Title: The ASAS-OMERACT Core Domain Set for Axial Spondyloarthritis

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ABSTRACT

Background: The current core outcome set for ankylosing spondylitis (AS) has had only minor adaptations since its development 20 years ago. Considering the significant advances in this field during the preceding decades, an update of this core set is necessary.

Objective: To update the ASAS-OMERACT core outcome set for AS into the ASAS-OMERACT core outcome set for axial spondyloarthritis (axSpA).

Methods: Following OMERACT and COMET guidelines, an international working group representing key stakeholders (patients, rheumatologists, health professionals, pharmaceutical industry and drug regulatory agency representatives) defined the core domain set for axSpA. The development process consisted of: i) Identifying candidate domains using a systematic literature review and qualitative studies; ii) Selection of the most relevant domains for different stakeholders through a 3-round Delphi survey involving axSpA patients and axSpA experts; iii) Consensus and voting by ASAS; iv) Endorsement by OMERACT. Two scenarios are considered based on the type of therapy investigated in the trial: symptom modifying therapies and disease modifying therapies.

Results: The updated core outcome set for axSpA includes 7 mandatory domains for all trials (disease activity, pain, morning stiffness, fatigue, physical function, overall functioning and health, and adverse events including death). There are 3 additional domains (extra-musculoskeletal manifestations, peripheral manifestations and structural damage) that are mandatory for disease modifying therapies and important but optional for symptom modifying therapies. Finally, 3 other domains (spinal mobility, sleep, and work and employment) are defined as important but optional domains for all trials.

Conclusion: The ASAS-OMERACT core domain set for AS has been updated into the ASAS-OMERACT core domain set for axSpA. The next step is the selection of instruments for each domain.

INTRODUCTION

The management of axial spondyloarthritis (axSpA) has come a long way in the last two decades(1, 2). The development of new therapeutic options, especially pharmaceutical drugs, covering the entire spectrum of the disease has been a major advance (3, 4). This progress should go hand-in-hand with updating outcome measures, so that all studies consistently assess the most relevant domains and instruments for axSpA.

Clinical trials seek to evaluate whether an intervention is effective and safe. This is determined by comparing the effects of a specific intervention on selected outcomes versus a control to identify the possible beneficial or harmful effects of the intervention. Therefore, the careful selection of appropriate outcomes is crucial when designing clinical trials and other clinical studies. To avoid selective reporting of outcomes and to facilitate comparison of results across trials, it is important to use standardised outcomes(5). Moreover, it is important to use outcomes that are relevant to all stakeholders. Such issues can be addressed with the development and application of an agreed standardised set of outcomes for all clinical trials, which is defined as the core outcome set for a specific health condition, population and setting(6).

The core outcome set represents the minimum that should be measured and reported in all clinical trials. Nevertheless, this does not imply that the outcomes in a particular study should be restricted to those in the core outcome set(7). Rather, there is an expectation that the core outcomes will be collected and reported to allow the results of trials and other studies to be compared, contrasted and combined as appropriate. Therefore, the use of a core outcome set may reduce heterogeneity of outcomes between studies in axSpA, will lead to research that is more likely to have measured relevant outcomes, and is of potential value to use in clinical audit and meta-analyses. Also, it enhances the value of evidence synthesis by reducing the risk of outcome reporting bias and ensuring that all trials contribute relevant information(5, 6).

Although the core outcome sets are essential, not many have been developed according to the highest standard and/or have been implemented adequately. The most notable work relating to outcome standardisation has been conducted by the Outcomes Measures in Rheumatology (OMERACT) collaboration, which is an independent initiative of international multi-stakeholders interested in outcome measures in rheumatology, integrating patient, clinician, trialist, methodological and industry perspective. OMERACT had its first meeting and definition of a core outcome set in 1992(8). This successful initiative was followed by a more global group also addressing other fields outside of Rheumatology, set up as the Core Outcome Measures in Effectiveness Trials (COMET) Initiative in 2010. The aim of COMET is to promote the development of core sets and bring together researchers interested in the development and application of core outcome sets(9).

The Assessment of SpondyloArthritis international Society (ASAS) is an international group of experts in the field of spondyloarthritis (SpA), with the ultimate goal to improve the overall health and outcome of patients with SpA(10, 11). Outcome assessment has always been the focus of ASAS, similar to OMERACT, and both organisations have collaborated closely. In fact, the development of the ASAS-OMERACT core set for outcome measures in ankylosing spondylitis (AS) was the first activity undertaken by ASAS after its launch in 1995. The first preliminary ASAS core set for AS was published in 1997(12). This was followed by a publication in 1999 on the selection of the instruments for each outcome in the core set(13). And finally, the core set was endorsed by OMERACT in 1999(14, 15). In 2007 minor changes in relation to a few selected instruments were implemented by a consensus process by ASAS(16).

As shown by a recent systematic literature review, the ASAS-OMERACT core set for AS was well implemented after its original publication two decades ago(17). However, since then, there have been major advances in the field of SpA as well as in the methodology to develop core

sets, which may have an impact on the agreed outcomes two decades ago. Main accomplishments in the field of axSpA outcomes include the use of magnetic resonance imaging (MRI), the development of the Ankylosing Spondylitis Disease Activity Score (ASDAS)(18), validated enthesitis scores(19), and the ASAS Health Index(20, 21). With regards to the methodology to develop core sets, there is no gold standard yet but during the last years OMERACT and COMET have intensively worked to provide specific guidance about how this should be done, e.g. OMERACT handbook and Filter 2.0, COMET handbook and Core Outcome Set-STAndards for Development (COS-STAD) (5, 7, 22, 23).
Moreover, there have been developments with respect to the definition of the disease. The presence of definite sacroiliitis on radiographs is mandatory to define AS. With the availability of MRI became evident that there are also forms without radiographic sacroiliitis. This so-called non-radiographic axSpA (nr-axSpA) together with AS, also known as radiographic axSpA (r-axSpA) defines the entire spectrum of the disease, called axSpA(1, 24). The new classification thus also requires an update of the ASAS-OMERACT core outcome set for axSpA.
The ASAS group decided to update the original version into the ASAS-OMERACT core outcome set for axSpA and started working on this process in 2018 according to the currently accepted methodology. The first step of this project is the selection of *what to measure* (core domain set). Thereafter, it needs to be defined *how to measure* each of the chosen domains – selecting instruments or tools (core measurement set). Both, *what to measure* and *how to measure* will form the final core outcome set. Here we present the results of the first step.

METHODS

For this project, OMERACT and COMET guidelines were followed (5, 22, 25-27), but taking into account that the goal of this process was an update of an existing core set and not a completely new one. The main phases of the development process for a core set are summarised in
Figure 1.

Define the scope

First of all, the steering committee of the project defined the scope of the core set, which was established as follows:
Health condition: axSpA, with or without peripheral rheumatological manifestations (arthritis, enthesitis and dactylitis) and with or without extra-musculoskeletal manifestations (uveitis, inflammatory bowel disease and psoriasis). Pure peripheral SpA was excluded.
Population: Patients 18 years or older with axSpA, covering the whole spectrum of the disease including nr-axSpA and r-axSpA, early disease and established disease. The lower limit of the age range (18 years) was based on ethical considerations arguments, as this is the common limit required to include patients in interventional studies.
Types of intervention: Pharmacological and non-pharmacological interventions, excluding surgery. According to the type of intervention, two main scenarios are considered: i) Symptom modifying antirheumatic therapies (SMART). This type of therapy improves the symptoms and clinical features of inflammatory manifestations and include non-pharmacological treatment (e.g. physical exercise) and symptom modifying antirheumatic drugs (SMARD) such as non-steroidal anti-inflammatory drugs (NSAIDs). ii) Disease modifying antirheumatic drugs (DMARDs). This type of intervention changes the course of the disease by a) improving and sustaining functioning and overall health and b) preventing or significantly decreasing structural damage (e.g. cytokine inhibitors).

Settings: Two main settings are described: i) Research: clinical trials and longitudinal observational studies (including registries); and ii) Clinical practice. Nevertheless, due to the known differences in the development process between the different settings, ASAS decided to work first on a core set for the research setting and later develop a core set for the clinical practice setting.

Register in the COMET database

The COMET Initiative database is a repository of studies relevant to the development of core outcome sets. At the beginning of the project, the steering committee checked in this database that no other group was working on the update of this core set. Once this was confirmed, the project was registered in the COMET database on 19th of March 2018. Further details are available at COMET website.(28)

A detailed protocol of the project was written by two of the co-chairs (VN-C and DvdH) and reviewed by all members of the steering committee. OMERACT and COMET guidelines were considered for this purpose.

Working group

First, a steering committee was formed. This consisted of the four co-chairs of the project (DvdH, VN-C, AB and PM), two additional ASAS members with expertise in OMERACT and COMET methodology (RL, MD), one patient representative (UK) and one fellow (AB). The steering committee invited the members of the axSpA working group based on their background, geographical region, knowledge, experience with trials and the stakeholder group to which they belong. Potential conflicts of interest of the invited members were listed and discussed by the steering committee. The working group was formed at the beginning of 2018 involving a total of 28 participants (including the steering committee), representing those stakeholders who will use the core set in research, including rheumatologists and methodologists (17), healthcare professionals (2), patient research partners (3), representatives from pharmaceutical companies (4) and drug regulatory agencies (1), and a research-fellow (1).(29)

OMERACT workshop application

In December 2018 the steering committee submitted an application for having an axSpA workshop to vote on the core domains at the OMERACT 2020 meeting, initially scheduled for April in Colorado. This application was accepted in February 2019. Nevertheless, due the COVID-19 pandemic the face-to-face meeting was postponed and eventually replaced by a virtual workshop in November 2020.

Identify all candidate and relevant domains for stakeholders

Figure 2 shows a summary of the different phases of the process to identify the possible domain candidates and to select the final set of core domains by means of reducing the extensive list to a concise set. This part has been published in detail in a separate manuscript(30) (*Boel et al, submitted*). Briefly, a list of the candidate domains was identified using three different sources and later two groups of stakeholders (patients and experts) selected the domains that should be considered for inclusion in the core set via two identical but separate Delphi surveys, which were launched between November 2nd and December 30th 2018.

Working group consensus

The working group met twice during the update process. The first meeting took place in January 2019 in Amsterdam and the second virtually in November 2019. The views from all key stakeholder groups were considered. The purpose of these meetings was to provide all stakeholders the opportunity to discuss the results of the Delphi survey and to agree on a proposal for a final core set according to the new format of the OMERACT onion(25). As shown in figure 3, this follows a structure in which the domains are placed in concentric spheres by decreasing importance classifying the outcomes in three categories: i) mandatory, ii) optional but important and iii) for research agenda.

ASAS consensus

After discussion with the working group, the results of the Delphi survey were presented and discussed with all ASAS members in a plenary session during the ASAS annual workshop 2019 in Amsterdam. By consensus, the following decisions were made:

- If a domain was included in the original core set, there should be a strong reason for excluding the domain in the updated core set.
- If a domain had been selected for the SMART scenario, this should be selected for the DMARD scenario too. This thinking is in line with registration of drugs: drugs can show disease modification in addition to relieving of signs and symptoms. No registered treatment for axSpA has been shown to only impact structural damage progression, and even in such a trial, signs and symptoms should be assessed to know if an effect on these is lacking.

Finally, the agreed domains by the working group in the virtual meeting were presented to all the ASAS members in a plenary session during the annual ASAS workshop, in January 2020 in Houston. After discussion, each full ASAS member voted anonymously using a digital voting system (engagenow.live) on agreement with the final proposed set of domains by answering the following question "Do you agree with the proposed onion of domain core set"? The predefined requirement to accept the proposed outcomes was that at least 50% of the members voted positively.

OMERACT endorsement

Finally, the ASAS proposal of the core domain set was presented at a specific OMERACT 2020 virtual meeting, which took place on November 13th. In total, 125 participants recruited by ASAS and OMERACT attended the meeting in two different time zone sessions to ensure that participants around the world could partake. Pre-reading material was sent to all participants, which included a whiteboard video (accessible at https://omeract.org/working-groups/axial-spa), one-pager with the definitions for each of the selected domains (shown in table 1) and a lay summary. Each meeting lasted for 90 minutes and included a plenary session, 5-7 breakout sessions (with a facilitator, a content expert, a reporter, at least one patient research partner and 5 representatives from other stakeholders) and a final voting session. All participants were asked to vote anonymously on two questions using the Zoom polling feature for meetings: i) can you accept the proposed set as mandatory domains for all trials? and ii) can you accept the proposed additional domains as mandatory for disease modifying drug trials? The results were summarised in two groups: patient research partners and other stakeholders. The predefined requirement to endorse the core set was that at least 70% of the participants in each group accepted the proposal.

RESULTS

Relevant Domains for stakeholders

As mentioned, the results for the selected domains to be considered for inclusion in the final core outcome set have been published in detail separately (*Boel A et al, submitted*). In summary, the selected domains required to be voted as critical by ≥70% of participants and not important by ≤15% of participants for both stakeholder groups, separately. After the three Delphi-rounds, a total of 7 domains (pain, physical function, stiffness, disease activity, mobility, overall functioning and health, and peripheral manifestations) were selected to be considered for inclusion in the SMART setting. For the DMARD setting, 6 domains (physical function, disease activity, mobility, structural damage, extra-musculoskeletal manifestations, peripheral manifestations) were selected. All domains selected by experts were also selected by patients. Patients selected all offered domains except 'emotional function', including fatigue, work and employment and sleep for both settings in addition to the selected domains.

Working group proposal

After the virtual meeting in November 2019, the working group agreed on a proposal for the core domains, distributed across the OMERACT onion (Figure 3), which took into account the two decisions previously taken (i.e., only delete a previous domain for strong reasons and all mandatory domains for the SMART setting should also be mandatory for the DMARD setting). This proposal included 7 mandatory domains for all trials independently of the therapy investigated. These mandatory domains were: disease activity, pain, morning stiffness, fatigue, physical function, overall functioning and health, and adverse events including death. In addition, 3 extra domains (extra-musculoskeletal manifestations, peripheral manifestations, and structural damage) were included as mandatory for DMARDs, leaving them as optional but important for SMART. As a clarification, structural damage was included as a mandatory domain for at least one trial during the development program of a specific DMARD but not in every trial on that DMARD. Finally, 3 other domains (spinal mobility, sleep, and work and employment) were included as important but optional for all trials. No domain was included in the research agenda layer.

ASAS voting

In total, 92% (n=57) of ASAS full members participating in the annual workshop voted to accept this proposal. Furthermore, three other aspects related to the domains included in the final onion were voted on. Most members agreed that the most appropriate term when referring to inflammatory bowel disease, uveitis and psoriasis in patients with axSpA is 'extra-musculoskeletal manifestations (EMMs)'. In addition, the assessment of this domain should include the three mentioned manifestations. The domain "peripheral manifestations" should include arthritis, enthesitis and dactylitis. The working group proposal for the onion was slightly adjusted to include these points.

OMERACT endorsement

The ASAS proposal for the core domains is depicted in Figure 3 and the definition for each of the domains is provided in Table 1. The proposal was broadly accepted. Combining the results of the two sessions, 100% (n=18) patient research partners and 99% (n=95) representatives of other stakeholders voted to accept the 7 mandatory domains set for all trials. Furthermore, 95% (n=17) patient research partners and 99% (n=97) representatives of other stakeholders accepted to include the three additional mandatory domains for DMARDs. Finally, some minor edits proposed by OMERACT participants were implemented in the final version of the onion.

DISCUSSION

The definition of the core domain set responds to one of the relevant unmet needs in the field of axSpA(31). The original core set was developed more than 20 years ago and was well implemented(12, 17). However, after more than two decades this core set became outdated and required revision to address all the advances achieved recently in the field of axSpA and to address the current recommended methodology for development of a core outcome set(32). This manuscript presents the result of a crucial collaborative initiative between ASAS and OMERACT to update the ASAS-OMERACT core outcome set for AS into the ASAS-OMERACT core outcome set for axSpA.

Compared to the original core set, the updated core set for axSpA represents a substantial advance both in content and in the methodology employed. The most recent guidelines for development of a core set were followed as closely as possible. In this sense, the OMERACT and COMET handbooks have been the basis for updating the core set to the highest possible quality(5, 22). The procedure associated with these guidelines is extensive and meticulous. An important aspect of this procedure is the working group and stakeholders participating in the

selection of the domains. The updated core set involved all key stakeholders. Furthermore, the number and heterogeneity of participants also increased. While the original core set involved approximately 40 participants the update of the core set involved 376 participants in total, with 50% experts (from more than 40 countries worldwide) and 50% patients, representing both genders equally and covering the entire spectrum of the disease.

Importantly, it should be stressed that the updated core set is meant to be employed in a research setting (i.e. studies evaluating the effect of therapies) but not necessarily in all observational studies or clinical practice. These two latter settings require a different methodology to the one followed in this procedure. Similar to the original core set, the updated core set applies to two scenarios depending on the type of intervention investigated in the trial, splitting the core domains in those that should apply for all trials and those that are mandatory only for DMARDs, while still considered to be important but optional for SMARTs. Like the original core set, the following four domains remained mandatory for all trials: pain, morning stiffness, fatigue and physical function. However, there are some differences between the core sets. The original core set included as mandatory domains for all trials the patient global assessment and spinal mobility. For the updated core set the patient global assessment was removed as this is not really a domain but an instrument, while mobility was moved to being optional but an important domain for all trials. Reasons for this change are lack of standardisation and poor reliability and sensitivity to change.(21) Additionally, overall functioning and health is now included as mandatory for all trials. This domain was considered relevant when the original core set was defined (at that moment called quality of life); however, the lack of an appropriate instrument to assess this domain in axSpA drove the decision to leave it out. Over time several instruments were developed to assess overall functioning and health(20, 33), which led to the inclusion of this domain as mandatory for the updated core set. Furthermore, the original core set also includes two domains as optional but important for all trials, which are sleep and work and employment. Over the last decades, it was shown that sleep disorders and the impact on work and employment are important aspects for patients with axSpA(34-36). Two new domains have been added as mandatory for all trials in the updated core set. One of them is included in all OMERACT core sets, which is death and adverse events(25). The other one is disease activity. This was not included as a specific domain in the original set but several instruments assessing this domain such as patient global assessment and acute-phase reactants were included, which reflects that this was already considered relevant*(3, 37)*. The importance of objective measures to assess disease activity such as imaging and serological acute phase reactants was stressed in the breakout sessions, but this will be further discussed during the selection of instruments for this domain.

Importantly, the update of the core outcome set for axSpA is not final. After deciding *what to measure* (core domain set) the next step is deciding *how to measure* the domains by selecting instruments or tools for each domain(5, 22). An important aspect of this step is the assessment of the measurement properties of candidate instruments. The working group is currently working on this. With this information, the selection of the most appropriate instruments will be achieved by consensus of the key stakeholders. Moreover, we cannot forget one of the most important steps in the development of a core set, which is its implementation. The original core set was successfully implemented(17). For the update we will design strategies for a broad dissemination and implementation. We are convinced that having the support from ASAS and OMERACT will help in this process.

A few potential limitations should be considered. First, the working group followed as closely as possible the current guidelines to develop a core outcome set. Even so, minor modifications had to be made as this process was an update of a previously developed core set and no specific guidelines are currently available to update a core outcome set. Another possible limitation is that instead of running specific qualitative studies to update the core outcome set, we employed

the data from the qualitative studies to develop the ASAS/World Health Organisation (WHO) Comprehensive and Brief Core sets of the International Classification of Functioning, Disability and Health (ICF)(38). These data were used only to identify the candidate domains. After this, all participating stakeholders could add extra domains during the first round of the Delphi survey if they thought these were missing. Hence, we do not think this has influenced the outcome of the process.

In conclusion, this manuscript presents the updated ASAS-OMERACT core domain set for axSpA, which is an essential tool for research in this disease. This core set includes the minimum but mandatory set of domains that should be assessed in all clinical trials and longitudinal observational studies evaluating a therapy in patients with axSpA. As this is a minimum, it does not exclude that other domains may be additionally assessed within specific trials. This core set will contribute to ensure that the most relevant aspects of the disease are assessed in all studies and that this is done in a standardised and homogeneous way that will allow comparisons of results across studies.

FIGURES AND TABLES

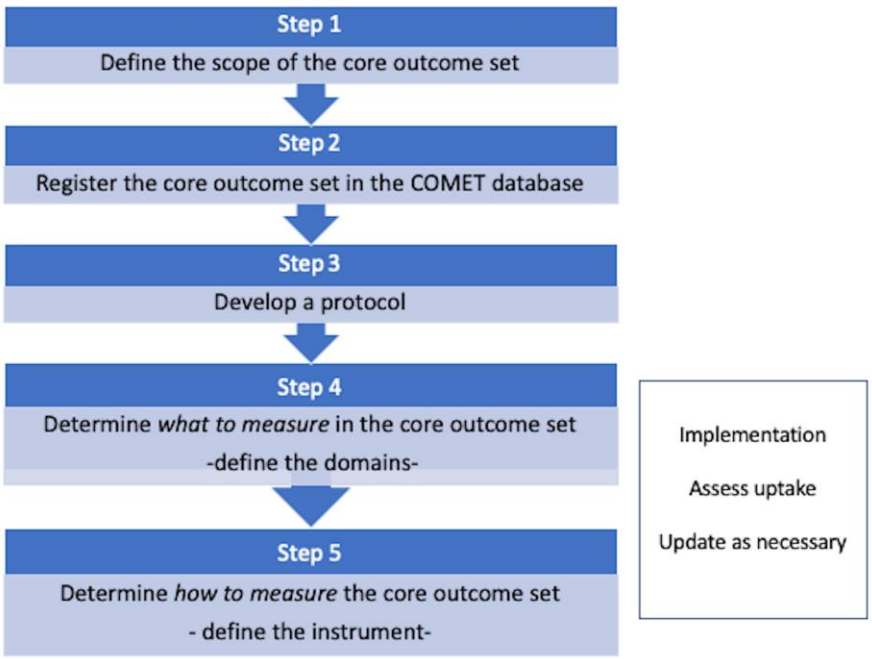

Figure 1: The core outcome set development process. Adapted from Williamson PR et al. Trials. 2017;18(Suppl 3):280. COMET: Core Outcome Measures in Effectiveness Trials.

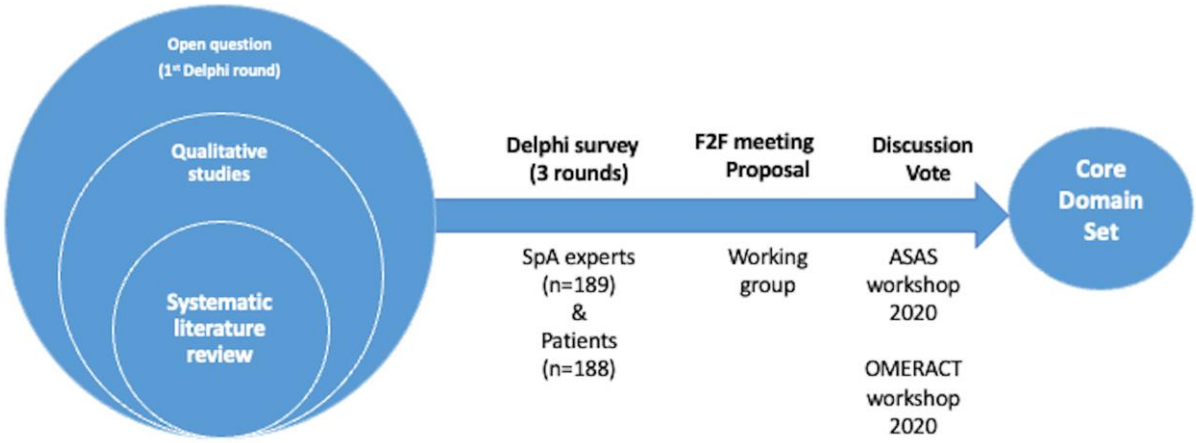

Figure 2: Development process to determine the core domain set. SpA: Spondyloarthritis; F2F: face to face; ASAS: Assessment of SpondyloArthritis international Society; OMERACT: Outcomes Measures in Rheumatology.

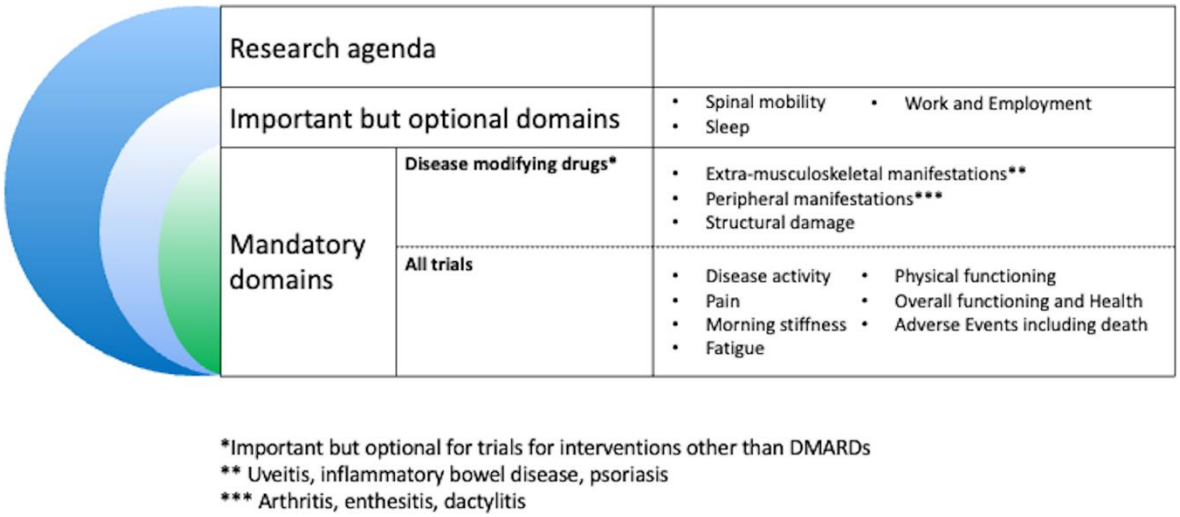

Figure 3: Update core domain set for axial spondyloarthritis presented according to the OMERACT onion. OMERACT: Outcomes Measures in Rheumatology; DMARDs: Disease Modifying AntiRheumatic Drugs.

Table 1: Definitions of domains included in the OMERACT onion.

Mandatory domains for all trials

1. Disease activity

The domain 'disease activity' covers the level of activity of the disease including signs and symptoms but also objective inflammation that can be assessed by imaging or in the lab.

2. Pain

Pain, includes overall pain, peripheral pain (pain in the hands and feet, wrists, elbows, shoulders, ankles and knees) and/or spinal pain (pain in the neck and spine) experienced throughout the day as well as pain at night. The sensation of pain (sensation of unpleasant feeling indicating potential or actual damage to some body part or throughout the body) as well as pain intensity (how much pain) and duration are included in this domain.

3. Morning stiffness

A feeling of stiffness in the back upon getting up in the morning, which influences the ability to move about.

4. Fatigue

Fatigue describes the overall feeling of tiredness and/or lack of energy; inability to optimally use mental or physical capacity.

5. Physical functioning

Physical functioning is defined as one's ability to carry out various activities that require physical capability, ranging from self-care (activities of daily living) to more vigorous activities that require increasing degrees of mobility, strength, or endurance. An important aspect in this domain is physical difficulty: any problems with physical activity resulting from impairment, any activity limitations and participation restrictions; and the ability to transfer oneself from one place to another (i.e. walking, cycling).

6. Overall functioning and health

In general, overall functioning and health is the perceived quality of an individual's daily life, that is, an assessment of their well-being or lack thereof. This includes all emotional, social and physical aspects of the individual's life. Overall functioning and health is an assessment of how the individual's well-being may be affected over time by a disease, disability or disorder Participation at work, at home and leisure, overall well-being, daily function, social support from family and friends, interpersonal relationships and social roles are all included in overall functioning and health. Also included in this domain are any impairments experienced during the day as a result of sleep problems.

7. Adverse events (including death)

An unexpected medical problem that happens during treatment with a drug or other therapy. Adverse events may be mild, moderate, or severe, and may be caused by something other than the drug or therapy being given.

Additional mandatory domains for trials investigating the effect of disease modifying drugs

1. Extra-musculoskeletal manifestations (uveitis, inflammatory bowel disease, psoriasis)

Extra-musculoskeletal manifestations include uveitis, inflammatory bowel disease (Crohn's disease and Ulcerative Colitis) and psoriasis. These are frequently occurring in patients with axial spondyloarthritis and belong to the disease spectrum. Other extra-musculoskeletal manifestations that occur more frequently than in the healthy population but do not belong to the disease spectrum are problems with cardiovascular and pulmonary functioning.

- Uveitis is a form of eye inflammation. It affects the middle layer of tissue in the eye wall (uvea), hence its name uveitis and occurs in attacks.
- Inflammatory bowel disease (IBD) is an umbrella term used to describe disorders that involve chronic inflammation of your digestive tract. Types of IBD include Crohn's disease and Ulcerative Colitis
- Psoriasis: a common chronic, inflammatory skin disease characterized by redness of the skin and small dry pieces of skin across the body.

This domain is considered important but optional for all axial spondyloarthritis trials other than those investigating disease modifying drugs.

2. Peripheral manifestations (arthritis, enthesitis, dactylitis)

Peripheral manifestations include enthesitis, dactylitis and arthritis

- Enthesitis is the term used to describe inflammation at tendon, ligament or joint capsule insertions. A common location for enthesitis is at the heel, particularly the Achilles tendon.
- Dactylitis is severe inflammation of the finger or toe joints. The puffy nature of the inflammation can make your digits look like sausages, which is why they are sometimes called sausage fingers or toes
- Arthritis: Inflammation of a joint. When joints are inflamed, they can develop stiffness, warmth, swelling, redness and pain.

This domain is considered important but optional for all axial spondyloarthritis trials other than those investigating disease modifying drugs.

3. Structural damage

Structural damage, determined by any method (e.g. imaging), including structural damage to the spine, peripheral joints (hands and feet, elbows, wrists, ankles, and knees), and root joints (shoulders and hips). Damage to the organs is another manifestation of 'structural damage'.

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