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

Project Plan

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ORGANIZATIONAL LEADERSHIP AND SUPPORT

This guideline is being developed as a collaborative project of the American College of Rheumatology (ACR), the Spondylitis Association of America (SAA) and the Spondyloarthritis Research and Treatment Network (SPARTAN). The ACR and SAA are funding the project.

BACKGROUND

Ankylosing spondylitis (AS) is a form of chronic inflammatory arthritis characterized by sacroiliitis, spinal and peripheral enthesitis, and a propensity for sacroiliac joint and spinal fusion[1]. The prevalence of AS in the United States is estimated to be 0.2%-0.5%[2]. Symptoms commonly include back and hip pain, peripheral joint pain, and fatigue, and are variable in severity. Spinal fusion develops gradually and may lead to reduced spine and neck flexibility. AS typically begins in young adulthood, although sacroiliitis and enthesitis may also occur in older children and adolescents. In a minority of patients, AS may be complicated by iritis or inflammatory bowel disease.

Although the cause of AS is unknown, evidence suggests that it is a genetically-determined immune-mediated disease[3]. HLA-B27 confers the largest proportion of the genetic risk of AS. AS shares several

genetic risk factors and has clinical features that overlap to some degree with several other conditions, including psoriatic arthritis, reactive arthritis, and enteropathic arthritis, which together form a family of conditions termed seronegative spondyloarthritis (SpA) [4]. In addition, some patients have features of several types of SpA, and thus are not easily classifiable. The hallmarks of AS are symmetric sacroiliitis, more extensive spinal fusion, and a stronger association with HLA-B27 than in other types of SpA [5]. The sacroiliac and spinal features are emphasized in the modified New York criteria for the classification of AS [6]. However, a limitation of these criteria is that these features may take years to develop, thereby excluding patients early in the course of SpA who may not yet have developed radiographically evident changes. Recently, classification criteria that would apply to both early and later stage patients have been proposed by the Assessment of Spondyloarthritis International Society, included under the umbrella term axial SpA [7]. Companion criteria for peripheral SpA have also recently been developed. 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 [8, 9]. Patients meeting the Amor criteria or ESSG criteria may have only peripheral joint manifestations without axial skeletal involvement.

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 children with the enthesitis-related arthritis form of juvenile idiopathic arthritis [10]. Studies of patients meeting the Amor criteria or ESSG criteria will be included to the extent that they inform the treatment of axial SpA.

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 mainstays of treatment have been nonsteroidal anti-inflammatory medications and exercise. Over the past decade, tumor necrosis factor-alpha inhibitors have greatly altered the approach to treatment of AS and axial SpA. With the availability of more treatment options, recommendations for the treatment of patients with AS and axial SpA are needed to help clinicians optimize the care of these patients.

OBJECTIVES

The objective of this project is to develop recommendations 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. Specifically, we aim to:

1. Develop recommendations for the use of nonsteroidal anti-inflammatory medications, conventional disease-modifying medications, and biologics in these conditions

2. Develop recommendations for the use of physical therapy and recreational exercise as treatments for these conditions

3. Develop recommendations for the use of total hip arthroplasy and thoracic kyphoplasty

4. Develop recommendations for preventive care, including osteoporosis screening and treatment, fall prevention, and cardiovascular screening

5. Develop recommendations for disease activity monitoring in clinical practice

6. Develop recommendations for pharmacological and non-pharmacological treatment of children with spondyloarthritis, of adults with non-radiographic axial spondyloarthritis, and of patients whose axial SpA is complicated by iritis or inflammatory bowel disease

METHODS

Identification of studies

Literature search strategies, based on PICO questions (Population/patients, Intervention, Comparator, and Outcomes; *see Appendix A*) will be developed by the PI (MW), the systematic review leader (LC), and a research librarian (JJ), with input from the Core Leadership Team. The strategies for each PICO question will be peer reviewed by another medical librarian using Peer Review of Electronic Search Strategies (PRESS) [11]. Searches will be performed in OVID Medline (1946 +), Embase (1974 +), the Cochrane Library, and PubMed (mid-1960's +).

The search strategies will be developed using the controlled vocabulary or thesauri language for each database: Medical Subject Headings (MeSH) for OVID Medline, PubMed and Cochrane Library, and Emtree terms for Embase. Text words will also be used in OVID Medline, PubMed, and Embase, and keyword/title/abstract words in the Cochrane Library. For example, in Medline, to retrieve studies on the adult patient populations of interest, the search will include MeSH terms *Spondylarthritis*; *Spondylarthropathies*; *Spondylitis*; *Spondylitis*, *Ankylosing*; and text words *spondylarthritis*, *spondyloarthritis*, *spondylarthropath$* (where $ denotes truncation), *spondyloarthropath$*, and *spondylitis*. For children up to age eighteen, the terms used will include MeSH terms *Arthritis, Juvenile Rheumatoid/* and textwords *juvenile idiopathic arthritis*, *JIA*, *juvenile arthriti$, juvenile-onset arthriti$, pediatric or paediatric arthriti$,* and *child$ arthriti$* combined with textwords *enthesitis* and *entheses*.Similarly, terms for specified interventions (e.g., drugs, other therapies), and terms to describe outcomes will be used.

Search Limits

Only English language articles will be retrieved. See Appendix B for an example of a search for PICO question 1, developed in OVID Medline.

Grey Literature

Grey literature will be searched, specifically *meta*Register of Controlled Trials, to identify ongoing and completed trials, and the literature will then be searched to determine if there are published results. The websites of appropriate agencies, such as the Agency for Healthcare Research and Quality (AHRQ), will be searched for peer-reviewed reports not indexed by electronic databases. Conference abstracts will be searched via Embase database, reviewed, and tracked to determine if the studies have subsequently been published.

Literature searches will be updated after the Voting Panel meeting but prior to publication of the guidelines, to ensure completeness.

Inclusion/Exclusion Criteria

See PICO questions, which outline the defined patient population, interventions, comparators and outcomes. Only English language studies will be included.

Management of Studies and Data

References and abstracts will be imported into bibliographic management software (Reference Manager) [12], duplicates removed, and exported to Distiller SR, a web-based systematic review manager [13]. Screening and data abstraction forms will be created in Distiller SR. Search results will be divided among reviewers, and two reviewers will screen titles/abstracts, and manuscripts, with disagreements being discussed and adjudicated by the systematic review leader (LC), if necessary.

Phases

1. A search for systematic reviews of studies about axial spondyloarthritis, including ankylosing spondylitis and the enthesitis-related arthritis form of juvenile idiopathic arthritis, will be performed to determine if there are existing reviews covering outcomes of interest. Subsequently, identified systematic reviews will be quality-assessed using the AMSTAR tool [14]. Chosen systematic reviews will be updated, as necessary, for use in this project.
2. For outcomes of interest not covered by existing systematic reviews, a search for randomized controlled trials for each PICO question will be conducted. Chosen studies will be quality-assessed using the Cochrane Risk of Bias Tool [15].
3. As necessary, observational studies for the outcomes of interest will be identified and appraised by appropriate tools such as the Cochrane Effective Practice and Organisation of Care Risk of Bias Tool [16] or the Newcastle-Ottawa Scale [17].

GRADE methodology

A final determination will be made of the relative importance of outcomes. The systematic review team will analyze and synthesize data, according to GRADE methodology, as described in GRADE guidelines – best practices using the GRADE framework, a 15-part *Journal of Clinical Epidemiology* series [18].

Analysis and Synthesis

Summary of Findings tables and GRADE evidence profiles will be prepared for each PICO question using Review Manager (RevMan) [19] and GRADEprofiler (GRADEpro) software [20]. The Summary of Findings table contains the benefits and harms for each outcome across studies, the assumed and corresponding risk for comparators and interventions (95% CI), the absolute risk and relative effect (95% CI), the number of participants/ number of studies, and number needed to treat, and the quality of evidence for each critical and important outcome (i.e., high, moderate, low or very low).

The Evidence Profile documents the quality of the evidence across studies for each critical and important outcome, and summarizes the quality factors (i.e., limitations of study design, inconsistency, indirectness, imprecision, and other considerations).

The systematic review team (CEP) will recommend the direction and strength of the recommendation (i.e., strong for, conditional for, conditional against, or strong against), taking into account the balance of benefits and harms, and patient preferences.

Development of Recommendations for Guidelines

Using the GRADE Evidence Profiles and Summaries of Findings tables, the voting panel, consisting of adult and pediatric rheumatologists, an orthopedic surgeon, and a patient representative, will consider the proposed recommendations in two stages. The first assessment will be done individually and the results will be anonymous. 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.

PLANNED APPENDICES (AT MINIMUM)

A. Final literature search strategies

B. GRADE Evidence Profiles and Summary of Findings Tables for each PICO question

AUTHORSHIP

Authorship of the guidelines will include Dr. Michael Ward, PI, as the lead author; Dr. Liron Caplan, literature review leader; Drs. Atul Deodhar and John Reveille, core leadership group members; and Dr. Elie Akl, core leadership group member and GRADE consultant. Members of the systematic review team will also be authors. The PI will determine final authorship, dependent on the efforts made by individuals throughout the guideline development process, using ICMJE Uniform Requirements for Manuscripts as guidance.

Voting panel members will receive special acknowledgement for their participation in the development of the guidelines and will also be listed as collaborators in the PubMed reference for the guidelines.

DISCLOSURES / CONFLICTS OF INTEREST

The ACR's disclosure and COI policies for guideline development will be followed for this project. These can be found in the ACR Guideline Manual on the ACR web site under Policies & Procedures. *See Appendix C for participant disclosures.*

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Project Plan

APPENDIX A

PICO QUESTIONS

OUTCOMES FRAMEWORK

The guidelines will consider the following outcomes:

- Mortality
- Health status
    - Symptoms (pain, stiffness, fatigue, sleep disturbance, swelling)
        - Measures: e.g., BASDAI, pain scales, SF-36 subscales, fatigue questionnaires
        - Surrogates: physical exam, ASDAS, acute phase reactants, inflammation on imaging
    - Mental health (depression, anxiety)
        - Measures: e.g., SF-36 subscales, CES-Depression scale
    - Quality of life (social interaction, sexual health, body image)
        - Measures: e.g., SF-36 subscales, ASQOL
- Functional status
    - Physical function
        - Measures: e.g., BASFI, HAQ-S, Dougados Functional Index, SF-36 subscales
        - Surrogates: range of motion, BASMI, structural damage on imaging
    - Work ability or school performance
- Serious adverse events
- AS-related morbidities
    - Morbidities include aortic valve disease, pulmonary fibrosis and cavitation, amyloidosis, anemia, IgA nephropathy, NSAID nephropathy, iritis, inflammatory bowel disease, osteoporosis, vertebral fractures, ischemic heart disease and cauda equina syndrome.

Relevant data will primarily be based on data on the measures. When insufficient data on an outcome are available for measures, data on surrogates will be used to inform guideline development.

These outcomes are ordered in descending priority. Not all outcomes will be considered for each intervention. The matrix below indicates the relevant outcomes to be studied for each type of intervention.

APPENDIX A

Outcomes matrix

	Pharmacological therapy	Rehabilition/physical therapy	Surgical therapy	Preventive care
Mortality	X		X	X
Health Status	X	X	X	X
Functional status	X	X	X	X
Significant Adverse Events	X		X	X
AS related morbidities	X			X

Definition of disease activity: Activity refers to the level of symptoms experienced by the patient, as noted in the framework. We define:

- *Active disease:* when disease is causing symptoms at an unacceptably bothersome level as reported by the patient, and judged by the examining clinician to be due to AS or axial SpA. The measures and surrogates noted above may inform the assessment of activity but should not substitute for clinician judgment.
- *Stable disease:* when disease is asymptomatic or causing symptoms that are bothersome at an acceptable level as reported by the patient.

APPENDIX A

Medication Categories

Pharmacological therapy can involve several classes of medications. The table below lists the classes of medication considered, and the constituent medications.

Nonsteroidal anti-inflammatory drugs (NSAIDs)	Aspirin, Celecoxib, Diclofenac, Diflunisal, Epirizole, Fenoprofen, Flurbiprofen, Ibuprofen, Indomethacin, Ketoprofen, Ketorolac, Ketorolac tromethamine, Meclofenamic acid, Meloxicam, Nabumetone, Naproxen, Oxaprozin, Piroxicam, Salicylate, Sodium salicylate, Sulindac,Tolmetin
Tumor necrosis factor-alpha inhibitors (TNFi)	Adalimumab, Certolizumab, Etanercept, Golimumab, Infliximab
Non-TNFi biologicals	Abatacept, Anakinra, Rituximab, Tocilizumab, Secukinumab
Non-biological disease modifying anti-rheumatic drugs (DMARDs)	Apremilast, Leflunomide, Methotrexate, Sulfasalazine, Thalidomide, Tofacitinib

Medication classes will be considered unless otherwise specified. In cases where individual medications are of interest, these medications will be specifically noted.

PHARMACOLOGICAL THERAPY
1. In adults with active AS, are NSAIDs more effective than no treatment with NSAIDs in improving outcomes?
2. In adults with active or stable AS, is continuous treatment with NSAIDs more effective than on-demand treatment with NSAIDs in improving outcomes?
3. In adults with active AS, are certain NSAIDs more effective than other NSAIDS in improving outcomes?
4. In adults with active AS despite treatment with NSAIDs, are DMARDs more effective than no treatment with DMARDs in improving outcomes?
5. In adults with active AS despite treatment with NSAIDs, are TNFi more effective than no treatment with TNFi in improving outcomes?
6. In adults with active AS, are certain TNFi more effective than other TNFi in improving outcomes?
7. In adults with stable AS on treatment with TNFi and NSAIDs, is continuing both medications more effective in improving outcomes than continuing treatment with TNFi alone?

APPENDIX A

8. In adults with stable AS on treatment with TNFi and DMARD, is continuing both medications more effective in improving outcomes than continuing either TNFi or DMARD alone?
9. 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?
10. In adults with active AS despite treatment with a TNFi agent, is switching to a different TNFi more effective than switching to non-TNFi biologics or than changing to a new DMARD (tofacitinib or apremilast) in improving outcomes?
11. In adults with active AS despite treatment with NSAIDs and who have contraindications to TNFi, is treatment with a non-TNFi biologic more effective than treatment with DMARDs in improving outcomes?
12. In adults with active AS, are systemic corticosteroids more effective than no treatment with systemic corticosteroids in improving outcomes?
13. In adults with AS with stable axial disease and active peripheral arthritis despite treatment with NSAIDs, are locally administered parenteral corticosteroids more effective than no treatment with local corticosteroids in improving outcomes?
14. In adults with AS with stable axial disease and active enthesitis despite treatment with NSAIDs, are locally administered parenteral corticosteroids more effective than no treatment with local corticosteroids in improving outcomes?
15. In adults with AS with stable axial disease and active peripheral arthritis despite treatment with NSAIDs, is treatment with local corticosteroids more effective than sulfasalazine or methotrexate in improving outcomes?
16. In adults with AS with stable axial disease and active enthesitis despite treatment with NSAIDs, is treatment with local corticosteroids more effective than sulfasalazine or methotrexate in improving outcomes?
17. In adults with AS with stable axial disease and active peripheral arthritis despite treatment with NSAIDs, is treatment with local corticosteroids more effective than TNFi in improving outcomes?
18. In adults with AS with stable axial disease and active enthesitis despite treatment with NSAIDs, is treatment with local corticosteroids more effective than TNFi in improving outcomes?
19. In adults with AS and isolated active sacroiliitis despite treatment with NSAIDs, is treatment with local corticosteroids more effective than no treatment with local corticosteroids in improving outcomes?
20. In adults with AS and isolated active sacroiliitis despite treatment with NSAIDs, is treatment with local corticosteroids more effective than treatment with TNFi in improving outcomes?

APPENDIX A

REHABILITATION/PHYSICAL THERAPY
21. In adults with active AS, is any form of PT more effective than no PT in improving health status and functional status?
21a. In adults with active AS, Are aquatic PT interventions more effective than land-based PT interventions in improving health status and functional status?
21b. In adults with active AS, Are active PT interventions (supervised exercise) more effective than passive PT interventions (massage, ultrasound, heat) in improving health status and functional status?
21c. In adults with active AS, Is group PT more effective than no group PT in improving health status and functional status?
22. In adults with stable AS, is any form of PT more effective than no PT in improving health status and functional status?
23. In adults with active or stable AS, are unsupervised back exercises more effective than no exercise in improving health status and functional status?
24. In adults with active or stable AS, is recreational physical activity more effective than no recreational physical activity in improving health status and functional status?
25. In adults with active or stable AS, is spinal manipulation (chiropractic or osteopathic) more effective than no spinal manipulation in improving health status and functional status?

SURGICAL TREATMENT
26. In adults with AS and hip arthritis, is total hip arthroplasty more effective than no surgery in improving outcomes?
27. In adults with AS undergoing total hip arthroplasty, is local radiation therapy in the perioperative period more effective than no radiation therapy in improving outcomes?
28. In adults with AS undergoing total hip arthroplasty, is treatment with NSAIDs in the perioperative period more effective than no treatment in improving outcomes?
29. In adults with AS undergoing total hip arthroplasty, is treatment with NSAIDS in the perioperative period more effective than local radiation therapy in improving outcomes?
30. In adults with AS and severe kyphosis**,** is spinal osteotomy more effective than no surgery in improving outcomes?

APPENDIX A

SPECIAL POPULATIONS
Iritis
31. In adults with AS, is education regarding the warning signs of iritis more effective than no education in decreasing delay in treatment, duration of symptoms, or complications of iritis?
32. In adults with AS, is prescription of topical corticosteroids for prompt at-home use in the event of eye symptoms effective in decreasing the severity or duration of iritis episodes compared to no at-home use?
33. In adults with AS, is treatment of acute episodes of iritis by an ophthalmologist more effective in decreasing the severity, duration, or complications of episodes compared to no ophthalmologist care?
34. In adults with AS who have no musculoskeletal indications for TNFi and no active iritis, is treatment with TNFi more effective in decreasing the rate of recurrence of episodes of iritis than no treatment with TNFi?
35. In adults with AS, are TNFi monoclonal antibodies more effective in decreasing the occurrence or rate of recurrence of episodes of iritis than etanercept?
36. In adults with AS who develop iritis while treated with a TNFi, is switching the TNFi more effective in decreasing recurrences of iritis than continuing the same TNFi?
Inflammatory Bowel Disease
37. In adults with AS and inflammatory bowel disease, are certain NSAIDs more likely to worsen IBD symptoms than other NSAIDs?
38. In adults with AS and inflammatory bowel disease, are certain TNFi more effective in improving outcomes than other TNFi?
Children and Adolescents
39. In children and adolescents with active SpA, is treatment with NSAIDs more effective than no NSAID treatment in improving outcomes?
40. In children and adolescents with active SpA, are certain NSAIDs more effective than other NSAIDs in improving outcomes?
41. In children and adolescents with active SpA despite treatment with NSAIDs, is sulfsalazine more effective than no treatment in improving outcomes?
42. In children and adolescents with active SpA despite treatment with NSAIDs, is methotrexate more effective than no treatment in improving outcomes?
43. In children and adolescents with active SpA despite treatment with NSAIDs, is methotrexate more effective, less effective, or as effective as sulfasalazine in improving outcomes?
44. In children and adolescents with active SpA despite treatment with NSAIDs, is treatment with TNFi more effective

than no treatment with TNFi in improving outcomes?
45. In children and adolescents with active SpA, are certain TNFi more effective than other TNFi in improving outcomes?
46. In children and adolescents with active SpA despite treatment with NSAIDs, is treatment with systemic corticosteroids more effective than no treatment with systemic corticosteroids in improving outcomes?
47. In children and adolescents with active SpA despite treatment with NSAIDs, is treatment with systemic corticosteroids more effective, less effective, or as effective as sulfasalazine or methotrexate in improving outcomes?
48. In children and adolescents with active SpA despite treatment with NSAIDs, is treatment with TNFi more effective, less effective, or as effective as sulfasalazine, methotrexate, or systemic corticosteroids in improving outcomes?
49. In children and adolescents with SpA and active peripheral arthritis despite treatment with NSAIDs, is treatment with local corticosteroids more effective than no treatment with local corticosteroids in improving outcomes?
50. In children and adolescents with SpA and active enthesitis despite treatment with NSAIDs, is treatment with local corticosteroids more effective than no treatment with local corticosteroids in improving outcomes?
51. In children and adolescents with SpA and active peripheral arthritis despite treatment with NSAIDs, is treatment with local corticosteroids more effective than sulfasalazine, methotrexate, or TNFi in improving outcomes?
52. In children and adolescents with SpA and active enthesitis despite treatment with NSAIDs, is treatment with local corticosteroids more effective than sulfasalazine, methotrexate, or TNFi in improving outcomes?
53. In children and adolescents with SpA and isolated active sacroiliitis despite treatment with NSAIDs, is treatment with local corticosteroids more effective than no treatment with local corticosteroids in improving outcomes?
54. In children and adolescents with SpA and isolated active sacroiliitis despite treatment with NSAIDs, is treatment with local corticosteroids more effective than sulfasalazine, methotrexate, or TNFi in improving outcomes?
55. In children and adolescents with active SpA, is any form of PT more effective than no PT in improving health status and functional status?
56. In children and adolescents with active SpA, are aquatic PT interventions more effective than land-based PT interventions in improving health status and functional status?
57. In children and adolescents with active or stable SpA, is recreational physical activity more effective than no recreational physical activity in improving health status and functional status?
Non-radiographic axial SpA
58. In adults with active non-radiographic axial SpA, is treatment with NSAIDs more effective than no treatment with NSAIDs in improving outcomes?
59. In adults with active or stable non-radiographic axial SpA, is continuous treatment with NSAIDs more effective than on-demand NSAID treatment in improving outcomes?
60. In adults with active non-radiographic axial SpA, are certain NSAIDs more effective than other NSAIDs in improving

outcomes?
61. In adults with active non-radiographic axial SpA despite treatment with NSAIDs, are DMARDs more effective than no treatment with DMARDs in improving outcomes?
62. In adults with active non-radiographic axial SpA despite treatment with NSAIDs, are TNFi more effective than no treatment with TNFi in improving outcomes?
63. In adults with active non-radiographic axial SpA, are certain TNFi more effective than other TNFi in improving outcomes?
64. In adults with stable non-radiographic axial SpA on treatment with TNFi and NSAIDs, is continuation of both medications more effective in improving outcomes than continuing treatment with TNFi alone?
65. In adults with stable non-radiographic axial SpA on treatment with TNFi and DMARD, is continuation of both medications more effective in improving outcomes than withdrawing one treatment and continuing either TNFi or DMARD alone?
66. In adults with active non-radiographic axial SpA despite treatment with the first TNFi agent used, is switching to a different TNFi more effective than adding a DMARD in improving outcomes?
67. In adults with active non-radiographic axial SpA despite treatment with NSAIDs and who have contraindications to TNFi, is treatment with a non-TNFi biologic more effective than treatment with DMARD in improving outcomes?
68. In adults with active non-radiographic axial SpA, are systemic corticosteroids more effective than no treatment with systemic corticosteroids in improving outcomes?
69. In adults with non-radiographic axial SpA and active peripheral arthritis despite treatment with NSAIDs, are locally administered parenteral corticosteroids more effective than no treatment with local corticosteroids in improving outcomes?
70. In adults with non-radiographic axial SpA and active enthesitis despite treatment with NSAIDs, are locally administered parenteral corticosteroids more effective than no treatment with local corticosteroids in improving outcomes?
71. In adults with non-radiographic axial SpA and active peripheral arthritis despite treatment with NSAIDs, is treatment with local corticosteroids more effective than treatment with sulfasalazine, methotrexate, or TNFi in improving outcomes?
72. In adults with non-radiographic axial SpA and active enthesitis despite treatment with NSAIDs, is treatment with local corticosteroids more effective than treatment with sulfasalazine, methotrexate, or TNFi in improving outcomes?
73. In adults with non-radiographic axial SpA and isolated active sacroiliitis despite treatment with NSAIDs, is treatment with local corticosteroids more effective than no treatment with local corticosteroids in improving outcomes?
74. In adults with non-radiographic axial SpA and isolated active sacroiliitis despite treatment with NSAIDs, is treatment with local corticosteroids more effective treatment with TNFi in improving outcomes?
75. In adults with active non-radiographic axial SpA, is any form of PT more effective than no PT in improving health status and functional status?
75a. Are aquatic PT interventions more effective than land-based PT interventions in improving health status and

functional status?
75b. Are active PT interventions (supervised exercise) more effective than passive PT interventions (massage, ultrasound, heat) in improving health status and functional status?
76. In adults with active or stable non-radiographic axial SpA, is recreational physical activity (leisure time physical activity) more effective than no recreational physical activity in improving health status and functional status?

PREVENTIVE CARE
77. In adults with AS, is group or individual self-management education more effective than no formal self-management education in improving outcomes?
78. In adults with AS, is screening for osteopenia/osteoporosis with DEXA scanning yearly, every other year, every five years, more effective than screening after insufficiency fractures or no screening in improving outcomes?
79. In adults with AS and syndesmophytes or spinal fusion, is screening for osteopenia/osteoporosis with DEXA scanning of the hip or other non-spine sites more effective than DEXA scanning of the spine in improving outcomes?
80a. In adults with AS, is treatment with bisphosphonates more effective than no treatment in preventing osteopenia/osteoporosis?
80b. In adults with AS, is treatment with bisphosphonates more effective than no treatment in improving osteopenia/osteoporosis?
81. In adults with AS, is fall evaluation and counseling more effective than no evaluation and counseling in improving outcomes?
82. In adults with AS and an ankylosed spine, is counseling of the patient regarding standard intubation practices and the need to communicate modifications to intubation with anesthesiologists, EMTs and surgeons more effective than no counseling in improving outcomes?
83. In adults with AS, is screening for cardiovascular risk factors (hypertension, BMI, serum lipids, smoking) regardless of age, sex and family history yearly, every other year, or every five years more effective than no screening in improving outcomes?
84. In adults with AS, is screening for cardiac conduction defects with electrocardiogram at diagnosis, yearly, every other year, or every five years more effective than no screening in improving outcomes?

85. In adults with AS, is screening for valvular heart disease with echocardiogram at diagnosis, yearly, every other year, or every five years more effective than no screening in improving outcomes?

DISEASE ACTIVITY MONITORING
86. In adults with active or stable AS, is regular interval use and monitoring of the Bath Ankylosing Spondylitis Disease Activity Index (BASDAI) or AS Disease Activity Score (ASDAS) more effective than usual care without monitoring of the BASDAI or ASDAS in improving outcomes?
87. In adults with active or stable non-radiographic axial SpA, is regular interval use and monitoring of the Bath Ankylosing Spondylitis Disease Activity Index (BASDAI) or AS Disease Activity Score (ASDAS) more effective than usual care without monitoring of the BASDAI or ASDAS in improving outcomes?
88. In adults with active or stable AS, is regular interval use and monitoring of C-reactive protein (CRP) levels or erythrocyte sedimentation rate (ESR) more effective than usual care without CRP or ESR monitoring in improving outcomes?
89. In adults with active or stable non-radiographic axial SpA, is regular interval use and monitoring of C-reactive protein (CRP) levels or erythrocyte sedimentation rate (ESR) more effective than usual care without CRP or ESR monitoring in improving outcomes?
90. In adults with active or stable non-radiographic axial SpA, is monitoring of serial MRI of sacroiliac joints more effective than monitoring of conventional radiograph or clinical assessment in improving outcomes?

APPENDIX B

Database: Ovid MEDLINE(R) In-Process & Other Non-Indexed Citations and Ovid MEDLINE(R) <1946 to Present>

Search Strategy:

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1 Spondylarthritis/ (666)
2 spondylarthritis.tw. (770)
3 spondyloarthritis.tw. (1018)
4 Spondylarthropathies/ (661)
5 spondylarthropath$.tw. (750)
6 spondyloarthropath$.tw. (2072)
7 Spondylitis/ (2952)
8 Spondylitis, Ankylosing/ (11200)
9 ankylosing spondylitis.tw. (8810)
10 spondylitis.tw. (11111)
11 or/1-10 (19244)
12 exp Anti-Inflammatory Agents, Non-Steroidal/ (152166)
13 ((non-steroidal or nonsteroidal) adj (anti-inflammator$ or antiinflammator$)).tw. (26487)
14 NSAID$.tw. (16999)
15 (aspirin or meloxicam or nabumetone).tw. (36548)
16 (diclofenac or diflunisal or epirizole or fenoprofen or flurbiprofen or ibuprofen or indomethacin or ketoprofen).tw. (49038)
17 (ketorolac or ketorolac tromethamine or meclofenamic acid or naproxen or oxaprozin).tw. (6691)
18 (piroxicam or salicylate$).tw. (11582)
19 (sodium salicylate or sulindac or tolmetin).tw. (3830)
20 cyclo-oxygenase 2 inhibit$.tw. (324)
21 cyclooxygenase 2 inhibitors/ (7105)
22 cyclooxygenase 2 inhibit$.tw. (2032)
23 COX-2 inhibitor$.tw. (6061)
24 celecoxib.tw. (3884)
25 or/12-24 (192884)
26 exp Mortality/ or mo.fs. (537869)
27 11 and 25 and 26 (13)
28 exp Health Status/ (97133)
29 exp Health Status Indicators/ (182304)
30 health status.tw. (34476)

31 exp pain/ (290009)
32 Pain Management/ (15440)
33 Pain Measurement/ (56367)
34 pain$.tw. (420843)
35 stiffness.tw. (33709)
36 exp Fatigue/ (18811)
37 fatigue.tw. (53269)
38 exp sleep disorders/ (56900)
39 sleep disturbance$.tw. (7828)
40 edema/ or swelling.tw. (83674)
41 (Bath AS Disease Activity Index or BASDAI).tw. (561)
42 (SF-36$ or SF36$).tw. (12608)
43 exp Physical Examination/ or physical exam$.tw. (992787)
44 (Ankylosing Spondylitis Disease Activity Score or AS Disease Activity Score or ASDAS).tw. (1873)
45 exp acute phase proteins/ or acute phase reactant$.tw. (146045)
46 exp Inflammation/ and exp Diagnostic Imaging/ (15274)
47 (inflammat$ and imaging).tw. (15665)
48 Mental Health/ (20010)
49 exp Mental Disorders/ (900544)
50 exp Mental Processes/ (716567)
51 (CES-D or Center for Epidemiological Studies Depression).tw. (2664)
52 (depression or anxiety).tw. (263354)
53 "Quality of Life"/ (108084)
54 (quality of life or (QOL or HRQOL or HRQL)).tw. (134767)
55 exp interpersonal relations/ (246646)
56 Reproductive Health/ (405)
57 (social interaction or sexual health or body image).tw. (15946)
58 Ankylosing Spondylitis Quality of Life.tw. (35)
59 (AS Quality of Life or ASQOL).tw. (133387)
60 or/28-59 (3741059)
61 11 and 25 and 60 (661)
62 functional status.tw. (15877)
63 exp "Activities of Daily Living"/ (48347)
64 (activit$ of daily living or physical funct$).tw. (25786)
65 disabilit$.tw. (99034)
66 (Bath Ankylosing Spondylitis Functional Index or BASFI).tw. (435)

67 (Health Assessment Questionnaire for the Spondylarthropathies or HAQ-S).tw. (41)
68 (Dougados Functional Index or DFI).tw. (779)
69 SF-36.tw. (11806)
70 exp "Range of Motion, Articular"/ (30957)
71 range of motion.tw. (17020)
72 (Bath Ankylosing Spondylitis Metrology Index or Bath as metrology index or BASMI).tw. (164)
73 (exp disease progression/ or spinal fusion/ or (bone destruction or structural damage).tw.) and exp Diagnostic Imaging/ (20845)
74 (exp disease progression/ or spinal fusion/ or (bone destruction or structural damage).tw.) and imaging.tw. (7596)
75 exp Work/ or exp Disability Evaluation/ or Achievement/ or Educational Status/ or exp schools/ or school performance.tw. (173444)
76 or/62-75 (380232)
77 11 and 25 and 76 (161)
78 (ae or po or to or ci).fs. (1766995)
79 exp Drug Toxicity/ (37141)
80 Adverse Drug Reaction Reporting Systems/ (5270)
81 pharmacovigilance/ (313)
82 Product Surveillance, Postmarketing/ (5357)
83 harm.tw. (21714)
84 or/78-83 (1798318)
85 11 and 25 and 84 (447)
86 exp Heart Valve Diseases/ (87300)
87 exp Pulmonary Fibrosis/ (16433)
88 pulmonary cavitation.tw. (124)
89 exp Amyloidosis/ or amyloidosis.tw. (22535)
90 exp anemia/ or (anemia or anaemia).tw. (171243)
91 Glomerulonephritis, IGA/ or ((immunoglobulin a or IgA) adj nephropathy).tw. (5878)
92 exp Nephrosis/ or nephropathy.tw. (52236)
93 Iritis/ or iritis.tw. (1655)
94 exp Inflammatory Bowel Diseases/ (56182)
95 (IBD or inflammatory bowel diseas$ or Crohn$ or ulcerative colitis).tw. (61802)
96 exp Osteoporosis/ or osteoporo$.tw. (61032)
97 Spinal Fractures/ (9605)
98 ((vertebral or spinal) adj fracture$).tw. (6087)
99 exp Myocardial Ischemia/ (342004)

100 ((ishemic or ischaemic) adj heart disease).tw. (7030)
101 Polyradiculopathy/ (2177)
102 cauda equina syndrome.tw. (917)
103 or/86-102 (821488)
104 11 and 25 and 103 (216)
105 27 or 61 or 77 or 85 or 104 (1027)
106 (randomized controlled trial or controlled clinical trial).pt. or randomized.ab. or placebo.ab. or randomly.ab. or trial.ab. or groups.ab. (1835164) [*See below]
107 105 and 106 (287)
108 exp animals/ not humans.sh. (3845615)
109 107 not 108 (285)
110 limit 109 to english language (245)
111 exp cohort studies/ (1260915)
112 cohort$.tw. (242129)
113 controlled clinical trial.pt. (86248)
114 epidemiologic methods/ (29231)
115 limit 114 to yr=1966-1989 (11248)
116 exp case-control studies/ (604734)
117 (case$ and control$).tw. (305463)
118 (case$ and series).tw. (113472)
119 case reports.pt. (1621325)
120 (case$ adj2 report$).tw. (361242)
121 (case$ adj2 stud$).tw. (136111)
122 or/111-113,115-121 (3431779) [**See below]
123 105 and 122 (355)
124 exp animals/ not humans.sh. (3845615)
125 123 not 124 (354)
126 limit 125 to english language (280)

*Cochrane Highly Sensitive Search Strategy for identifying randomized trials in MEDLINE: sensitivity- and precision-maximizing version (2008 revision); Ovid format

**BMJ Clinical Evidence Medline cohort, case-control, case series, and case study strategy

APPENDIX C

DISCLOSURES OF RELATIONSHIPS

In order for the College to most effectively further its mission and to otherwise maintain its excellent reputation in the medical community and with the public, it is important that confidence in the College's integrity be maintained. The cornerstone of the ACR's Disclosure Policy is disclosure of actual and potential conflicts so that they can be evaluated by the College in order to avoid undue influence of potential conflicts.

The purpose of the ACR's Disclosure Policy is identification of relationships which may pose actual or potential conflicts. These actual or potential conflicts can then be evaluated by the College so that adjustments can be made that will avoid any undue influence. This policy is based on the principle that, in many cases, full disclosure of the actual or potentially conflicting relationship will of itself suffice to protect the integrity of the College and its interests.

Participants	**Role**	**Primary employer**	**Sources of personal income to include speakers bureau, honoraria, royalties, expert witness fees, advisory boards, or any other sources of income (excludes salary from primary employer)**	**Intellectual Property to include copyrights, patents, or licenses**	**Research Grants/Contracts**	**Investments to include medical industry and non-medical industry**	**Organizational Benefit**	**Activities with other organizations**	**Family or other relations**
Michael Ward	PI; Voting Panel Leader	U.S. Dept. of Health and Hum Services	N/A	N/A	ACR Research and Education Fund	N/A	N/A	ACR; Ann Rheum Dis; Clinical Exp Rheum	N/A
Liron Caplan	Core Oversight Team; Lit Review Leader	Denver Veterans Affairs Medical Center; Univ of Colorado Denver	N/A	N/A	Denver Veterans Affairs Medical Center; VA CRICC; ACR/REF; VA HSR&D	N/A	N/A	National Data Bank for Rheumatic Diseases	N/A
Elie Akl	GRADE Consultant	American University of Beirut	N/A	N/A	Physicians' Services Incorporated Foundation; World Health Organization Alliance for Health Policy and Systems Research	N/A	N/A	N/A	N/A
Atul A. Deodhar	Core Oversight Team	Oregon Health & Science University	Abbott; Pfizer; UCB	N/A	Novartis; UCB; Abbott; J&J; Amgen	N/A	SPARTAN-GRAPPA	SPARTAN	N/A
John Reveille	Core Oversight Team	University of Texas Health Science Center at Houston	Abbott Pharmaceuticals; UCB Pharmaceuticals	N/A	NIH-NIAMS; NIH/NIAID; Abbott Pharmaceuticals; UCB Biosciences (2)	N/A	N/A	Spondylitis Assn. of America; Pan American League of Affiliated Rheumatology Society; Spondyloarthritis Research and Treatment Network	N/A
David Borenstein	Lit Review Team	Arthritis and Rheumatism Associates	Iroko; Abbott; Clinical Care Options	N/A	N/A	N/A	N/A	Patient Access Network Foundation	N/A
Daniel O. Clegg	Lit Review Team	University of Utah; Department of Veterans Affairs	UCB	N/A	Department of Veterans Affairs	N/A	N/A	WIBR	N/A
Joerg Ermann	Lit Review Team	Brigham and Women's Hospital Boston	ACINDES	N/A	Harvard Institute of Traditional Immunology/Helmsley Trust	N/A	N/A	N/A	N/A
Lianne S. Gensler	Lit Review Team	UCSF	Abvie (formerly Abbott), UCB; Vaccine Injury Compensation Program	N/A	NIH; UCB	N/A	N/A	Spondylitis Association of America	N/A
Robert Hart	Lit Review Team	Oregon Health & Science University	DePuy; Seaspine; Medtronic; Kyphon; Synthes; Eli Lilly	N/A	Medtronic; DePuy	Spine Connect	OREF; Synthes	AAOS; American Orthopaedic Assn; Cervical Spine Research; Lumbar Spine Research Society; North American Spine Society; Oregon Assn. of Orthopaedics; OREF; Scoliosis Research Society; CSRS Editorial Committee; Spine	N/A
Jayme Hiratzka	Lit Review Team	Oregon Health & Science University	N/A	N/A	N/A	N/A	N/A	N/A	N/A

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Robert Inman	Lit Review Team	University Health Network; University of Toronto	Abbott; Janssen; Amgen/Pfizer; UCB	N/A	Novartis; Celgene; Amgen	N/A	N/A	SPARCC; SPARTAN; ASAS	N/A
Vikas Majithia	Lit Review Team	University of Mississippi Medical Center	Glaxo-Smith-Kline (prev. HGS)	N/A	N/A	N/A	N/A	N/A	N/A
Walter Maksymowych	Lit Review Team	University of Alberta	Abbvie; UCB; Pfizer; Amgen; Janssen; Augurex	A diagnostic test for rheumatoid arthritis based on the 14-3-3 eta biomarker.	Abbvie; Janssen; Amgen/Pfizer	N/A	Abbvie; Amgen/Pfizer; Janssen	Assessments in Ankylosing spondylitis international society	N/A
Judith Smith	Lit Review Team	University of Wisconsin-Madison	N/A	N/A	N/A	N/A	N/A	N/A	N/A
Pamela Weiss	Lit Review Team	Children's Hospital of Philadelphia	N/A	N/A	NIH, NIAMS; ACR	N/A	N/A	N/A	N/A
James Witter	Lit Review Team	NIAMS/NIH	N/A	N/A	N/A	N/A	N/A	N/A	N/A
Bruce Clark	Voting Panel	Self Employed	Abbott; Amgen; BMS	N/A	N/A	N/A	N/A	N/A	N/A
Robert Colbert	Voting Panel	NIH/NIAMS	American Board of Pediatrics; March of Dimes	N/A	NIH	N/A	N/A	Spondylitis Ass'n of America; SPARTAN	N/A
Mark P Figgie	Voting Panel	Hospital for Special Surgery; Self-Employed	Medtronics	N/A	Ethicon	Mekanika	N/A	N/A	N/A
John Flynn	Voting Panel	Johns Hopkins University School of Medicine	N/A	N/A	N/A	N/A	N/A	N/A	N/A
David S. Hallegua	Voting Panel	Self Employed	Abvie (formerly Abbott); Q-Med AB; Cedars-Sinai Medical Center; UCB	N/A	Abvie; Q-Med AB; UCB; Bristol Myers Squib; UCB; Abbott; Centocor; Amgen; IDEC; XOMA; Novartis; Roche; Isis; Pharmacia; NIH; La Jolla Pharma; Genentech; Proctor & Gamble; Genelabs; Medimmune; HGS; Array Biopharma, Inc.; Cipher	N/A	N/A	Spondylitis Association of America	N/A
Pamela Prete	Voting Panel	Veterans Administration Hospital , Long Beach , CA; University of California, Irvine	Kaiser Pemanente Symposium	N/A	Abbott	N/A	N/A	N/A	N/A
James Rosenbaum	Voting Panel	OHSU; Legacy Health System	UCB; Regeneron; XOMA; LUX; Elan; UptoDate; Allergan; Santen; Teva; Novartis; Sanofi	N/A	Abbott; Bristol Myers Squibb; Celgene; Genentech	N/A	N/A	Spondylitis Association of America	N/A
Judith Stebulis	Voting Panel	U. Massachusetts Medical School; UMass/Memorial medical group	N/A	N/A	N/A	N/A	N/A	N/A	N/A
Filip van Den Bosch	Voting Panel	Ghent University Hospital; Ghent University	Abbvie; Bristol Myers Squibb; Celgene; Janssen/J&J; UCB	N/A	Ghent University Hospital (2)	N/A	N/A	Royal Belgian Society Rheumatology; ASAS	N/A
David Tak Tan Yu	Voting Panel	Qingdao Municipal Hospital, China	UpToDate	N/A	N/A	N/A	N/A	N/A	N/A

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Charlotte Howard	Other	Exxon Mobile Corp.	ExxonMobil Dividends	N/A	N/A	Mylan Inc.; CVS Caremark; Conmed Corp.; Hill Rom Holdings; National Healthcare Corp.	N/A	N/A	N/A
Laurie Savage	Other	Spondylitis Assn. of America	N/A	N/A	N/A	N/A	Abbott; Pfizer; Centene; Janssen	N/A	N/A