The Axial SpA Public Comment was posted on the ACR website Monday, May 13, 2013. The announcement was emailed to ACR membership on Tuesday, May 14. As of June 4, 24 responses were received. The public comment period closed on the morning of Tuesday, June 4.

1. Tracy Brenner, Clinical Staff Rheumatologist
Indiana University Health Physicians/ Dept. Rheumatology
Nothing to disclose
Comment:
Thank you for your email regarding the development of recommendation for the management of axial spondyloarthritis, including ankylosing spondylitis, and children with the enthesitis-related arthritis form of juvenile idiopathic arthritis. I am both a practicing rheumatologist as well as a mother with a 10 year old son with Crohn's related spondyloarthropathy (diagnosed at 7 years old). As a physician and mother, I think two important issues to cover are the following:

1. Prognosis for children diagnosed with enthesitis-related arthritis and/or IBD related spondyloarthropathy. The general risk factors are clear including concern for overall morbidity and mortality but it would be helpful to have more statistics regarding these issues (e.g. CVD, long term use of methotrexate, long term use of biologics with initiation of therapy in the pediatric years, etc). I realize some of this is available, certainly, but continued observance is warranted.
2. Question of risk vs. benefit regarding use of Remicade with young male patients (documented ages were 12-early 20's) with Crohn's related SPA as this group seems to represent a rare, but unfortunate correlation to the largely fatal hepatosplenic T cell lymphoma. I have asked the pharmaceutical company for the numbers of male juvenile patients treated with Remicade but they stated those numbers are not available.

Thank you for your consideration. I truly appreciate your time and effort in this endeavor. If there is any way I can help please let me know.

2. Lisa Suter, Assistant Professor
Yale School of Medicine
Disclosure: I am a member of the ACR Quality Measurement Subcommittee
Comment:
I have reviewed the proposed plan for developing management guidelines for the spondyloarthropathies and agree with the proposed approach. Publication bias is a significant concern in this kind of analysis. I recommend the work group consider the following approaches to addressing publication bias in their project:

1. Use rigorous methods to identify preliminary and unpublished data through contact with experts and study authors;
2. Create funnel plots (of effect estimates versus sample size) and use Egger's test to assess the asymmetry within the funnel plots (eg, if significant asymmetry is identified, suggesting publication bias, one could use the "trim and fill" approach to estimate upper and lower boundaries around the summary estimate to account for the potential publication bias);
3. Estimate the number of null studies needed to alter the study findings;
4. Cross-reference the published and available literature against funded clinical trials registered at www.ClinicalTrials.gov in order to partially assess funded trials that have not been published (as negative studies are more likely to never be published).

3. Eric Matteson, Consultant
Mayo Clinic
Nothing to disclose
Comment:
Looks like an excellent plan. One further question to consider is whether it is worthwhile to screen/evaluate patients with AS for the lung disease that some develop.

4. Brandt Groh, Pediatric Rheumatology Division Chief
Penn State Children's Hospital
Nothing to disclose
Comment:
Regarding children presenting with enthesitis in advance of arthritis, I think it would be useful to know if there is enough literature/experience to support US examination as a diagnostic modality. This question is particularly relevant in teenage girls who walk the fine line between enthesitis versus fibromyalgia discomfort.

5. Robert Colbert, Senior Investigator
NIAMS/NIH
Nothing to disclose
Comment:
The inclusion of children with spondyloarthritis is important, but restricting the process to 'ERA' only is too limiting. The majority of children with spondyloartrhtis will fall into three ILAR categories:

1. ERA,
2. psoriatic arthritis, and
3. undifferentiated arthritis (ILAR categories)

6. Jinoos Yazdany (QOC member)
UCSF
Nothing to disclose
Comment:
The scope of the project is too broad. The precedent is for ACR projects of this nature to be much more narrowly focused to make the final product clear, and also for feasibility reasons. I see at least four or five separate guidelines in what the authors propose: treatment in adults (analogous to RA treatment recommendations); treatment in kids (analogous to JIA recommendations); measurement of disease activity in clinical practice (analogous to RADAM paper); treatment of co-morbidities (analogous to projects such as GIOP recommendations).I am afraid the authors have proposed something that is far too ambitious and will have difficulty completing the scope of work with the resources available. My recommendation is to eliminate all of the topics except treatment recommendations in adult patients.

7. Robert Inman
UHN
Nothing to disclose
Comment:
I would suggest including health-related QOL as a primary treatment target, and I would use the term spinal osteotomy (rather than thoracic kyphoplasty) in the outline.

8. Liana Fraenkel, Associate Professor of Medicine (QOC member)
Yale University
Nothing to disclose
Comment:
The authors have developed an extremely comprehensive plan to provide the membership with information for the management of axial spondyloarthritis. The scope of domains proposed, however, may be overly ambitious. Concerns are the:

1. Feasibility of examining 90 PICO questions.
2. Difficulty of leveraging relevant expertise for the breadth of domains described.
3. Inclusion of some items which may be less relevant to the practicing rheumatologist (example immediate post-op care).
4. Likelihood of 90 PICO questions being translated into a practical/manageable set of recommendations.

9. Carol Oatis, Professor (QOC member)
Arcadia University
Nothing to disclose
Comment:
The proposed project is important and I am particularly enthusiastic about the focus on rehabilitation issues in the Axial SpA project. The authors have identified very important issues which would benefit from a synthesis of the evidence. That said, I have two concerns regarding the plan.

I am very concerned by the number of overall topics proposed for the projects as well as the number of specific PICO questions. The topical areas and specific questions are all important. But I believe it is impossible to accomplish all of this in a timely manner. Timeliness is essential in guidelines. I believe it would be much better to focus on no more than two areas, perhaps pharmacology and rehabilitation and let the other areas wait for another project.

My second area of concern is that despite a large focus on rehabilitation with its large number of PICO questions, there is only one rehabilitation expert (a PT) on the panel. While that individual is certainly well qualified to participate, I believe if you are focusing on rehabilitation you need at least three rehab experts with a minimum of two PT's.

10. Frank Vasey, Rheumatologist
Essential Health
Nothing to disclose
Comment:
After a career studying these conditions, I think more attention should be paid to understanding the intracellular mishandling of bacteria. My own research argues psoriatic arthritis is reactive arthritis to streptococci. This work by RT-PCR was recently confirmed and extended to staphylococci in psoriasis by Barbara Baker a London dermatologist. The 20 fold increase in the prevalence of psoriasis in inflammatory bowel disease argues gram positive bacteria possibly enterococci are critical to the clinical expression of IBD arthritis. This is supported by Balfour Sartor's IL-10 deficient rat studies. When rats were raised germ free, no colitis, with enterococci and adhesive invasive E Coli, colitis occurs. These observations raise the question of the role of antibiotics in the treatment of spondyloarthritis, as shown by John Carter, in curing some patients with reactive arthritis to chlamydia with prolonged Azithromax. A paper from India claimed benefit for psoriatic arthritis patients in an open label study with q 3 weekly

bicillin IM. Group A streptococci remain 100% sensitive to penicillin. In view of the cost differential between TNF blockers and penicillin, this deserves study especially in patients with psoriatic arthritis and guttate psoriasis.

11. Mark Figgie, Professor (*Axial SpA voting panel member*)
Hospital for Special Surgery
Disclosure: ethicon- research grantmedtronic- honorariummekanika- stock
Comment:
Regarding surgical treatment:

1. Should we also consider other joints (i.e. knees) or just restrict this to total hips?
2. Is it better to use cemented or cementless devices in AS?
3. If radiation therapy is used to prevent heterotopic ossification, what dosage? Pre- or post-op?
4. If hip replacement and spinal osteotomy are to be performed, which should be done first?

12. John Healey, Chief of Orthopaedic Surgery
Memorial Sloan Kettering Cancer Center
Disclosure: Trustee, Orthopaedic Research and Education Foundation Trustee, Musculoskeletal Transplant Foundation President, Musculoskeletal Tumor Society Board Member, past president Association of Bone and Joint Surgeons Associate Editor Clinical Orthopaedics and Related Research Member American Academy of Orthopaedic Surgeons: 1) Council on Research and Quality; 2) also Women's Health Issues Advisory Board.
Comment:
The review and/or voting committees should also include an orthopedic spine surgeon and a representative of the Bone and Joint Decade. Major research initiatives have been started this year with the Orthopaedic Research and Education Foundation in collaboration with the Neurosurgery research society regarding directed research in spinal disease. This is funded by industry (largely Medtronic at the moment) and will be administered by the Orthopaedic Research and Education Foundation. They will have a role in evaluating and initiating new treatment for spinal disease. Thus, they should be involved at some point early in the process. Certainly anything regarding research should be vetted with them.

13. Douglas Mintz, Radiologist
Hospital for Special Surgery
Nothing to disclose
Comment:
I got sent this link by Mark Figgie, one of the surgeons in my hospital, for open comments .As a radiologist, my interest and expertise is in the imaging of diseases. As an outside, my interest is in helping the organization to present a clear document. In reading the document, I am unclear as a few things. One is the diagnosis of disease. There are scores that are mentioned but there is no description of what the scores represent. I would present those in addenda. Also, I do not understand appendix A. Are these questions that the project wants to answer? Putting on my imaging hat, nowhere that I saw are imaging criteria for disease explained or used. The only reference to imaging is in appendix A, where there is a question concerning radiographically occult disease. I do not know if any of your rating schemes include imaging, but there are ones that do. In summary of my random thoughts, the submitted document is not as clear as I think it could or should be when embarking on such a large and important project.

14. Giorgio Perino
Hospital for Special Surgery
Nothing to disclose
Comment:
I looked at the project plan and it is obviously related to clinical management. In the past, we received a few cases of femoral heads from young patients with enthesitis related severe arthritis, which were not easily classifiable. From a pathologist perspective it would be important that these specimens are collected with a different modality and coordination with a basic research laboratory, such as the cartilage and immunology labs here at HSS, would be necessary to assure a proper examination. Joint fluid analysis, cartilage cell/synovial culture, examination of gene expression and/or microarrays could be performed to shed some light on the pathological process together with histological examination. These specimens are very infrequent and therefore it would be valuable to study them in depth and an international protocol for pathological examination of surgical specimens might be considered by the panel.

15. Thomas Lehman, Chief, Division of Pediatric Rheumatology
Hospital for Special Surgery
Nothing to disclose
Comment:
It is unclear how the literature reviewers will deal with the fact that enthesitis associated arthritis is considered a subcategory of juvenile idiopathic arthritis and as such many of the articles describing these patients include many other children with other forms of arthritis. Much of the literature regarding these patients fails to identify them properly by not distinguishing them from other children with juvenile idiopathic arthritis.

16. Anonymous
Refuse to disclose
Comment:
Since this is an international group, why are non-English papers being excluded? In addition, the countries that have the highest incidence of the disorders should not be excluded.

17. Joerg Ermann, Instructor in Medicine
Brigham and Women's Hospital Boston
Nothing to disclose
Comment:
There appears to be a contradiction between the background section which emphasizes that these "recommendations will be focused on patients with axial SpA (meeting the ASAS axial SpA criteria), including AS (meeting the modified New York criteria)" and the PICO section. Here, nr-axial SpA is treated as a special population and the focus is on AS. The PICO questions may need to be rephrased or at least re-arranged.

The evidence base for many of the questions to be answered is weak. I would therefore add the identification of knowledge gaps and "development of recommendations for future research" as another objective of the project.

Consider adding the pharmacological management of peripheral arthritis/enthesitis in patients with primarily axial SpA under current objective 6 (special situations).

A few items to be considered as additional PICO questions:

- Are there situations when anti-TNF is preferable to NSAIDs as first line medication in axial disease (e.g. in the presence of co-morbidities)?
- In stable axial disease and active arthritis/enthesitis are DMARDs more effective than placebo?
- In axial disease is long-term treatment with NSAIDS safer than long-term treatment with TNFi (or vice versa)?
- In patients with stable axial disease on TNFi is continuous administration of TNFi better in improving outcomes than intermittent administration driven by symptoms?
- Is monitoring using conventional radiographs better than clinical assessment (and not monitoring with conventional radiographs) with regard to outcome?
- Is monitoring using clinical measurements like Schober, occiput to wall distance etc. better than not monitoring these parameters?

18. Alan Friedman, Medical Director, Rheumatology, Global Medical Affairs, U.S., Rheumatology
AbbVie, Inc.
Disclosure: I am employed by AbbVie, Inc. as Medical Director, Rheumatology Global Medical Affairs, US Rheumatology.
Comment:
AbbVie Inc. Global Medical Affairs thanks the ACR, working in partnership with the Spondylitis Association of America and the Spondyloarthritis Research and Treatment Network, as you work together to develop recommendations for the management of axial spondyloarthritis, including ankylosing spondylitis, and children with the enthesitis-related arthritis form of juvenile idiopathic arthritis.

At your request made to members and the public, AbbVie is providing its comments to the Project Plan, which we understand is intended to be focused on patients with axial SpA (meeting the ASAS axial SpA criteria), including AS (meeting the modified New York criteria) and children with the enthesitis-related arthritis form of juvenile idiopathic arthritis.

Representatives from the Medical Affairs, Clinical Development and Health Economics Outcomes Research groups at AbbVie met to discuss the upcoming 2014 ACR/SAA/SPARTAN Recommendations for the Management of Axial Spondyloarthritis, including Ankylosing Spondylitis, and Children with the Enthesitis-Related Arthritis Form of Juvenile Idiopathic Arthritis. We are truly grateful for the considerable effort that will go into this project, and the remarkable expertise of the teams that have been assembled for this task. In the end, these evidence-based guidelines will greatly benefit patients with axial SpA and the health care professionals (HCPs) who care for them.

Axial SpA: General Comments
We suggest that AS and non-radiographic axial SpA (nr-axSpA) be combined for evaluation as they really represent one disease with a continuum of outcomes. The burden of disease has been shown to be nearly identical and treatment efficacy and safety also appear to be very similar (1, 2). This approach also fits with the ASAS classification scheme, which was referenced in the background section of the ACR Axial SpA Project Plan.

One of the biggest hurdles in treating axial SpA is getting the patients to a Rheumatologist who can make the correct diagnosis and work with the patient to find the most appropriate therapy. We ask that

ACR consider drafting guidelines for appropriate referral of individuals with chronic "inflammatory" back pain (versus "mechanical" back pain). These guidelines could be broadly disseminated to those HCPs who care for chronic back pain patients and reduce the time these patients spend seeking appropriate therapy.

When considering more aggressive pharmacologic therapy for "active" axial SpA despite full prescription doses of at least 2 NSAIDs, we suggest that there should be objective evidence of active inflammation, such as "positive" MRI of the SI joints and/or spine or elevated serum CRP. This would insure that more aggressive therapies are offered only to those with the greatest possible benefit-to-risk ratio.

Clarifications of the Project Plan

1. Would it be possible to clarify the term "DMARDs" for SpA, as used in this project? The drugs included are defined clearly in the Project Plan (Appendix A), but for the specific questions, sometimes MTX and SSZ are spelled out, and other times tofacitinib and apremilast are mentioned. Thalidomide and leflunomide are also in this category but not mentioned in specific questions.
2. "Juvenile SpA": Is this all pediatric enthesitis-related illness or something different/more?
3. The term "locally administered parenteral corticosteroids" is a bit confusing. We assume this refers to joint and soft tissue (i.e. entheses) injections. Is this correct?

Some specific comments on the Project Plan

Question 6: "In adults with active AS, are certain TNFi more effective than other TNFi in improving outcomes"? Without head-to-head data from trials, this question, while very important, is difficult to assess accurately. In addition, one needs to consider active AS as a condition that includes axial disease as well as peripheral musculoskeletal and extra-articular features, which might be affected differently by different pharmacologic agents.

Question 9, 10, 11 (and others): "In adults with active AS despite treatment with a first TNFi agent, is switching to a different TNFi more effective than adding a DMARD in improving outcomes"? As MTX and SSZ (and LEF and thalidomide) have not been shown to be effective for axial disease, nor have tofa or apremilast (thus far), is it fair to call them DMARDs for axial SpA (AS or nr-axSpA)? It seems more appropriate to consider these agents for peripheral arthritis when the treatment for axial disease is not fully effective at controlling the peripheral manifestations (i.e. questions 15, 16, 71 and 72 in the Project Plan). We note that for sacroiliitis, the hallmark of spondylitis/axial disease, there are no plans to compare "DMARDS" with any treatment (questions 19 & 20 in the Project Plan), which suggests that the organizers agree with the lack of efficacy of these agents for axial disease.

References

1. Van der Heijde D, Kivitz A, Schiff MH, et al. Efficacy and safety of adalimumab in patients with ankylosing spondylitis. Results of a multicenter, randomized, double-blind, placebo controlled trial (ATLAS). Arthritis Rheum. 2006; 54(7):2136-46.
2. Sieper J, Van der Heijde D, Dougados M, Mease PJ, Maksymowych, Brown MA, Arora V and Pangan AL. Efficacy and safety of adalimumab in patients with non-radiographic axial spondyloarthritis: results of a randomized placebo-controlled trial (ABILITY-1). Ann Rhem Dis 2013; 72:815-822

Thank you in advance for taking on this important topic and for considering our comments.

19. Alfonse Masi, Professor
University of Illinois College of Medicine at Peoria
Nothing to disclose
Comment:
"Value and Limitations of the Proposed Questions to Achieve Treatment Goals from the 2014 ACR/SAA/SPARTAN Project" The goals of treatment of AS and axial SpA are to reduce symptoms, improve and maintain spinal flexibility and normal posture, reduce functional limitations, and decrease complications of the disease.

The objectives of the 2014 ACR/SAA/SPARTAN project are to develop recommendations for disease activity monitoring in clinical practice and for the pharmacological and non-pharmacological treatment of patients with axial spondyloarthritis (SpA), including ankylosing spondylitis (AS) and juvenile SpA and their common selected comorbidities.

This project may be analogous to the preceding ASAS/EULAR Management Recommendations in Ankylosing Spondylitis, published in 2006 (Ann Rheum Dis 65:423-432 and 442-452). That project performed a systematic search of the literature published between, 1966-2004. Evidence was obtained for a large number of management propositions of AS to determine efficacy, adverse effects, and cost effectiveness.

The proposed 2014 ACR/SAA/SPARTAN literature search strategies are based on PICO questions (Population/patients, Intervention, Comparator, and Outcomes; see Appendix A), as is specified, and the search results will be divided among reviewers. The systematic review team will analyze and synthesize data to achieve a final determination of the relative importance of best practice to outcomes, as is described. However, it is not clear if statements on cost effectiveness or accessibility to care will be covered in the survey and be included as desired outcomes of the study?

Regarding a priority of outcomes of interest, it is not evident how recommendations will be graded according to the specific characteristics of patients? Considerable patient variability is anticipated, depending upon sex, onset age, degrees of limitations of mobility or function, and gradients of disease severity in the setting of initial therapy vs. preceding treatment modalities. In other words, how can the derived recommendations be specified or “tailored” most effectively to the particular patients who will need either initial or additive management? Anticipation of such applications before initiating the results of the extensive survey and synthesis may be valuable in its ultimate success.

In the ASAS/EULAR survey, a great number of initial propositions were raised for a general literature search. Those results were then used to reduce the final number to 10 propositions, by 3 rounds of Delphi technique. Thereafter, “an intervention-specific literature search” was undertaken to identify evidence for each of the selected final 10 propositions and their respective interventions (Ann Rheum Dis 2006; 65:423-432 and 442-452).Please refer to proposition #1, in Table 2 of the specific recommendations paper (Ann Rheum Dis 2006; 65: 442-452). It specified that treatment of AS patients should be tailored. However, the report found little evidence to draw conclusions in this regard, but indicated examples of such relations. Hopefully, the 2014 ACR/SAA/SPARTAN Recommendations can achieve further success in deriving recommendations along the lines of tailored therapy for the variety of patients who will need initial or additive management modalities. At least such propositions should be clearly endorsed.

Regarding Pharmacological Therapy, a total of 20 questions are listed. An outcome of the survey may be to identify which of these many questions are supported in the literature as common challenges in management of active or stable AS patients? Currently, systemic and local corticosteroids are included in the survey questions, but the issues of dosages and durations would need to be rationalized in recommendations. This comment would apply to all subsequent questions which refer to local or systemic corticosteroids. One can expect that different personal and disease categories of patients, besides those specified (the activity and the age groups), will have varied outcome responses. Will the results of the survey be able to derive a decision tree of specific drug therapy outcomes for the varied AS patients from the particular types of therapy questions and their literature reviews? Will cost effectiveness be addressed?

Under Rehabilitation/Physical Therapy, the 5 major questions are rather specifically framed for derivation of literature review of outcomes. Under Surgical Treatment, the 5 questions are rather specifically framed for derivation of literature review of outcomes. Under Special Populations, in the section on Children and Adolescents, does question #53 regarding isolated active sacroiliitis imply that such patients would be treated with local (intra-articular) sacroiliac joint (SIJ) corticosteroids? This comment also applies to adults with non-radiographic axial SpA (#73 and #74).In the Section on Non-radiographic Axial SpA, question #65 seems preferable to #64, since the former is more balanced, and should include information requested in #64. The same comment could be made for patients with radiographic AS.The heading, "Preventive Care", deserves consideration of editing, since the questions address "improving outcomes". Also, do these questions apply to juvenile onset disease? Under Disease Activity Monitoring, do these questions also apply to juvenile onset disease?

Overall, the literature search plan follows preceding, effective methodology and promises to derive considerable and valuable information on the multiple preliminary questions. Hopefully, those results can be effectively synthesized into a set of final recommendations, which will be clinically applicable to the considerable variation in individual patient management challenges in AS, and will include cost-effectiveness considerations.

20. Walter P. Maksymowych, MD (*Axial SpA voting panel member*)
(Comments received by e-mail)
Comment:
I have reviewed the word format of the document. The time available for providing comment has been far too short in my view. I have substantial concerns with the approach to the questions taken in several of the sections, as noted:

- The italicized portion of the following statement from the background section is incorrect: "These criteria follow the rubric of the Amor criteria and European Spondyloarthropathy Study Group (ESSG) criteria previously proposed for the SpA family of diseases, *with the important distinction that classification of axial SpA requires the presence of inflammatory back pain*." These criteria require only back pain in someone less than 45 years of age.
- "Smoking cessation" should be added to Objective 4.
- Re: the lit review phase of the project, "some of the best systematic reviews have been published in textbooks that many not become evident using this search strategy."
- In the description of the analysis and synthesis phase, the following phrase is most crucial: "At the face-to-face meeting, chaired by the PI (MW), the panel will discuss the evidence, supported by the systematic review leader (LC), the GRADE expert (EA), and selected members of the

systematic review team, to arrive at consensus on the final recommendations." It will require those individuals with the most content expertise. However, this statement lacks clarity as to how "selected members of the systematic review team" will actually be selected. How will voting be conducted, what will be the cut-offs for selection of recommendations, how many rounds of voting, how will disagreements be resolved. This should be pre-specified as much as possible rather than relying on the attainment of consensus at a face-to-face meeting.

- Dr. Maksymowych also added many edits/comments in the PICO section of the document (see attached).

21. **Robert Landewé, President**

ASAS-organisation

Nothing to disclose

Comment:

The authors of this response have read with great interest the project plans of your conjoint committee to design recommendations for the management of patients with axial SpA (http://www.rheumatology.org/Practice/Clinical/Guidelines/Recommendations_for_the_Management_of_Axial_Spondyloarthritis/). You may consider this response reflecting the opinion of the Assessment in SpondyloArthritis international Society (ASAS), which is an international organisation founded in 1995, consisting of rheumatologists, scientists, epidemiologists and patients, all with an interest in clinical, translational and basic research in SpA in its broadest sense. ASAS also has many US-members.

First of all, ASAS members all over the world appreciate that there is so much interest among ACR members in axial SpA, that ACR has taken the decision to develop management recommendations for patients with axial SpA, and that they do this in a concerted action with the patient organisation (SAA) and the US experts in axial SpA (SPARTAN).

Second, we are very pleased to read that your consortium has adopted the ASAS-criteria for axial SpA, rather than the modified New York criteria, as a starting point for further research and discussions. It is of tremendous help for the further development of the diagnosis, classification, treatment and advocacy of patients with axial SpA that the non-radiographic and radiographic 'components' of the disease are recognised by ACR as a continuum, and that the ASAS-criteria serve that aim as a basis. We have more problems with the following: ASAS has developed its management recommendations in a collaborative effort with EULAR already in 2006. These recommendations were based on a thorough and systematic search of the literature (Zochling et al) in combination with consensus building among experts (including patients), according to EULAR standard operating procedures, culminating in a broadly accepted set of 10 practical recommendations that have been implemented world-wide.

Since then, ASAS has also developed widely used criteria about the use of biologicals in AS (later axial SpA) and has subsequently updated both sets by incorporating and weighing new evidence in a systematic manner. One of the most recent accomplishments in the field in collaboration with ASAS, though still unpublished in full-text format, are the criteria for 'treat-to-target' in axial and peripheral SpA. While we fully accept the freedom to dispute existing management criteria as inapt for the US context, or as having insufficient scientific robustness that does not meet the US standard of doing proper research, we regret the fact that your consortium does not even refer to the existence of these criteria in the body of the text, or in the references, thus leaving the uninvolved US rheumatologist potentially unaware of what is already there in the field. This, in our opinion, is a bit tendentious, and should better be corrected.

There are also other, though more trivial, reasons to choose a collaborative rather than a competitive approach: Our research collaborators have done meticulous literature research, including regular updates, to bring the existing evidence above sea level, using almost identical research questions

(except juvenile SpA) as you do. While we admit that the weighing of the existing literature by experts may result in slightly different conclusions regarding the content of treatment recommendations applicable in the US context, we do not believe that you may reveal new evidence that is entirely 'untouched' by us.
As such, the effort you propose seems to be a bit redundant in this regard, and manpower could better be served to address truly new topics. Besides, an exercise that 're-invents the wheel' does neither add to the credibility of those working in the field of SpA nor does it serve the interest of those that receive and provide care for patients with axial SpA. The analogy is the unwarranted situation of two sets of guidelines for the management of rheumatoid arthritis: One in Europe and one in the US, both with different focus and unexplainable discrepancies, leaving the rest of the world behind in confusion. We should know better. ASAS therefore strongly recommends to take a collaborative route to arrive at recommendations that at least take the ASAS/EULAR recommendations as a starting point for further development, and at best use the ASAS/EULAR recommendations as the basic template, whilst implementing country-specific amendments where necessary.
Being aware of the fact that you have incorporated into your committee a number of ASAS-members that can perfectly echo the 'ASAS-view', we are confident that a collaborative approach that we propose here can be fully implemented without too many tribulations, and we are very interested to hear your opinion about this proposal. For reasons of transparency we will put this letter on the ACR website, and send it in cc to the president of ACR, to the president of EULAR and to all members of ASAS.

22. **John Hicks, Rheumatologist**
Greenwood Regional Rheumatology Center
Nothing to disclose
Comments:
I reviewed the many questions in need of answers and would hope that this becomes a working plan with continuous updates rather than a one-time set of answers that may negatively impact refinements in treatment by practicing rheumatologists which then lead to new approaches to treatment which then need to be tested. So please make this a working ongoing guideline for updates rather than a one-time set of answers that will be out of date before it's published.
The questions are terrific questions. Keep up the good work.

23. **Sjef Van Der Linden, Professor of Rheumatology**
University of Maastricht, The Netherlands
Nothing to disclose
Comments:
I very much welcome a thorough scientific review and discussion of the literature by ACR to come up with Management Recommendations for Axial Spondyloarthritis, including Ankylosing Spondylitis, and Children with the Enthesitis-related Form of Juvenile idiopathic Arthritis. I have a number of suggestions.

- Gender issue: Is the outcome of axial-SpA and AS different among males and females?
- Medication Categories: include etoricoxib among the NSAIDs.
- General Issues: Structural and functional Outcome of axial-SpA / AS related to disease duration. This would include degree of spinal fusion (number of syndesmophytes) and functional status related to duration of disease in years.
- General Issues: Can non-radiographic axial SpA be regarded as one disease or is it a group of conditions manifested by similar signs and symptoms that might have different outcomes and different responses to treatment (NSAIDs, DMARDs, Biologics)? To put it differently: Is axial-SpA just one disease or a collection of conditions that can be classified together by the ASAS

classification criteria for axial SpA and that include (i) AS by modified New York criteria); (ii) true non-radiographic axial SpA/AS; and (iii) false non-radiographic axial SpA.

This last group of 'look-alikes' might be characterized by no/low association with HLA-B27 and atypical features on MR-imaging.

- General Issues: Does treatment with biologic prevent structural damage in axial-SpA and AS? Does treatment with bisphosphonates (with or without biologic) prevent (or promote) structural damage in axial-SpA and AS?
- Rehabilitation/Physiotherapy: In adult patients with stabile and inactive AS while on biologic, is continuation of any kind of exercises or PT more effective than no exercises or PT (in particular regarding posture and osteoporosis)?
- Non-radiographic axial SpA: See also Q#61 & Q#62: In adults with active non-radiographic axial SpA despite treatment with NSAIDs, are TNFi more effective than treatment with DMARDs in improving outcomes?

24. **Muhammad Asim Khan, Rheumatologist** (***added 07/08/13)***

MetroHealth

Disclosure: Nothing to disclose.

Comment:

This is my public comment on the project proposed to the ACR to develop management recommendations for patients with axial SpA that would be funded by ACR and SAA, and to be conducted in collaboration with SPARTAN.

I am a rheumatologist and an AS/Axial SpA patient, and I have devoted my academic career primarily researching and writing about this disease. I am a member of the ACR for 40 years, a founding member of SPARTAN and a member of SAA. I had also served on the Medical and Scientific Advisory Board of SAA for over 25 years, and I am a founding member of ASAS.

Therefore, I feel that I am not only scientifically qualified but also obligated to honestly comment on this project that has been proposed to ACR.

I must also mention up front that I was unaware of the above mentioned project, and I only came to know about it on June 6th when Dr. Robert Landewé, President of ASAS, sent a letter to ACR commenting on the proposed project from ASAS perspective.

I am very saddened and surprised to find that the authors of this proposed project failed to cite or even mention the existing ASAS/EULAR recommendations for management of patients with axial SpA (Zochling et al. 2006). It is especially surprising when one finds that one of the members of the "Core Leadership Team" of the proposed project is also a member of the executive committee of ASAS.

ACR and all of its members have the right and the freedom to develop Axial SpA management recommendations that have more relevance and applicability in the context of USA. But the authors of the proposed project should have cited and discussed the existing ASAS/EULAR recommendations that are based on a thorough and systematic search of the literature, and are broadly accepted and implemented world-wide. By not citing these recommendations in their proposal, one wonders if the authors of this proposed project are trying to convey that they are not "reinventing a wheel" because an uninformed reader may not know that there are already internationally accepted recommendations on how to manage axial SpA.

I have the following humble suggestions to the ACR:

1. The authors of the proposed project should cite and discuss the already existing ASAS/EULAR recommendations for managing Axial SpA. It would therefore require them to explain why they want to avoid those internationally accepted recommendations as a starting point for their proposal to ACR to develop new recommendations.

2. ACR can develop its own recommendations, but it may be better if it follows a collaborative route with ASAS and EULAR by using the ASAS/EULAR recommendations as a starting point to come up with the recommendations that would meet the approval of ACR.

Best regards and I would be very pleased to get a response from ACR, and would be pleased to provide any assistance if needed.