Raising the bar for classification and outcome assessment for clinical studies in axial spondyloarthritis

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CHAPTER 1

GENERAL INTRODUCTION

AXIAL SPONDYLOARTHRITIS

Axial spondyloarthritis (axSpA) is a chronic inflammatory rheumatic disease which usually starts in the second or third decade of life and is characterised by chronic back pain (present for at least 3 months) and spinal stiffness[1-3]. Contrary to other rheumatic diseases that are characterised by bone loss, axSpA is characterized by new bone formation, resulting in bone fusion and sclerosis of the sacroiliac joints and spine. The fusion of the sacroiliac joints and/or spinal vertebra contribute to limitations in mobility and physical function, further affecting many activities of daily living[4,5]. As axSpA usually occurs at a relatively young age, patients have to adjust to their disease for most of their lives[6]. Alongside pain and stiffness, many patients experience fatigue and sleep problems, all of which have a major impact on quality of life and their ability to partake in day-to-day activities, such as the ability to remain employed, conduct domestic work and participate in leisure activities[4,5]. Consequently, quality of life in patients with axSpA is reduced compared to the general population[5,7].

In addition to the characteristic spinal complaints, there are several other clinical features that are common among patients with axSpA, the so called spondyloarthritis (SpA) features[1,8]. Information on the following three SpA features can be collected by taking history of the patient: inflammatory back pain (IBP), a good response to non-steroidal anti-inflammatory drugs (NSAIDs) and a positive family history of SpA. IBP is considered if at least four of the following five parameters are present: 1) age at onset before the age of 40; 2) insidious onset; 3) improvement with exercise; 4) no improvement with rest; and 5) night pain with improvement upon getting up[9]. A good response to NSAIDs is reflected by a significant reduction in, or complete absence of back pain in the 24-48 hours after taking a full dose of NSAIDs[8]. Lastly, a positive family history of SpA is present in case of a family history of axSpA, psoriasis, reactive arthritis, uveitis, or inflammatory bowel disease (IBD) in a first-degree (i.e. parents, siblings and children) or second-degree relative (i.e. grandparents, aunt, uncle, niece, and nephew)[10]. Clinical examination can provide insight in peripheral manifestations, including (peripheral) arthritis, enthesitis and dactylitis. Peripheral arthritis can be present in any of the peripheral joints, but there is a preference for asymmetrical involvement of joints of the lower limbs such as the knee. Enthesitis is inflammation at the site of the insertion of the tendon, ligaments, or capsule into bone; the most common enthesitis is heel enthesitis[2,8]. Arthritis and enthesitis are the most common peripheral manifestations and found in ~30–50% of patients axSpA[2,11,12]. Dactylitis is swelling of an entire digit -finger or toe- and much less prevalent than arthritis or enthesitis (6-8% prevalence)[2,11,12]. Additional features are the so-called extra-musculoskeletal manifestations, which include psoriasis, IBD and uveitis. Uveitis is the most frequent extra-musculoskeletal manifestation and occurs in approximately 20-30% of patients with axSpA[12-14]. Uveitis is inflammation of the uveal tract (the middle

layer of the eye) and typically presents as uveitis anterior in axSpA, which is often of short duration, acute in onset, occurs unilaterally, and frequently alternates between eyes[1,2,13]. IBD includes both Crohn's disease and ulcerative colitis, both have a chronic character and are characterised by inflammation of the digestive tract. Prevalence of IBD among patients with axSpA ranges from ~5-10%[12,14,15]. Psoriasis is characterised by red, dry, thick, and raised patches on the skin, which are often covered with a silvery-white coating called scale, and they tend to itch. Prevalence is estimated to be ~10-20% in patients with axSpA[12,14,15]. For the three peripheral and three extra-musculoskeletal SpA features it is assessed whether they are currently present or were present in the past and if the diagnosis was confirmed by a physician[8]. Laboratory tests are used to evaluate whether acute phase reactants (i.e. C-reactive protein (CRP) or erythrocyte sedimentation rate (ESR)) are elevated -which occurs in approximately 50–60% of patients with r-axSpA and 30–40% of patients with nr-axSpA[16]-, and to establish presence/absence of Human Leukocyte Antigen B27 (HLA-B27). Prolonged high levels of disease activity due to inflammation can results in irreversible structural damage to the sacroiliac joints and spine of patients with axSpA[16-20].

Finally, as axSpA affects the sacroiliac joints in most patients, imaging of sacroiliac joints has a pivotal role in diagnosis and classification of axSpA. Radiographs and Magnetic Resonance Imaging (MRI) are the most commonly used imaging techniques in clinical practice[8]. However, there are limitations to the use of radiographs of the sacroiliac joints in patients with early disease, because structural changes generally take years to occur[19]. Therefore, if radiographs are normal or ambiguous, MRI of the sacroiliac joints can provide valuable information, as it allows for the identification of active inflammation (i.e. presence of bone marrow oedema in subchondral bone), as well as the presence of post-inflammatory structural changes (i.e. erosions, sclerosis, and fatty lesions). Both imaging modalities are used to assess sacroiliitis, but use a different definition. Sacroiliitis on radiographs is defined as bilateral grade 2–4 or unilateral grade 3–4, according to the modified New York criteria[21], which represents irreversible structural damage to the sacroiliac joints, whereas sacroiliitis on MRI as a SpA feature is defined as active inflammatory lesions of the sacroiliac joints with definite bone marrow oedema/osteitis suggestive of sacroiliitis associated with SpA[8]. For making a diagnosis also the structural abnormalities on MRI are important. All SpA features are very useful in diagnosis of axSpA as well as classification of patients for clinical trials. Furthermore, these features can provide important information regarding disease prognosis[14].

There are two major subtypes of axSpA[1]: 1) radiographic axSpA (r-axSpA, also known as Ankylosing Spondylitis (AS)), characterised by substantial structural damage to the sacroiliac joints visible on radiographs; and 2) non-radiographic axSpA (nr-axSpA), characterised by clinical symptoms of axSpA in absence of definite sacroiliitis visible on radiographs. Nr-axSpA is often considered an early stage of the disease, which implies patients can progress from nr-axSpA to r-axSpA dependent on risk factors, such as male sex, HLA-B27 positivity, high inflammatory activity (i.e. elevated CRP or inflammation visible on MRI), and smoking status[3,17-19,22-25]. However, progression from nr-axSpA to r-axSpA occurs in approximately 5-20% of patients in a time-period of 2-5 years[17,19,26-29], whereas a proportion of patients may never develop radiographic sacroiliitis and thus never progress to r-axSpA[23,28], emphasising nr-axSpA is more than an early stage of disease, it is also an disease-expression[22,30,31]. Nevertheless, complaints and disease activity of the patients with nr-axSpA have been reported to be equally severe and limiting as those from patients with r-axSpA[32,33].

INTERNATIONAL CHARACTERISATION OF AXIAL SPONDYLOARTHRITIS

Ever since it was recognised that axSpA is in fact a spectrum of disease rather than only AS, there was no longer one single feature (i.e. radiographic damage to the sacroiliac joints) that was present in all patients with axSpA. Therefore, axSpA is a good example of a disease that lacks pathognomonic symptoms and signs, and in particular, specific serological or immunological biomarkers[30]. Disease features are hardly ever identical among patients, hence a clinical diagnosis of axSpA requires careful consideration and exclusion of differential diagnoses as well as pattern recognition using clinical, laboratory, and imaging findings characteristic of axSpA by an experienced rheumatologist[22,31,34]. Furthermore, geographic disease prevalence and the clinical setting affect pre-test probability to make a diagnosis[35]. Thus, a complex multistep process using expert opinion is required to make a diagnosis that cannot be captured by counting features or ticking boxes[34-36]. This is why there are no diagnostic criteria for axSpA and it is currently unlikely that they will ever be developed[36].

Contrary, classification criteria are primarily intended to create well-defined, relatively homogeneous groups of patients for clinical research and validated classification criteria are critical to the interpretation of study findings and comparisons of results between studies[36]. Classification criteria do not capture the whole spectrum of manifestations of a disease, but should be highly specific in order to minimize false-positive errors (i.e. incorrectly labelled as having a disease)[31]. As rheumatic diseases are heterogeneous in nature, classification criteria would fail to identify some patients with axSpA.

This is due to the fact that classification criteria are aimed at a more homogeneous population and a narrower range of disease severity than that seen in routine clinical practice, thus classification criteria should not be used to diagnose patients, but solely to include patients in clinical studies[3,36].

Prior to the currently employed Assessment in SpondyloArthritis international Society (ASAS) classification criteria for axSpA, the most well-known and widely used classification criteria were the 1984 modified New York (mNY) criteria[21], which are used to classify patients with r-axSpA (figure 1).

Modified New York Criteria:

Clinical criteria (need at least one of the three):

1. Low back pain and stiffness >3 months which improves with exercise, but is not relieved by rest

2. Limitation of lumbar motion in sagittal and frontal planes

3. Limitation of chest expansion relative to normal values corrected for age and sex

PLUS

Radiographic criterion

Sacroiliitis grade 2 bilaterally, or sacroiliitis grade 3-4 unilaterally, or bilaterally

Figure 1 Modified New York criteria for ankylosing spondylitis by van der Linden et al. (1984)[21]

The most prominent feature in the mNY criteria is the definition for radiographic sacroiliitis, which is used as the working definition for sacroiliitis to this day. However, the mNY criteria do not allow identification of patients with axSpA early in the course of the disease when radiographic changes in the sacroiliac joints-which as described earlier can take years to manifest- are not yet present[1,2]. Furthermore, radiographic damage reflects the consequences of inflammation, rather than inflammation itself[37,38]. This is why MRI was included in the new set of classification criteria in 2009 by ASAS[37,39]. In the ASAS criteria, the radiographic criterion remains unchanged compared to the mNY criteria, but is complemented with the presence of sacroiliitis on MRI. Patients with sacroiliitis on either MRI or radiographs and at least one other SpA feature fulfil the so-called imaging arm (figure 2, left panel). Including sacroiliitis on MRI in addition to sacroiliitis on radiographs allows for classification of patients with early disease as well as established axSpA, and subsequently for the inclusion of these patients in clinical trials investigating the efficacy and safety of treatments[37,39].

Patients with r-axSpA may be classified using the mNY criteria, or the more recent ASAS criteria. Both the mNY and the ASAS axSpA classification criteria use an identical radiographic criterion (as shown in figures 1 and 2). However, the additionally required (clinical) features of the mNY and ASAS classification criteria differ. Patients without the inflammatory character of back pain fulfil the ASAS criteria if another SpA feature is present, but only fulfil the mNY criteria if spinal mobility is limited. In this thesis we look into the differences and similarities between the two criteria sets, and assess whether both classify the same patients with axSpA if radiographic sacroiliitis is present.

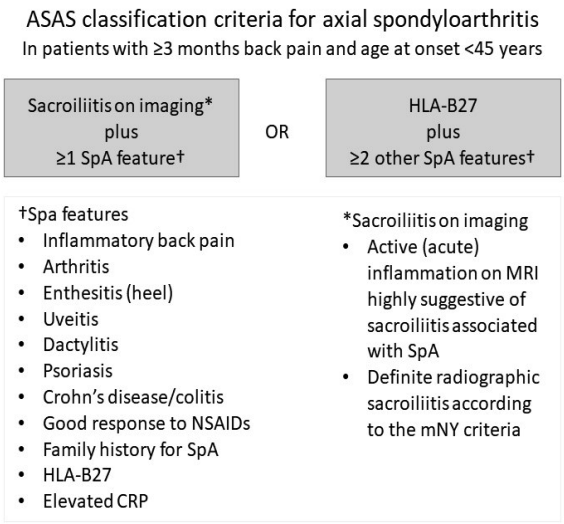

Figure 2 ASAS classification criteria for axial spondyloarthritis by Rudwaleit et al. (2009)[10]
ASAS, Assessment in SpondyloArthritis international Society; CRP, C-reactive protein; HLA-B27, Human Leukocyte Antigen B27; MRI, Magnetic Resonance Imaging; NSAIDs, non-steroidal anti-inflammatory drugs; SpA, spondyloarthritis

In case of absence of sacroiliitis on imaging, the presence of HLA-B27 is required to fulfil the ASAS classification criteria, which represents the so-called clinical arm. The clinical arm was originally intended for situations when imaging is not available (e.g. in large epidemiological studies), and patients are classified using the clinical arm if they are HLA-B27 positive and have at least 2 other SpA features (figure 2, right panel)[3]. The prominent role of HLA-B27 is understandable when one considers that the prevalence of axSpA, ranging between 0.3% and 1.4% is linked to the prevalence of HLA-B27 in a given population[40,41]. Both the prevalence of axSpA[40] and HLA-B27[42] vary considerably throughout the world. Furthermore, the association between HLA-B27 and axSpA varies between races and different subtypes of HLA-B27 are found in different parts of the world (e.g. HLA-B*27:05 and HLA-B*27:09 in Europe and HLA-B*27:04 and HLA-B*27:06 in Asia)[42]. The vast majority (>80%) of patients with r-axSpA is HLA-B27 positive, and this

percentage is only slightly lower in nr-axSpA[22,32,33,43]. HLA-B27 has been related to an earlier age at symptom onset[16,44,45] and better disease prognosis with appropriate treatment[46-48], yet also to an increased likelihood of developing radiographic damage[29,45,49].

There is a genetic link between HLA-B27 carriership and a positive family history of (ax) SpA, as HLA-B27 positive first-degree relatives of HLA-B27 positive patients with axSpA are more likely to develop axSpA than HLA-B27 positive individuals in the general population[50]. Furthermore, the risk of developing axSpA in HLA-B27 positive first-degree relatives of patients with axSpA is approximately one-in-five whereas the risk in HLA-B27 negative relatives is very low (≤1%)[51]. Hence, a positive family history of SpA can be useful in identifying patients with axSpA[52].

In recent years, the value of a positive family history has been questioned[3]. Research has shown that its diagnostic value is limited once HLA-B27 status is known, and the value of a positive family history is probably restricted to identifying chronic back pain patients that might be HLA-B27 positive[52]. Furthermore, studies investigating the association between HLA-B27 and all individual components in (ax)SpA cohorts suggest the association is driven by a positive family history of axSpA and possibly uveitis, but not by other forms of SpA[53,54]. This might leave one to wonder whether a positive family history is overvalued in the classification criteria, as HLA-B27 and a positive family history have an equal weight, and the definition might be too broad by including all five diseases. Nonetheless, it is important to keep in mind that a family history is easily accessible and can provide valuable information in identifying patients suspected of axSpA who first present to the general practitioner with chronic back pain complaints.

Another valuable and easily accessible piece of information in identifying chronic back pain patients suspected of axSpA is the age at onset of back pain complaints[55]. Multiple studies showed that the vast majority of patients with axSpA develop symptoms before the age of 45 years[44,56,57] (figure 3), thereby further emphasizing the importance of the age at symptom onset. These findings provided the basis to include the age criterion in definitions for inflammatory back pain[58,59] and also as an entry criterion in the ASAS criteria[37,39]. However, the majority of the data on which the age at onset criterion was based originates from Western Europe.

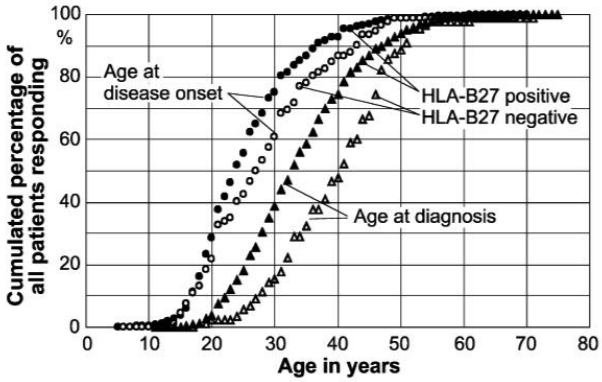

Figure 3 The cumulative distribution in age at disease onset stratified by HLA-B27 status by Feldtkeller et al. (2003)[44]

Given that both prevalence of axSpA[40] and its main genetic risk factor HLA-B27[42] vary considerably throughout the world, a similar distribution in age at onset to the patients in the Feldtkeller study[44] in other parts of the world is not a given. Yet, classification criteria should be applicable to all patients with axSpA worldwide to ensure consistency in the patients who get selected for participation in clinical trials. The same principle applies to the value of a positive family history. Here too, the definition was created using data limited to mostly Western European patients. Should the definition of a positive family history be revised in the future, a new definition must be applicable to patients all around the world. In this thesis we aim to provide an international perspective on the characterisation of patients with axSpA-specifically with regards to the age at symptom onset and positive family history of axSpA-, to investigate whether classification criteria are indeed applicable worldwide.

ASAS-OMERACT CORE SET FOR AXIAL SPONDYLOARTHRITIS

Similarly, it is equally important that all trials executed in various parts of the world assess the same outcomes and report them in a similar way, such that data from American studies can be compared to those initiated in Asia. This is where core outcome sets come in.

Core outcome sets describe the minimum set of mandatory outcomes that should be assessed and reported in all clinical studies of a specific health condition, population and setting[60,61]. A core outcome set consists of domains (*what to measure*) and instruments (*how to measure*). Through standardisation of measurements and reporting, the use of a core outcome set enables direct comparisons between clinical trials on the

effectiveness and safety of the investigated therapies and avoids selective reporting (i.e. only the favourable outcomes)[61]. Using a core outcome set for axSpA thereby reduces heterogeneity of outcomes between studies and the risk of reporting bias because it ensures that all trials contribute relevant and valuable information, which will ultimately result in better research[62]. In this light -taking into account the development of new outcome instruments-, regular review and update of existing core sets is important to ensure the included instruments are still relevant and important[62].

In 1997, ASAS developed a preliminary core outcome set for ankylosing spondylitis, followed by the selection of instruments for each domain[63,64]. The core set for AS was endorsed by OMERACT (Outcome Measures in Rheumatology) in 1999[65,66]. Figure 4 represents the domains that were selected as part of the original core set. The original core set was developed for three different scenarios, which are represented by the different ellipsoids in figure 4[65]:

1. Disease modifying antirheumatic drugs (DMARDs, here indicated as DC-ART where T stands for therapy), presented in the outer ellipsoid in dark grey: therapy that changes the course of disease, both by decreasing inflammatory manifestations, improving or preserving function and preventing or significantly decreasing progression of structural damage.
2. Symptom modifying antirheumatic drugs (SMARD), presented in the inner ellipsoid in white: therapy which improves the symptoms and clinical features of inflammatory manifestations in axSpA. Nonpharmacological interventions belong also to this scenario (e.g. physical therapy).
3. Clinical record keeping in daily practice (presented in the middle ellipsoid in light grey), to facilitate uniform clinical record keeping to strengthen research from clinical records and to monitor patient care in a standardized way.

The ASAS-OMERACT core set was well implemented since its introduction 20 years ago[67], but its development was limited to patients with r-axSpA, whereas it is now well-known that the axSpA spectrum includes both patients with r-axSpA and nr-axSpA[2,31,68]. Additionally, many new outcome instruments have been developed and validated for use in axSpA (such as the Ankylosing Spondylitis Disease Activity Score (ASDAS)[69], the ASAS Health Index[70], and validated enthesitis scores[71]), and with time it became known that it is important to include all stakeholders that will use the core set in its development too[62]. These advances combined with the improvements in the methodology surrounding the development of core sets made ASAS decide it was necessary to update the original ASAS-OMERACT core set for AS. The new core set needs to be applicable to the entire spectrum of axSpA and be developed according to the current recommended methodology.

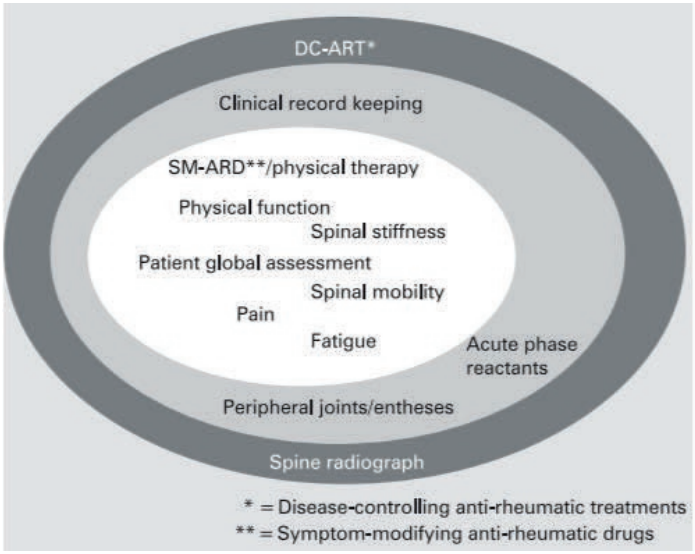

Figure 4 ASAS-OMERACT core domains for ankylosing spondylitis by van der Heijde et al. (1999)[64]
ASAS, Assessment in SpondyloArthritis international Society; OMERACT, Outcome Measures in Rheumatology; DC-ART, disease-controlling antirheumatic treatments; SM-ARD, symptom modifying antirheumatic drugs

The first step to be taken when developing or updating a core set is the selection of *what to measure*, which is defined in so-called domains that are combined to form the core domain set. Thereafter, it needs to be defined *how to measure* each of the chosen domains – through the selection of instruments or tools (core measurement set). The final end product will include both the selected domains and instruments, which will define the new or updated core outcome set.

To enable selection of *what to measure*, a complete overview of all potential domains is required to determine which domains should eventually be included in the core set. Herein, the domains included in the original core outcome set[65,66] and the literature (i.e. all domains reported in trials assessing (non)pharmacological therapies) provide a good starting point, as these represent domains currently measured in clinical research. Additionally, there is an important role for the stakeholders who will end up using the core outcome set to ensure no domains of importance are missed[62]. This includes direct input from patient representatives, which can be collected through qualitative studies and patient focus group interviews[72,73]. Once an extensive list of all potential domains is established, all stakeholders (e.g. patients, rheumatologists, physiotherapists, radiologists, researchers and representatives from pharmacological agencies and drug regulatory agencies) should be involved to ascertain which domains are relevant and should be considered for inclusion in the core outcome set, as they will become the end-users once the core outcome set is in place[74].

For this purpose, the Delphi survey is a valuable tool in collecting opinions from a large group of participants, as it is easily accessible, guarantees anonymity, does not require travel -thereby enabling the inclusion of participants from different continents and time-zones- and does not require public speaking, which increases patient participation[75]. A common application of the Delphi survey is ranking a set of concepts in order of importance or decreasing a voluminous list to a more workable list by prioritizing concepts[76,77], making it the perfect tool to determine which domains are considered relevant by the stakeholders who will use the updated core outcome set. A Delphi survey consists of multiple rounds, which provides participants the opportunity to alter their responses in between rounds in light of the responses of peers. For this purpose, participants receive the aggregated information of peers as well as their own score after each round, which allows them to take the opinions of others into account when answering the questions for a second/third time[78]. The Delphi process ends when (the predefined level of) consensus is achieved, or when the prespecified number of rounds has been completed[79]. In this thesis we have employed the Delphi survey to gather opinions of patients and experts to define the most relevant disease domains to be included in the core set. Next, the results of this Delphi survey will be discussed amongst the ASAS members and shaped into a proposal for the core domain set for axSpA. Once consensus is reached a formal voting session will decide whether the proposed core domain set will be accepted.

Standardisation of methodology is as important as standardisation in measurements. However, there is little guidance on the methodology underlying a Delphi survey[76,79,80], which results in large variability in its execution. One of the aspects that lacks specification is how to invite participants to consecutive rounds of the Delphi survey, which can have an impact on the results and conclusions that are drawn from these results. There are two invitation approaches: 1) Invite only participants that have completed the previous round for the consecutive round; 2) Invite every participant for all consecutive rounds irrespective of whether they have responded or not. Scientific evidence to guide Delphi researchers on whether participants who miss a round can be included in a subsequent round is sparse. In this thesis we investigate whether a different invitation approach influences the final results of the Delphi survey.

After defining the core domain set, the next step is to determine the core measurement set (i.e. the selection of instruments that can be used to measure the domains). At least one instrument needs to be chosen for each selected domain. Herein, once again, there is an important role for previously published literature, as a thorough literature search can provide inside in all instruments currently assessed in clinical trials evaluating treatment effects in axSpA as well as ensure the most recently developed instruments are included too. Once all candidate instruments are identified, all psychometric properties of the

instruments should be collected, as these provide valuable information on the performance of the instruments. They include truth (domain match, face and content validity), feasibility, construct validity, and discrimination (test-retest reliability, responsiveness, clinical trial discrimination and thresholds of meaning)[81]. The truth aspect informs users whether the instrument measures what it is intended to measure and whether the scores are truthful. Feasibility relates to the ease of use, the burden related to completing the instrument for the respondent and/or administrator and the cost related to the use of the instrument. Discrimination describes whether the instrument is able to discriminate between situations of interest, this includes discrimination between treatment arms in a trial, as well as change over time as a result of treatment[81]. Herein it is important to determine whether the same result will be obtained if assessed twice in a situation where there is no change, and improvements/deteriorations reported in trials can thus be ascribed to the treatment rather than measurement error. Test-retest reliability assesses just that, and is therefore an important psychometric in choosing the instruments with the best fit for a given domain. In this thesis we will describe the test-retest reliability of the instruments used in the most recent randomised controlled trials in axSpA, to provide a basis for the selection of the most appropriate instruments for the axSpA core set.

For many outcomes -such as pain or health-related quality of life- rheumatologists and researchers rely on data provided by the patient, as there are no objective measures available for these outcomes. Hence, a large proportion of the outcome measures often used in the assessment of axSpA are so-called patient reported outcome measures.

PATIENT REPORTED OUTCOMES IN EARLY AXIAL SPONDYLOARTHRITIS

Patient reported outcomes are of great importance in axSpA, as most outcomes such as pain, physical functioning and quality of life are subjective measures that cannot be fully captured using objective outcome measures. Furthermore, previous studies have shown that physicians and patients have different perceptions of disease activity[82-85] and physical functioning[86], further emphasizing the importance of patient reported outcome measures. Building on this, patient reported outcomes played a crucial role in the recognition that the burden of disease is comparable between patients with r-axSpA and patients with nr-axSpA[32,33,87].

AxSpA can have a detrimental impact on health-related quality of life[30,88-91], which is why optimising long-term health-related quality of life and social participation has been defined as the main treatment goal in axSpA in the ASAS-EULAR (European Alliance of Associations for Rheumatology) recommendations[92,93]. Limitations of health-related quality of life in

patients with axSpA can be assessed using generic and disease-specific questionnaires. Generic instruments are less specific for a certain disease but allow for comparisons between diseases or with the general population[94]. The SF-36 (Medical Outcomes Study 36-Item Short-Form Health Survey)[95] is an example of a generic questionnaire that is often used in the field of axSpA. The SF-36 has 2 main components: sub-scores for physical health (physical component score) and mental health (mental component score). Standardized population scores are available for the SF-36, which facilitates comparisons between patients with axSpA and healthy individuals, as well as comparisons with other (rheumatic) diseases. Previous research has shown that health related-quality of life is already affected in patients with early axSpA and can be improved by reducing disease activity with effective treatment[96,97].

Additionally, as complaints start early in life in the majority of patients, axSpA is associated with significant risk of limiting work productivity over the patient's life course[30,88-91], which contributes to substantial societal costs of axSpA[22,96]. Unemployment rates and work disability rates are substantially increased compared to the general population, and switching to a less physically demanding job or early retirement are common among patients with axSpA compared to the general population[98,99]. Reduced ability to perform one's job adequately (presenteeism) and an increase in the hours missed from work due to disease (absenteeism) result in reduced work productivity[100]. Furthermore, patients with axSpA report that the disease influences their job choice, and that they require workplace adaptation, which adds to the personal and societal impact of the disease[101].

The majority of studies on work productivity loss focused on patients with r-axSpA and patients with a long disease duration. However, as participating in work has a large impact not only on societal cost, but also on an individual's social and psychological well-being[100] and axSpA usually starts in young adulthood-which tend to be the most productive years[6], it is equally-or even more- important to assess work outcomes in early disease.

At the time of initiation of the SpondyloArthritis Caught Early (SPACE) cohort[102], little was known on the long-term impact of the early phase of axSpA on quality of life and the accompanying socio-economic burden of this disease. Hence, one of the research aims was to study the burden of axSpA in patients in an early stage of the disease, and the implications of diagnosis. In order to do so, the SPACE cohort includes patients with recent onset chronic back pain, referred to the rheumatology outpatient clinic with a suspicion of axSpA. Since then, data from the SPACE cohort and other early (ax)SpA cohorts have shown great improvement in quality of life and work productivity following diagnosis, suggesting a beneficial effect of early diagnosis and subsequent treatment[96,103,104]. However, in absence of a comparator group these results are difficult to interpret and it is particularly difficult to attribute the observed improvement to axSpA treatment. In this thesis we will

provide additional insight in the burden of disease in terms of health-related quality of life and work productivity of patients with a diagnosis of axSpA in the first two years after diagnosis, by making a comparison with the patients who did not get a diagnosis of axSpA but were suspected of axSpA.

AIMS AND OUTLINE OF THIS THESIS

The first research aim of this thesis is to provide an international perspective on the characterisation of patients with axSpA, for which we investigated different aspects of the classification criteria. Herein, we started with assessing the similarities and differences between the modified New York criteria and ASAS axSpA criteria in the classification of patients with radiographic axSpA, which is described in **chapter 2**. For this purpose we included patients from eight cohorts from various countries and with various disease duration and severity: ASAS[37,39], Esperanza[105], GErman SPondyloarthritis Inception Cohort (GESPIC)[16], Outcome in Ankylosing Spondylitis International Study (OASIS)[83], Reuma.pt[106], Swiss Clinical Quality Management (SCQM)[107], SPondyloArthritis Caught Early cohort (SPACE)[102], and University of California San Francisco (UCSF) axSpA cohort[108]. Two cohorts (OASIS and UCSF axSpA) included patients with r-axSpA only, the other 6 cohorts included patients with r-axSpA as well as nr-axSpA.

The majority of the 8 cohorts included European patients, the ASAS cohort included American and Asian patients as well as European patients, and the UCSF axSpA cohort included only American patients. Esperanza, GESPIC and SPACE included patients with early disease, ASAS, Reuma.pt and SCQM patients with early or established disease and OASIS and UCSF axSpA patients with established disease only. Esperanza and SPACE required a maximum symptom duration of 2 years, GESPIC a maximum of 10 years, and the other cohorts did not employ a maximum symptom duration.

Another important aspect in the classification of patients with axSpA is age at onset, yet this criterion is based on mostly European data. Therefore, **Chapter 3** evaluates the age at onset of axial symptoms in a worldwide cohort of patients diagnosed with axSpA: the ASAS-PerSpA (ASAS peripheral symptoms in spondyloarthritis) cohort. In this international observational study with a cross-sectional design, 4465 consecutive patients with a diagnosis of axSpA, peripheral SpA or psoriatic arthritis (according to the treating rheumatologist) were included in 24 countries from 4 different geographical regions (Asia, Europe & North America, Latin America, and Middle East & North Africa).

Its international character, size and variety of symptom duration and disease severity enabled worldwide comparisons regarding age at symptom onset in the patients with axSpA. Using data from this same cohort, **chapter 4** provides insight in the geographical prevalence of a family history of a SpA-related disease and its relationship with HLA-B27.

The second research aim is to describe the process of the development of the core set for axSpA by updating the domains of the ASAS-OMERACT core set for ankylosing spondylitis, which is described in **chapters 5 to 8**. The first step in this process was to collect the opinions of patients with axSpA and experts in the field of spondyloarthritis regarding the importance of the domains. For this purpose, a 3-round Delphi survey was deployed, the results of which are presented in **chapter 5**. **Chapter 6** illustrates an additional unique aspect of the Delphi survey design: in a randomised experiment was assessed which invitation approach should be used when performing a Delphi survey. Using the results from the Delphi survey, the mandatory domains for the core set were formulated and endorsed by OMERACT, which is presented in **chapter 7**. Finally, **chapter 8** provides information on the test-retest reliability of measurement instruments used in axSpA, which is a vital step in the final selection of instruments that will become part of the core outcome set for axSpA.

The third and final research aim is to increase knowledge on work and activity outcomes and health-related quality of life over time in chronic back pain patients with a diagnosis of axSpA or a suspicion thereof. For this purpose, work and activity outcomes and health-related quality of life are assessed over time and a comparison is made between patients who get a definite diagnosis of axSpA after two years of protocolised follow-up and those who get diagnosed as no axSpA. This has been investigated in the SPACE cohort and can be found in **chapter 9**. The SPACE cohort is an ongoing international inception cohort[102]. Data was collected from Dutch, Italian, Norwegian and Swedish patients visiting the outpatient clinic with persistent back pain (>3 months and <2 years) with an onset before the age of 45, starting in 2009.

The final two chapters include a summary and general discussion of the findings of this thesis, in English in **chapter 10** and in Dutch for lay persons in **chapter 11**.

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