorporated in guidelines for research and practices. In this way, patients and HCPs can be supported with clinical reasoning and with composing a tailored treatment plan for fatigue in individual patients with RMDs.

Shared-decision making

For patients with axial SpA, the SDM process with respect to treatment has become increasingly complex in the last decade, as many b/tsDMARDs have become available with comparable effectiveness and safety, but different individual characteristics[38]. In an effort to support patients with axial SpA who face a treatment decision to initiate or switch a b/tsDMARD, we developed an up-to-date evidence-based decision aid and introduced this tool to patients and HCPs in several rheumatology settings across the Netherlands (**chapter 6**).

The engagement of its users in the development process of the decision aid can increase their trust in the content and contribute to broad acceptance and use in clinical practice. For this purpose, we based the development process on (i) a Dutch guidance document of the Dutch Health Care Institute for the development of patient information and decision aids in accordance with quality standards, and on (ii) the internationally accepted process development model of the IPDAS collaboration, which is based on the principles of patient-centered care[2,3]. In addition, we consulted patients with SpA and expert rheumatologists from the working group SpA of the Dutch Society for Rheumatology for their expert opinion throughout all phases of the development process. Our decision aid therefore includes all needed information to support SDM in line with patients' personal needs and preferences.

However, the overall impact on successful applying a decision aid does not only depend on patients' *knowledge* retrieved from the decision aid, but also on their *skills* and *power*[39]. For example, SDM requires that patients have health literacy and decision-making *skills,* such as applying health information, eliciting one's own preferences and communicating worries with HCPs[39]. In addition, patients need *power* to believe in their capacity to influence the decision-making process, including factors such as believing that they have permission to participate and ask questions, having confidence in the value of their own knowledge and ability to acquire medical knowledge[39]. Future research should therefore evaluate the overall impact of the decision aid on health outcomes of patients as well as improving the patient's experiences with the decision making process.

PREMs for rheumatology settings

Patients' perspectives on the quality of provided care should be assessed at regular intervals with PREMs to identify areas for improvement in the structure and processes of care. Next, HCPs should anticipate on these results to initiate necessary improvements and innovations in healthcare[40]. To facilitate assessing patient perspectives on the quality of rheumatology services in the Netherlands, we evaluated the psychometric properties of the Dutch version of the widely used, feasible CQRA-PREM and implemented this instrument in clinical practice using PDCA quality improvement cycles (chapter 7). PDCA cycles are a widely used systematic method

in healthcare improvement and consist of four phases (Plan, Do, Check and Act) mimicking the scientific method of formulating a hypothesis, collecting data to test this hypothesis, analysing and interpreting results and drawing a conclusions[41]. Based on the identified areas of improvement during these cycles, rheumatologists were able to take accountability by reflecting on their own and their team's performance. Afterwards, they organised several changes in the structure and processes of healthcare which might result in higher PREM scores.

Despite that the CQRA-PREM was added in SpA-Net, some measurement properties could not be examined due to missing data, such as test-retest reliability, sensitivity-to-change over time, convergent validity, and measurement error, as well the ability of the CQRA-PREM to discriminate between rheumatology units who have more or less attention for providing patient-centered care. These limitations of our study were also pointed out by a systematic review of Bryant *et al*. which aimed to identify and critically appraise the development and psychometric validation of PREMs in rheumatology settings[42]. This systematic review rated the overall content validity of the CQRA-PREM as 'sufficient' according to the COnsensus based Standards for the selection of health status Measurement INstruments (COSMIN) criteria for good measurement properties[43]. Results of our study and this systematic scoping review warrant further studies on the measurement properties of the Dutch version of the CQRA-PREM that have not yet been evaluated.

When interpreting recorded results from PREMs, one should be aware of the risk of social desirability bias or ceiling effects[44]. Moreover, PREM results might be confounded by factors not directly related to the structure and processes of quality of healthcare, such as disease activity, levels of pain as well as socio-demographic factors such as age, gender and level of education health outcomes[45]. Further studies should therefore examine the relationship between these factors and patient experiences with provided healthcare to study whether subgroups of patients have different healthcare needs.

Conclusion

All studies presented in this thesis were initiated to address encountered challenges related to monitoring of disease outcomes and providing patient-centered care in rheumatology settings. The findings of our studies are useful for improving the quality of rheumatology care and can result in better health and disease outcomes and experiences with healthcare for patients with RMDs. Moreover, from the discipline of rheumatology care, we contributed to the aspiration of the FMS that by 2025 Dutch medical specialist healthcare is among the most innovative, efficient and best-quality healthcare worldwide

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ADDENDA

Impact paragraph

About the author

Nederlandstalige samenvatting

Dankwoord

Impact paragraph

The overarching aim of this thesis was to improve the quality of rheumatology healthcare by responding to challenges related to monitoring of disease outcomes and providing patient-centered care. When we initiated this thesis, some improvements and innovations were necessary to optimize these aspects in clinical practice. In this thesis, we addressed aspects related to monitoring of outcomes by using patient reported outcome- and experience measures (PROMs and PREMs, respectively). In addition, we responded to patient-initiated needs for improving the clinical management of fatigue and for supporting the decision making process for patients facing high-impact treatment decisions. Throughout this thesis, we paid explicit attention to the usability and feasibility of introducing new innovations and management recommendations in rheumatology care. In this chapter, we reflect on the scientific, clinical and societal relevance of this thesis. In addition, we describe how patients were involved in our research and in the dissemination of results.

Challenges related to monitoring of disease outcomes

To facilitate monitoring of disease outcomes in clinical practice, we developed and implemented a web-based tool for systematic monitoring of patients with spondyloarthritis (SpA) in clinical practice in the Netherlands, called SpA-Net (**chapter 2**). We consulted rheumatologists (including experts in the field of SpA), nurses and experienced research partners for the content and design of this tool in efforts to maximize the impact and usability of this tool. After the initial development phase, we consulted patients with SpA for multiple rounds of internal and external testing, for evaluating its usability and acceptability in practice and for identifying barriers against its use. Finally, we used a multifaceted strategy to successfully implement SpA-Net as an electronic monitoring record as part of the standard workflow in five rheumatology centres in the Netherlands.

This patient registry can follow the patient journey in daily practice and facilitates monitoring of various disease aspects, including comorbidities, prescribed medication, adverse events and patient- and physician-reported outcome measures for disease activity, physical functioning and overall health status. Such up-to-date complete overview of all relevant health and disease aspects support healthcare providers (HCPs) and patients with clinical decision making, which in turn can result in better outcomes of care. In addition, monitoring of disease outcomes using PROMs can support patients in understanding their disease and can stimulate engagement in their own care. In response, this may improve communication with their HCPs, which in turn enhances making shared treatment decisions and improves treatment adherence.

Besides, longitudinal observational data on relevant health outcomes in daily practice can be useful for research purposes, as these data come from a large heterogeneous real world patient population without focusing on specific interventions, which has better external validity compared to data collected in randomized control trials (RCTs). In addition, SpA-Net also enabled us to run a pragmatic multicentre RCT evaluating whether telemonitoring combined with patient-initiated follow-up can reduce the number of outpatient consultations compared

to routine care in patients with SpA. Such self-monitoring strategy with the use of SpA-Net can potentially lower the number of follow-up outpatient visits, which can optimize use of time and resources in clinical practice.

Furthermore, this patient registry has societal impact as the effectiveness and safety of (expensive) drugs are securely monitored for the total SpA population, including elderly and those with comorbidities. Moreover, this patient registry is linked to the Dutch pharmacovigilance centre (Lareb) for reporting (serious) adverse events on medication. Finally, the recorded outcomes can be used to provide accountability towards external stakeholders who have the right to be informed on the quality of provided healthcare, such as patients, policy makers and society.

Evaluation of monitoring axial SpA in clinical care

At the start of this thesis, no data existed on the question to what extent the recommended management strategy 'treat-to-target' (T2T) was applied in clinical practice in patients with axial SpA. This T2T strategy includes both regular monitoring of disease activity with validated outcome measures and adequate treatment of patients towards pre-identified targets to prevent long term structural damage. Moreover, there was no insight to what extent T2T approach is applied in clinical practice, where patient populations are more heterogeneous, variation in behaviours of HCPs exists and stronger restrictions are present in terms of time, costs and resources compared to RCTs. We therefore evaluated the extent to which T2T was implemented in axial SpA using SpA-Net during a 1-year study period. Our study showed that available information on disease activity scores did not result in re-evaluation of disease activity within the recommended period of 3 months, nor into changes and/or escalation in therapy when the predefined target of inactive disease or low disease activity was not achieved (**chapter 3**). These findings imply that HCPs and patients experience some scientific, clinical or practical barriers for implementing T2T in practice. Future studies should therefore explore all barriers and facilitators of T2T in an effort to optimize outcomes of care. This newly obtained knowledge can form a starting point to draft a multifaceted implementation strategy for successfully implementing T2T in clinical practice, or, if necessary, adapting the T2T recommendations.

Outcome measures for disease activity in peripheral SpA

As 'peripheral SpA' is a relative new disease concept, no specific disease activity measurements instruments exist for this disease. Notwithstanding, some available disease activity instruments in other types of SpA have sufficient face validity to perform well in peripheral SpA. Therefore, we assessed the comparative performance of the Disease Activity Index for Psoriatic Arthritis (DAPSA), the Psoriatic Arthritis Disease Activity Score (PASDAS) and the Ankylosing Spondylitis Disease activity Score (ASDAS) (**chapter 4**). We showed that these three composite scores had acceptable measurement properties in peripheral SpA, but more research is needed to select one of these composite scores, or any other score, for this purpose. In a response to our study, an editorial by experts on assessing psoriatic arthritis confirmed the clinical and scientific relevance of our study and emphasized the complexity of assessing disease activity in peripheral SpA.

Challenges related to providing patient-centered care

An important element of providing patient-centered care is that patients should not only be actively engaged in their clinical care, but also in scientific research. We therefore responded to the knowledge gap 'fatigue and its treatment', which has been prioritized by a discussion panel of patients with rheumatic and musculoskeletal diseases (RMDs) as the most important topic that should be addressed to improve the management of their rheumatic disease in daily life. As a first step to act towards this prioritized impactful topic, we performed an elaborated reviews of reviews on aspects of fatigue that are relevant for clinical practice for patients with rheumatoid arthritis (RA), SpA, osteoarthritis and fibromyalgia (**chapter 5**). Interpretation and usability of findings of this review were discussed with a patient discussion panel. The extensive amount of evidence summarised in our scoping review is highly relevant for both clinical and research settings.

We identified several important knowledge gaps and research areas that need further investigation. Our findings emphasize the need for an agreed research agenda for unravelling and ultimately improving fatigue in RMDs. This research agenda should be drafted in cooperation with patients to align research with their preferences and needs. Such research requires merging areas to efficiently develop more insights into and solutions for this complex symptom. All newly obtained knowledge should be incorporated in guidelines for research and practice as this can ultimately reduce the personal and societal burden of excessive fatigue in these patients.

From a clinical perspective, the retrieved information on (types of) fatigue can reduce patients' struggles to communicate on their experiences with fatigue and can thereby also reduce patients' feelings of being misunderstood or isolated. In addition, our complete overview of available measurement instrument for fatigue enables HCPs to select the preferred instrument for each condition in clinical or research settings. Moreover, using clinical reasoning, the information retrieved on determinants and consequences can be used to propose a tailored treatment plan for (excessive) fatigue in patients with RMDs.

Shared-decision making

Another key principle of patient-centered care is shared-decision making (SDM). SDM is defined as the process of HCPs and patients jointly participating in making decisions related to patients' health after discussing the options, the benefits and harms, and considering the patients' values, preferences, and personal circumstances. To support the SDM process in patients with axial SpA who face a treatment decision to initiate or switch a biologic or target synthetic Disease-Modifying AntiRheumatic Drug, we developed an up-to-date evidence-based decision aid and introduced this tool to patients and HCPs in several rheumatology settings across the Netherlands (**chapter 6**).

We involved all intended users in the development process to increase their trust in the content and to contribute to broad acceptance and use of this tool in clinical practice. With this decision aid, we enabled patients who face a treatment decision to make well-informed

value-based personal treatment decisions. In this way, patients can become less passive in decision-making and experience less decisional conflicts. In turn, this may ultimately result in increased long-term satisfaction with provided healthcare and improved behavioural and health outcomes, such as better treatment adherence, better clinical outcomes and reduced healthcare costs.

PREMs for rheumatology settings

When evaluating the quality of provided healthcare, it is also essential to include patients' perspectives on this matter as these may differ from the perspectives of HCPs and policy makers. We facilitated assessing patient perspectives on the quality of Dutch rheumatology services by evaluating the psychometric properties of the Dutch version of the widely used Commissioning for Quality in Rheumatoid Arthritis PREM for rheumatology settings (CQRA-PREM) in patients with RA and SpA and by implementing this instrument in two rheumatology settings in the Netherlands (**chapter 7**). We evaluated results from the CQRA-PREM through repeated Plan-Do-Check-Act quality improvement cycles at several occasions with rheumatologists and rheumatology nurses from both medical centres. Afterwards, action plans were formulated and executed in clinical practice to improve the structure and processes of healthcare where possible. With this accomplishment, we serve as an example for researchers and HCPs in other rheumatic centres that it is feasible to implement PREMs in practice. Besides, the CQRA-PREM can be used to study the effect of changes on the quality of healthcare, to identify best practices within or between settings and to inform stakeholders, including patients, on the quality of healthcare.

Dissemination of results

Findings from this thesis contribute to new scientific insights, evidence and tools to improve the quality of rheumatology care. Our studies identified knowledge gaps and prompted new research questions to which can be acted upon to further improve outcomes of care for patients with RMDs. We informed researchers and HCPs on our findings through scientific publications in peer-reviewed rheumatology journals and presentations at national and international conferences on rheumatology. We successfully created a video-abstract about our study on assessing disease activity in peripheral SpA to increase the dissemination of the results of our study. Furthermore, we aimed to increase the impact of our findings by accepting two interview invitations. The first interview also addressed our study on assessing disease activity in peripheral SpA and was published at DOQ.nl, an online knowledge platform for HCPs which reflect on visions, experiences and current developments in a variety of fields of expertise. The second interview addressed our scoping review on fatigue in RMDs and was published in the journal of the Dutch Society for Rheumatology which targets an audience of Dutch HCPs. Our decision aid is publically accessible on the website of the Dutch Arthritis Society, a comprehensive and credible source of information on rheumatic and musculoskeletal diseases and available treatment options (in Dutch: www.reumanederland.nl).

By addressing encountered challenges in rheumatology practice, we also contribute to the goals, ambitions and expectations of the Dutch Federation of Medical Specialists for the role and position of medical specialists in the near future. In their most recent vision document they formulated the aspiration that by 2025 Dutch medical specialist healthcare is among the most innovative, efficient and best-quality healthcare worldwide.

About the author

Esther Anna Bartholomeus Beckers was born on April 13th 1994 in Heerlen, the Netherlands. She was raised in a loving and caring family together with two sisters and one brother. She completed secondary education (VWO) at the Sintermeerten College in Heerlen in 2012.

In that same year, she started with her Bachelor's degree in Biomedical Sciences at Maastricht University in Maastricht, the Netherlands. She enrolled in the track Molecular Life Sciences, from which she graduated in 2015.

Afterwards, Esther continued her education with a research master in Biomedical Sciences at the Radboud University in Nijmegen, the Netherlands, from which she graduated in July 2017. During this programme, she conducted two research projects, one in the field of Human Health Risk Assessment and the other in the field of Clinical Epidemiology.

In September 2017, Esther returned to Maastricht and kicked off her career as a PhD researcher at the Care and Public Health Research Institute (CAPHRI) of Maastricht University and the Department of Rheumatology of the Maastricht University Medical Center (MUMC+). Her PhD project was supervised by prof. dr. Astrid van Tubergen and prof. dr. Annelies Boonen.

During her time as a PhD researcher, Esther was also involved in educational activities for the bachelor programs in Medicine and Health Sciences. In 2021, she obtained her Basic Teaching Qualification (in Dutch: BKO) which is evidence of her skills in developing and delivering academic education. Highlights during her PhD project were oral presentations at the yearly conference of the European Alliance of Associations for Rheumatology) (EULAR) in Madrid, Spain, in 2019 and Copenhagen, Denmark, in 2022.

After completing her PhD, she decided to pursue a career outside academic research. Currently, Esther is employed as civil servant for the Provincie Limburg at the Department of Housing and Living Environment. In this position, she contributes to solving societal challenges related to housing in the Netherlands.

Nederlandstalige samenvatting

Reumatische en musculoskeletale aandoeningen *(in het Engels: rheumatic musculoskeletal diseases (RMDs))* zijn een diverse groep van meer dan 200 aandoeningen waarbij gewrichten, pezen, ligamenten, botten en/of spieren aangedaan kunnen zijn. Een belangrijke subgroep binnen de RMDs zijn de inflammatoire reumatische aandoeningen, waartoe reumatoïde artritis (RA), spondyloartritis (SpA) en artritis psoriatica behoren. Voorbeelden van niet-inflammatoire RMDs zijn artrose en fibromyalgie. Patiënten met een RMD ervaren doorgaans een afname van hun fysieke en mentale gezondheids-gerelateerde kwaliteit van leven. Ook hebben zij een verhoogd risico op een co-morbiditeit. Daarnaast zijn RMDs verantwoordelijk voor een groot deel van het zorggebruik en leiden RMDs tot verlies van arbeidsproductiviteit. Dit alles leidt tot aanzienlijke kosten voor de maatschappij. In dit proefschrift onderzoeken we hoe we de kwaliteit van zorg kunnen verbeteren voor patiënten met RMDs, in het bijzonder voor RA en SpA.

Reumatoïde artritis

RA is een chronische reumatische auto-immuun aandoening die zich typisch manifesteert met symmetrische gewrichtsontstekingen (artritis) van gewrichten van de handen en/of de voeten. Deze aandoening kan ook andere organen en weefsels aantasten, waaronder het hart, de longen, de huid en de ogen. Patiënten waarbij deze ziekte onvoldoende onder controle is, kunnen progressieve en onomkeerbare gewrichtsschade oplopen. Dit kan leiden tot beperkingen in het functioneren in het dagelijkse leven.

Spondyloartritis

SpA is een overkoepelende term voor een groep inflammatoire RMDs, die gemeenschappelijke klinische kenmerken en pathofysiologische mechanismen hebben. SpA komt in sterke mate voor binnen families en is gerelateerd aan een specifiek gen (HLA B27). Er wordt een onderscheid gemaakt tussen axiale en perifere SpA op basis van de overheersende klinische kenmerken van een patiënt. Axiale SpA wordt gekenmerkt door ontstekingen in de sacro-iliacale gewrichten in het bekken (sacroiliitis) en de wervelkolom (spondylitis). Perifere SpA wordt daarentegen gekenmerkt door verschillende soorten ontstekingen in de perifere gewrichten, zoals knieën, polsen en vingers, namelijk gewrichtsontstekingen (artritis), ontstekingen op de plaats waar een of meer pezen aan het bot hechten (enthesitis) en ontstekingen van de gehele vinger of teen (dactylitis). Patiënten met zowel axiale als perifere SpA kunnen daarnaast ontstekingen hebben op plaatsen buiten de gewrichten en pezen, zoals oogontstekingen (uveïtis anterior), huidontstekingen (psoriasis) en inflammatoire darmontstekingen (ziekte van Crohn en colitis ulcerosa).

Kwaliteit van zorg

Kwaliteit van zorg is gedefinieerd als “de mate waarin gezondheidszorg de waarschijnlijkheid vergroot op het behalen van gewenste gezondheidsresultaten voor personen en de mate waarin de gezondheidszorg de huidige wetenschappelijke kennis toepast”. Het Amerikaanse Institute for Medicine heeft in 2001 een baanbrekend rapport gepubliceerd waarin zij zes pijlers beschrijven waaraan zorg moet voldoen, namelijk: 1) effectiviteit, 2) veiligheid, 3) patiëntge-

richtheid, 4) tijdigheid, 5) efficiëntie en 6) rechtvaardigheid. Deze zes pijlers vullen elkaar aan en verbeteringen in één van de pijlers zal ook de andere pijlers verbeteren.

Binnen de reumatologie waren enkele jaren geleden een aantal verbeteringen en innovaties nodig om de kwaliteit van de reumatische zorg in de klinische praktijk te optimaliseren. Met dit proefschrift hebben wij vooral gereageerd op uitdagingen in de klinische praktijk met betrekking tot twee belangrijke aspecten van kwaliteit van zorg, namelijk het *monitoren van uitkomsten* en het *verlenen van patiëntgerichte zorg*.

Uitdagingen gerelateerd aan het monitoren van uitkomsten

Voor het verlenen van goede zorg voor patiënten met RMDs is het belangrijk om ziekte- en gezondheidsuitkomsten te monitoren en hierop te reageren. Hiervoor kunnen 'harde', objectieve uitkomsten gebruikt worden, zoals de mortaliteit na een operatie of ontstekingswaarden in het bloed, maar deze uitkomsten komen niet altijd overeen met hoe een patiënt zich voelt zich voelt of kan functioneren. Zogenaamde 'zachte' of subjectieve uitkomsten vanuit het patienten perspectief (*in het Engels: Patient Reported Outcomes (PROs)*), zoals bijvoorbeeld de mate van fysiek functioneren en mentaal welbevinden, kunnen gemeten worden met vragenlijsten (*in het Engels: Patient Reported Outcome Measures (PROMs)).*

Klinische richtlijnen voor patiënten met RMDs benadrukken het belang van PRO's in de praktijk om een volledig beeld te krijgen hoe het met een patiënt gaat. Bij aanvang van dit proefschrift werden PRO's nog beperkt ingezet in patiënten met RA en SpA in de klinische praktijk. Een mogelijke verklaring hiervoor is de beperkte tijd tijdens consulten voor het gebruik van papieren vragenlijsten. Dit vergt namelijk veel tijd en handelingen, zoals het invullen van de vragenlijsten door patiënten en het berekenen van de scores en het overzetten hiervan naar elektronisch medische patiëntendossiers door de zorgverlener. Een oplossing hiervoor kan zijn om deze uitkomsten *elektronisch* uit te vragen. Idealiter is een dergelijk online systeem ziekte-specifiek, gepersonaliseerd en eenvoudig toegankelijk voor zowel patiënten als zorgverleners. Door weergave van de uitkomsten in een dashboard (onder andere in grafieken), kunnen patiënten en zorgverleners geïnformeerd worden over het beloop van de ziekte in een individu. Behandelbeslissingen kunnen mede op basis van deze gegevens genomen worden. Hiermee kan een dergelijk systeem bijdragen aan het verlenen van gepersonaliseerde, hoogwaardige en efficiente zorg.

Patiënten monitoring instrument 'SpA-Net'

Voor Nederlandse patiënten met SpA was er bij aanvang van dit proefschrift nog geen elektronisch ziekte-specifiek gepersonaliseerd monitoring systeem voorhanden. Om aan deze behoefte te voldoen hebben we in **hoofdstuk 2** een dergelijk systeem, genaamd SpA-Net, ontwikkeld en geïmplementeerd in de klinische praktijk. In SpA-Net kunnen patiënten opgevolgd worden in de dagelijkse praktijk en wordt het monitoren van verschillende ziekteaspecten vereenvoudigd. In het systeem wordt informatie bijgehouden over onder andere patiënt en arts gerapporteerde uitkomsten, bevindingen tijdens lichamelijk onderzoek, laboratoriumuit-

slagen en voorgeschreven medicatie. Voor de ontwikkeling van dit systeem hebben we intensief samengewerkt met reumatologen (waaronder experts op het gebied van SpA), verpleegkundigen, ICT ontwikkelaars en ervaren patiënten onderzoekspartners. Uiteindelijk is SpA-Net in 2016 door middel van verschillende strategieën succesvol geïmplementeerd in de standaard werkwijze in vijf reumatologische centra in Nederland. In 2017 evalueerden we de bruikbaarheid en toepasbaarheid van SpA-Net door zowel patiënten als zorgverleners en identificeerden we belemmeringen voor het gebruik van SpA-Net in de klinische praktijk. Beide groepen vonden SpA-Net duidelijk, goed toegankelijk en eenvoudig te gebruiken. Ze vonden SpA-Net ook een nuttige aanvulling op de zorg. We concludeerden dat SpA-Net een waardevol systeem is dat gebruikt kan worden om de kwaliteit van zorg te verbeteren. Sinds de lancering zijn meer dan 1300 patiënten met SpA geregistreerd in SpA-Net.

Naast directe toepassing in de dagelijkse praktijk, heeft het gebruik van SpA-Net op meerdere manieren een maatschappelijke impact. SpA-Net wordt namelijk gebruikt voor het bewaken van de effectiviteit en veiligheid van (dure) geneesmiddelen en het is gekoppeld aan het Nederlandse meld- en kenniscentrum voor bijwerkingen van geneesmiddelen (Lareb). Daarnaast kunnen de verzamelde gegevens in SpA-Net gebruikt worden om verantwoording af te leggen aan personen die recht hebben op informatie over de kwaliteit van de verleende zorg, zoals patiënten, beleidsmakers en de samenleving. Verder kunnen de verzamelde gegevens in SpA-Net gebruikt worden voor wetenschappelijk onderzoek naar de gezondheid en zorg van patiënten met SpA.

Uitkomstmaten voor ziekteactiviteit in patiënten met perifere SpA

Voor patiënten met RMDs is het essentieel om de activiteit van de ziekte goed onder controle te krijgen en te houden om schade op de lange termijn te voorkomen. Het is daarom belangrijk om op gezette tijden de ziekteactiviteit te monitoren en wanneer nodig de behandeling aan te passen. In patiënten met perifere SpA wordt ziekteactiviteit gewoonlijk gemeten met verschillende objectieve maten, zoals het aantal pijnlijke en gezwollen gewrichten en de aanwezigheid van enthesitis of dactylitis. Daarnaast worden ook (subjectieve) PROMs gebruikt, bijvoorbeeld voor het meten van pijn.

Voor vele RMDs, waaronder axiale SpA, wordt ziekteactiviteit vaak gemeten met een samengestelde maat, die zowel objectieve als subjectieve uitingen van de ziekte meeneemt en in één score uitdrukt. Voor perifere SpA was er nog geen samengestelde maat beschikbaar voor het meten van ziekteactiviteit. Er waren wel kandidaat meetinstrumenten beschikbaar, ontwikkeld voor een verwante aandoening van perifere SpA, zoals de Disease Activity Index for Psoriatic Arthritis (DAPSA) score en de PsA Disease Activity Score (PASDAS), die specifiek zijn ontwikkeld voor artritis psoriatica, of de Ankylosing Spondylitis Disease Activity Score (ASDAS) die specifiek is ontwikkeld voor axiale SpA.

In **hoofdstuk 3** bestudeerden we of de meeteigenschappen van de DAPSA, PASDAS en ASDAS geschikt zijn voor het meten van ziekteactiviteit in perifere SpA. We onderzochten hiervoor de

validiteit en discriminatie van deze meetinstrumenten en we onderzochten hoeveel patiënten in dezelfde ziekteactiviteit status werden geclassificeerd door deze drie meetinstrumenten.

Dit onderzoek toonde aan dat de validiteit en discriminatie van de DAPSA, PASDAS en ASDAS acceptabel zijn bij patiënten met perifere SpA met gemiddeld weinig ziekteactiviteit in hun perifere gewrichten. Een opvallend resultaat was dat deze drie instrumenten patiënten anders classificeerden in de ziekteactiviteit statussen inactieve ziekte/lage ziekteactiviteit en hoge ziekteactiviteit. Volgens de DAPSA had namelijk 22% van de patiënten hoge ziekteactiviteit, maar volgens de ASDAS 48% en volgens de PASDAS maar liefst 56% van deze patiënten. Een andere interessante bevinding was dat de ASDAS even goede meeteigenschappen heeft in patienten met perifere SpA als in de oorspronkelijk doelgroep axiale SpA.

Met ons onderzoek konden we geen conclusie trekken welk meetinstrument nu de voorkeur heeft voor het meten van ziekteactiviteit in perifere SpA. Twee experts op het gebied van artritis psoriatica bevestigden in een reactie op ons onderzoek de klinische en wetenschappelijke relevantie van het onderzoek en benadrukten de complexiteit van het meten van ziekteactiviteit in perifere SpA.

Toepassing behandelrichtlijnen voor patiënten met axiale SpA
Goede kwaliteit van zorg kan behaald worden door te voldoen aan kwaliteitsnormen en het opvolgen van aanbevelingen voor behandeling. Het doel van deze aanbevelingen is het vertalen van wetenschappelijk bewijs over optimale behandelingen naar de klinische praktijk. Voor axiale SpA wordt onder andere aanbevolen om patiënten doelgericht te behandelen *(in het Engels: treat-to-target (T2T))*. Hiervoor wordt de ziekteactiviteit van patiënten regelmatig gemonitord en wordt met de behandeling ernaar gestreefd om een doel te behalen. Voor de meeste patiënten is dit doel inactieve ziekte (remissie) of lage ziekteactiviteit. Indien dit doel niet wordt behaald, dient de behandeling te worden aangepast.

Bij aanvang van dit proefschrift was het voor patiënten met axiale SpA nog onbekend in welke mate de principes van T2T werden toegepast in de klinische praktijk, waar variatie te verwachten is tussen patiënten en het gedrag van zorgverleners. Ook zijn er beperkingen in de beschikbare tijd en middelen.

In **hoofdstuk 4** evalueerden we daarom de mate waarin volgens het T2T principe werd gewerkt in patiënten met axiale SpA in klinische praktijken waarin SpA-Net was geïmplementeerd. We gebruikten hiervoor geregistreerde informatie in SpA-Net gedurende één jaar.

Met dit onderzoek toonden we aan dat ziekteactiviteit minstens één keer per jaar werd gemeten in 84% van de patiënten met axiale SpA. In deze subgroep met tenminste één meting had 38% van de patiënten inactieve ziekte of lage ziekteactiviteit tijdens de eerste meting. In de groep met hoge ziekteactiviteit werd de aanbeveling om hun ziekteactiviteit binnen 3 maanden opnieuw te meten slechts in 23% van de patiënten opgevolgd. Ook werd in deze groep met

hoge ziekteactiviteit maar in 17% van de patiënten de behandeling binnen 6 weken aangepast. Uit deze resultaten concludeerden we dat T2T slechts beperkt wordt toegepast in de dagelijkse praktijk bij patiënten met axiale SpA, ondanks de elektronische ondersteuning door middel van SpA-Net . Hoge ziekteactiviteit scores leken geen aanleiding te zijn voor het opnieuw meten van ziekteactiviteit op korte termijn en voor het aanpassen van de behandeling.

Deze bevindingen suggereren dat zorgverleners en patiënten mogelijk wetenschappelijke, klinische of praktische barrières ervaren voor het implementeren van T2T in de praktijk. Toekomstige studies moeten daarom gericht zijn op het onderzoeken van deze barrières, maar ook mogelijke versnellers voor het toepassen van T2T in de praktijk. De nieuw opgedane kennis van dit vervolgonderzoek kan een startpunt vormen voor het opstellen van een veelzijdige strategie voor het succesvol implementeren van T2T in de klinische praktijk, of, indien daar aanleiding toe is, het aanpassen van de T2T-aanbevelingen**.** Op deze manier kan de kwaliteit van zorg verder verbeterd worden.

Uitdagingen gerelateerd aan het verlenen van patiëntgerichte zorg

Het verlenen van patiëntgerichte zorg is één van de zes pijlers voor goede kwaliteit van zorg die de afgelopen twintig jaar steeds meer aandacht heeft gekregen. Patiëntgerichte zorg is gedefinieerd als “het verlenen van respectvolle zorg die inspeelt op voorkeuren, behoeften en waarden van patiënten, en ervoor zorgt dat de waarden van patiënten de leidraad vormt voor alle klinische beslissingen”. Het verlenen van patiëntgerichte zorg heeft vergeleken met een traditionele benadering waarbij artsen eenzijdig beslissingen nemen over de zorg van patiënten voordelen, zoals betere klinische uitkomsten, betere therapietrouw en lagere zorgkosten. Het verlenen van patiëntgerichte zorg in de klinische praktijk vergt dat zorgverleners de persoon achter de patiënt moeten leren kennen in plaats van zich uitsluitend te richten op de aandoening zelf. Hiervoor is het ook nodig dat patiënten een actieve rol spelen in hun zorg en dat zij geïnformeerd worden over hun ziekte en symptomen, beschikbare behandelopties en mogelijke uitkomsten. Daarnaast dienen zij gestimuleerd te worden om hun persoonlijke waarden en voorkeuren voor behandeling te bespreken met hun zorgverleners. Patiënten en zorgverleners moeten zich daarom focussen op aspecten die voor hen beiden belangrijk zijn.

Vermoeidheid in patiënten met RMDs

Voor het verlenen van patiëntgerichte zorg is het nodig om te weten welke aspecten van zorg volgens patiënten de meeste prioriteit hebben om de reumatische zorg te verbeteren. Reuma-Nederland, een vereniging voor patiënten met RMDs, heeft met dit als doel meerdere bijeenkomsten georganiseerd. Patiënten concludeerden tijdens deze bijeenkomsten dat ‘vermoeidheid en de behandeling hiervan’ het belangrijkst aspect is waaraan meer aandacht besteed moet worden.

In het verleden zijn er al veel klinische studies uitgevoerd naar vermoeidheid in RMDs en een groot deel van deze studies zijn samengevat in literatuuronderzoeken, genaamd reviews. Desondanks was de kennis over verschillende onderzoeksgebieden gefragmenteerd, omdat

deze studies en reviews zich vaak beperken tot één RMD of een specifiek onderwerp binnen een groter onderzoeksgebied. Hierdoor is het lastig om de beschikbare kennis toe te passen in de klinische praktijk en om nieuwe wetenschappelijke inzichten te verkrijgen.

In **hoofdstuk 5** hebben we daarom een uitgebreid literatuuronderzoek uitgevoerd naar gepubliceerde literatuurreviews met betrekking tot vijf onderzoeksgebieden: (i) de definities van vermoeidheid; (ii) meetinstrumenten om vermoeidheid te meten en diagnosticeren; (iii) oorzaken van vermoeidheid; (iv) gevolgen van vermoeidheid; en (v) het effect van interventies op vermoeidheid. We onderzochten dit in patiënten met RA, SpA, artrose of fibromyalgie.

Voor dit literatuuronderzoek konden we 134 reviews over vermoeidheid includeren. In deze reviews werd er geen overeenstemming gevonden voor een definitie van vermoeidheid, maar er was wel overeenstemming dat patiënten met RMDs verschillende types vermoeidheid kunnen ervaren. Ook beschreven de reviews talrijke meetinstrumenten voor vermoeidheid, maar hiervan was slechts een klein deel ontwikkeld, gevalideerd en/of geschikt voor gebruik in de klinische zorg. Daarnaast beschreven de reviews vele factoren die geassocieerd werden met vermoeidheid als een oorzaak of als een gevolg. Over het algemeen was de sterkte van de verbanden klein waardoor we niet met zekerheid kunnen zeggen welke factoren een oorzaak en/of gevolg van vermoeidheid zijn. Tot slot concludeerden we dat interventies met geneesmiddelen een klein tot matig effect hebben op vermoeidheid bij patiënten met RA, vermoeidheid verbeteren bij patiënten met SpA, maar geen tot een klein positief effect hebben bij patienten met fibromyalgie. Andere interventies die niet gebaseerd zijn op geneesmiddelen, zoals beweeg-oefeningen of diëten, hadden over het algemeen geen tot een klein positief effect op vermoeidheid bij alle RMDs.

Dit onderzoek heeft ons inzicht gegeven in welke kennishiaten er nog zijn en welke onderzoeksgebieden verder bestudeerd moeten worden. Onze bevindingen benadrukken ook de noodzaak voor een onderzoeksagenda om vermoeidheid bij RMDs te ontrafelen en uiteindelijk te verminderen. Ons literatuuronderzoek is ook relevant voor de klinische praktijk, omdat de verzamelde inzichten over verschillende types van vermoeidheid de communicatie tussen patiënten en zorgverleners kan verbeteren en het zorgverleners kan ondersteunen in het opstellen van een persoonlijk behandelplan voor (overmatige) vermoeidheid.

Keuzehulp voor het maken van behandelbeslissingen

Eén van de belangrijkste principes van patiëntgerichte zorg is gedeelde besluitvorming. Dit is het proces waarbij zorgverleners en patiënten gezamenlijk gezondheid-gerelateerde beslissingen nemen na het bespreken van alle behandelopties en waarbij rekening wordt gehouden met de waarden, voorkeuren en persoonlijke omstandigheden van patiënten. Hiervoor is het essentieel dat zorgverleners informatie delen over de huidige medische situatie van patiënten en alle beschikbare behandelingen en de gevolgen daarvan voor het persoonlijke leven van patiënten. Keuzehulpen zijn hulpmiddelen die patiënten kunnen informeren over deze aspecten

en hen kunnen ondersteunen bij het maken van weloverwogen persoonlijke beslissingen over behandelopties.

Voor patiënten met axiale SpA was er behoefte aan een keuzehulp om hen te ondersteunen in het maken van behandelbeslissingen over het starten van medicatie in de klasse genaamd 'biologische of doelgericht-synthetische ziekte-modificerende anti-reumatische geneesmiddelen' *(in het Engels:* biologic or targeted-synthetic Disease-Modifying Anti Rheumatic Drugs (b/tsDMARD*s)).* Het maken van beslissingen rondom het starten van b/tsDMARDs is de laatste jaren steeds ingewikkelder geworden. Er zijn namelijk momenteel verschillende types medicatie beschikbaar die weliswaar een vergelijkbaar effect hebben op axiale SpA, maar verschillende eigenschappen, zoals de toedieningswijze (via een injectie, infuus of tablet), de toedieningsfrequentie (dagelijks, wekelijks, maandelijks of om de paar maanden), het verwachte effect op gerelateerde aandoeningen (uveïtis, psoriasis, inflammatoire darmontstekingen en mogelijke bijwerkingen.

In **hoofdstuk 6** ontwikkelden we daarom een keuzehulp om patiënten te ondersteunen met het maken van een behandelbeslissing rondom het starten/switchen van een b/tsDMARD. We volgden hiervoor een systematisch wetenschappelijk proces dat bestaat uit meerdere fases. Wij hebben als eerste hiervoor onder andere interviews uitgevoerd met patiënten en behandelaren om hun wensen en behoeften te verkennen. Daarna ontwikkelden we een prototype van de keuzehulp. De bruikbaarheid en toepasbaarheid van dit prototype hebben we intensief getest met behulp patiënten en zorgverleners. Tijdens alle fasen van dit ontwikkelingsproces betrokken we experts op het gebied van axiale SpA en patiënten zelf. De definitieve versie van de keuzehulp bestaat uit vier delen: 1) een gesprekshulp om patiënten voor te bereiden op hun volgende consult, 2) een overzicht met gedetailleerde informatie over b/tsDMARDs, 3) een keuzetabel om medicatie te vergelijken en 4) een vraag om te controleren of patiënten genoeg weten om een behandelbeslissing te maken. We introduceerden vervolgens onze keuzehulp bij patiënten en zorgverleners in verschillende Nederlandse reumatologische praktijken.

Met deze keuzehulp ondersteunen we patiënten met axiale SpA om actiever betrokken te zijn bij het nemen van behandelbeslissingen. Dit kan uiteindelijk leiden tot meer tevredenheid met de ontvangen reumatologische zorg en tot betere gedrags- en gezondheidsuitkomsten.

Evaluatie van zorg vanuit het patiënten perspectief

Om de kwaliteit van zorg accuraat te beoordelen is het essentieel om de verleende zorg te evalueren vanuit het patiënten perspectief. Hiervoor kunnen specifieke vragenlijsten gebruikt worden, genaamd patiënt-gerapporteerde ervaringsmaten (*in het Engels: Patient Reported Experience Measures (PREMs)*). Deze PREMs bevatten vragen zoals "Toen u hulp nodig had, kon u toen bij uw zorgverlener terecht?" en "Kreeg u informatie over uw behandeling?". Resultaten van PREMs kunnen belanghebbenden, waaronder patiënten, informeren over de kwaliteit van de geleverde gezondheidszorg. Zorgverleners kunnen de resultaten van PREMs ook gebruiken om te reflecteren op hun prestaties, om klinische en organisatorische verbeterpunten te identi-

ficeren en om te bepalen wat de optimale werkwijze is binnen of tussen klinische praktijken. Bij aanvang van dit proefschrift was er nog geen PREM beschikbaar voor patiënten met RA en SpA in Nederlandse reumatologie praktijken. Een meetinstrument dat mogelijk geschikt was voor dit doel was de Engelse *Commissioning for Quality in Rheumatoid Arthritis PREM* (CQRA-PREM).

In **hoofdstuk 7** hebben we daarom de CQRA-PREM vertaald naar het Nederlands en deze vragenlijst gedurende een jaar toegevoegd aan SpA-Net in twee reumatologie praktijken. Met behulp van de verzamelde resultaten in SpA-Net hebben we vervolgens verschillende methodologische eigenschappen van de CQRA-PREM bepaald, waaronder de toepasbaarheid, betrouwbaarheid en validiteit. We concludeerden dat deze meeteigenschappen van de Nederlandstalige versie van de CQRA-PREM acceptabel zijn. De verzamelde resultaten van de CQRA-PREM werden daarna gebruikt om de kwaliteit van zorg te verbeteren door verbetermogelijkheden in kaart te brengen en uit te voeren met behulp van Plan-Do-Check-Act (PDCA) cycli. Dit onderzoek dient daarmee als voorbeeld voor mede-onderzoekers en zorgverleners dat het haalbaar is om het gebruik van PREMs in de reumatologische praktijk te implementeren.

Conclusie en impact

Alle bevindingen uit dit proefschrift dragen bij aan nieuwe wetenschappelijke inzichten en omvatten wetenschappelijk bewijs en hulpmiddelen om de kwaliteit van de reumatologische zorg te verbeteren. We hebben ook expliciet aandacht besteed aan de bruikbaarheid en toepasbaarheid van innovaties en management aanbevelingen in de reumatologische zorg. Daarnaast identificeerden we kennishiaten en nieuwe onderzoeksvragen waarop kan worden voortgebouwd in toekomstige studies.

Dankwoord

Met dit proefschrift rond ik een bijzonder leerzame periode van mijn leven af. Het voltooien van dit project zou nooit gelukt zijn zonder de steun van velen. Ik wil daarom iedereen bedanken die direct of indirect heeft bijgedragen aan dit resultaat. Een aantal personen wil ik nadrukkelijk bedanken.

Allereerst wil ik mijn promotoren bedanken voor hun begeleiding tijdens dit gehele traject. Het was heel fijn om jullie als promotoren te hebben en om me bij jullie te kunnen ontwikkelen, zowel op academisch als persoonlijk vlak. Ik heb ontzettend veel van jullie geleerd.

Professor van Tubergen, Astrid, bedankt voor het vertrouwen dat je me hebt gegeven en het geduld waarmee je mijn werk steeds naar een hoger niveau bracht. De afgelopen jaren heb ik van jou vooral geleerd hoe belangrijk het is om grote projecten te verdelen in kleinere taken, om onderscheid te maken tussen hoofd- en bijzaken en om een realistische planning te maken (en me ook hieraan te houden). Ik bewonder de manier waarop jij complexe materie eenvoudig kunt uitleggen en jouw goede oog voor details. Hier kan ik nog veel van leren.

Professor Boonen, Annelies, ook voor u niets dan grote dank voor uw vertrouwen in mij en mijn project. Uw toewijding aan onderzoek doen en uw immense kennis over uiteenlopende zaken zijn inspirerend. Ik ben dankbaar dat ik daarvan heb mogen profiteren. Ondanks uw overvolle agenda wist u altijd tijd vrij te maken om even kort te sparren of om lang en intensief te discussiëren over de interpretatie van resultaten van mijn onderzoek.

Ik wil ook alle leden van mijn beoordelingscommissie bedanken voor het lezen en positief beoordelen van mijn proefschrift: Prof. dr. Marieke Pierik, Prof. dr. Daisy Janssen, Dr. Eline Mahler, Dr. Albine Moser en Prof. dr. Angelique Weel. Aansluitend wil ik dr. Maarten de Wit bedanken voor zijn deelname als opponent tijdens mijn verdediging.

Daarna wil ik alle coauteurs die hebben meegewerkt aan mijn onderzoeken van harte willen bedanken voor hun inzet en expertise. Jullie bijdrage en inzichten hebben mijn werk steeds beter gemaakt. In alfabetische volgorde: Casper Webers, Harald Vonkeman, Monique Efdé, Peter ten Klooster en Yvonne van Eijk- Hustings.

Een speciaal woord van dank gaat uit naar alle patiënten voor de geïnvesteerde tijd, energie en moeite om deel te nemen aan mijn onderzoeken. Zonder jullie was mijn onderzoek niet mogelijk geweest. Ik heb vooral vele waardevolle inzichten opgedaan tijdens de velen interviews waarmee jullie mij inzicht gaven in jullie persoonlijke ervaringen met reumatische aandoeningen en de bijkomende zorg. Hiermee hebben jullie een brug geslagen tussen mijn wetenschappelijke kennis en praktijkervaringen.

Ik wil ook mijn contactpersonen bij ReumaNederland, Nique Lopuhaä, Annemiek de Crom en Iris Koopmans, bedanken voor de fijne samenwerking tijdens ons gezamenlijke project om een keuzehulp te ontwikkelen om patiënten te ondersteunen in het maken van behandelbeslissingen.

Mirjam Hegeman, bedankt voor je warme ontvangst en praktische ondersteuning tijdens mijn bezoeken aan het Medisch Spectrum Twente.

De stafleden, AIOS en verpleegkundigen van de afdeling Reumatologie van het MUMC+ wil ik bedanken voor de leuke tijd, jullie interesse in mijn proefschrift en voor alle patiënten die jullie hebben gemotiveerd om mee te doen aan de onderzoeken. In het bijzonder Dr. Marloes van Onna, bedankt voor je waardevolle opmerkingen en adviezen tijdens de vele promovendi overleggen en journal clubs. Jij hebt presenteren tot een kunst verheven waarvan ik nog veel kan leren.

Daarnaast wil ik ook de secretariële ondersteuning bij de Reumatologie (Peggy, Patricia, Sandra en Yvonne) bedanken. Bij jullie kon ik niet alleen terecht voor praktische vragen en verzoeken, maar ook om even gezellig te kletsen.

Ook een groot woord van dank aan alle fantastische mede-promovendi bij de reumatologie, in alfabetische volgorde: Casper, Cindy, Dennis, Emmelie, Fiona, Kasper, Maarten, Marin, Marius, Mark, Mayke, Michiel, Nannan, Ritch en Saskia. Het was fijn om zulke betrokken en inspirerende collega's te hebben. In het bijzonder de mannen van mijn 'lichting': Ritch, Mark, Maarten en Kasper. Ik kijk met een grote glimlach terug op de jaren dat ik op met jullie een kamer heb gedeeld in het letterlijk krakende en piepende Provisorium van het MUMC+. Wij hebben niet alleen veel successen samen gevierd, maar we hebben ook de nodige tegenslagen samen doorstaan (denk aan onvoorziene vertragingen in projecten, de cyberaanval op de UM en de gevolgen COVID-pandemie, zoals afgelaste bijeenkomsten en de introductie van Zoom). Jullie hebben mijn promotietraject een gouden randje gegeven. Ik kijk ernaar uit om te zien wat jullie allemaal gaan bereiken.

Beste paranimfen, lieve Imke en Mark, wat ben ik blij dat jullie deze dag naast mij staan. Ik weet dat ik altijd op jullie kan rekenen, dus ook tijdens de laatste loodjes van mijn promotietraject. Imke, mijn lieve nichtje, met jouw sprankelende en benaderbare persoonlijkheid is het is een plezier om bij jou in de buurt te zijn. Het is mooi om te zien hoe jij van alles een feestje kan maken. Dr. Bakker, Mark, doordat onze promotietrajecten in ongeveer hetzelfde ritme verliepen, heb ik ook veel van jouw ervaringen kunnen opsteken. Dank daarvoor. Ik kan jouw kritische en eerlijke blik ook enorm waarderen, vooral als je vraagt: "Wil je advies of een luisterend oor?". Daar kunnen nog veel mensen wat van leren.

Lieve vrienden, ik mag mezelf gelukkig prijzen met zoveel lieve mensen om me heen. Bedankt dat jullie mijn leven een stuk leuker maken. Jullie staan niet alleen voor mij klaar wanneer het goed gaat, maar ook op momenten dat het even wat minder gaat. Jullie zorgen voor ontspanning, inspiratie, steun en kracht. Dit komt extra goed van pas tijdens het afronden van mijn promotietraject. In het bijzonder Laura en Simone, ik houd ervan hoe hard ik met jullie kan lachen.

Lieve papa en mama, bedankt voor alles wat jullie mij hebben bijgebracht. Het is een voorrecht om in zo'n warm en liefdevol gezin op te groeien. Jullie leren mij wat belangrijk is in het leven.

Lieve broer en zussen, wat is het eigenlijk bijzonder om te zien dat vier kinderen met dezelfde opvoeding toch opgroeien tot zo'n verschillende persoonlijkheden. Ik denk dat dat precies de kracht van onze sterke band is. Ik weet dat ik altijd voor alles bij jullie terecht kan. Linda, door jouw empathie, aandacht voor anderen en verantwoordelijkheidsgevoel past de rol van grote zus perfect bij jou. Dit doe je dan ook fantastisch. Samen zorgen voor jouw viervoeter Pax heeft onze band nog sterker gemaakt. Ik geniet enorm van de dagen dat Pax bij mij is, vooral als hij tijdens thuiswerkdagen op mijn schoot komt liggen. Ruud, ik ben onwijs trots op alles wat je al bereikt hebt. Je hebt niet alleen twee succesvolle bedrijven, maar je hebt ook een enorm groot sociaal netwerk en je staat altijd als eerste voor iedereen klaar. Carmen, hoe oud je ook bent, jij blijft altijd de Benjamin van onze gezin. Ik houd van onze zussen momenten, vooral onze risotto-filmavonden. Deze momenten zijn me dierbaar. Lieve Nick en Meaghan, jullie zijn een fantastische aanvulling op ons drukke en chaotische gezin. Jullie maken mijn zus en broer gelukkig en daarmee mij ook.

Lieve schoonfamilie, bedankt dat ik me bij jullie altijd zo thuis mag voelen.

Tot slot, liefste Sidney, wij vormen al bijna 10 jaar een fantastisch team. Jij weet vaak eerder dan ikzelf wat ik nodig heb. Bedankt voor alles wat jij voor me doet. Ik kijk ernaar uit wat de toekomst ons gaat brengen.