Appendix E: Evidence tables

E.1 Identifying new cases of spondyloarthritis

Review questions 1, 2, 12, 6 and 3

- 1. What signs and symptoms should prompt a healthcare professional to think of spondyloarthritis?
- 2. What risk factors should increase suspicion of spondyloarthritis?
- 12. What are the indications (signs, risk factors, test or scan findings) for referral for specialist advice at initial diagnosis?
- 6. What is the comparative effectiveness of different referral strategies in diagnosing spondyloarthritis?
- 3. What are the obstacles to a prompt diagnosis of spondyloarthritis?

E.1.1 Signs, symptoms and risk factors of spondyloarthritis

E.1.1.1 Inflammatory back pain

IBP (ASAS criteria)

Table 1: IBP (ASAS criteria) – evidence table

Study	Population	Risk of bias	N		Prevalence	Reference standard	Sensitivity & specificity	Predictive values	Likelihood ratios
			Cases	Non-cases					
AXIAL									
van den Berg 2013b (ASAS)	Diagnosis of axial SpA in people with undiagnosed chronic back pain	Not serious	421	264	0.615 (0.578, 0.650)	Rheumatologist diagnosis	Sens.: 0.770 (0.727, 0.807) Spec.: 0.527 (0.466, 0.586)	PPV: 0.722 (0.678, 0.761) NPV: 0.589 (0.525, 0.650)	LR+: 1.625 (1.417, 1.865) LR-: 0.438 (0.355, 0.539)
van den Berg 2013b (SPACE)	Diagnosis of axial SpA in people with back pain of between 3 months and 2 years	Serious[a]	65	92	0.414 (0.340, 0.493)	Rheumatologist diagnosis	Sens.: 0.800 (0.685, 0.880) Spec.: 0.424 (0.327, 0.527)	PPV: 0.495 (0.401, 0.590) NPV: 0.750 (0.616, 0.849)	LR+: 1.389 (1.122, 1.719) LR-: 0.472 (0.275, 0.811)
van Hoeven 2014	Diagnosis of axial SpA among people with chronic lower back pain	Not serious	86	278	0.236 (0.195, 0.283)	ASAS criteria for axial SpA, Modified NY criteria for AS	Sens.: 0.605 (0.498, 0.702) Spec.: 0.694 (0.638, 0.746)	PPV: 0.380 (0.302, 0.463) NPV: 0.850 (0.798, 0.891)	LR+: 1.978 (1.546, 2.529) LR-: 0.569 (0.434, 0.748)
van Hoeven 2015	Diagnosis of axial SpA in people with chronic low back pain	Serious[b]	95	475	0.167 (0.138, 0.200)	ASAS criteria for axial	Sens.: 0.484 (0.386, 0.584) Spec.: 0.691 (0.647, 0.730)	PPV: 0.238 (0.183, 0.304) NPV: 0.870 (0.832, 0.900)	LR+: 1.565 (1.222, 2.003) LR-: 0.747 (0.609, 0.916)
PERIPHERAL									
no data									
MIXED AXIAL AND PERIPHERAL									
no data									

[a] *Some tests only performed in subset of participants*
[b] *Retrospective study*

IBP (Berlin criteria)

Table 2: IBP (Berlin criteria) – evidence table

Study	Population	Risk of bias	N		Prevalence	Reference standard	Sensitivity & specificity	Predictive values	Likelihood ratios
			Cases	Non-cases					
AXIAL									
Rudwaleit 2009 (ASAS)	Diagnosing axial SpA among people with chronic back pain	Serious[a]	391	258	0.602 (0.564, 0.639)	Rheumatologist diagnosis	Sens.: 0.632 (0.583, 0.678) Spec.: 0.640 (0.579, 0.696)	PPV: 0.726 (0.677, 0.771) NPV: 0.534 (0.478, 0.589)	LR+: 1.752 (1.465, 2.097) LR-: 0.576 (0.491, 0.675)
van Hoeven 2014	Diagnosis of axial SpA among people with chronic lower back pain	Not serious	86	278	0.236 (0.195, 0.283)	ASAS criteria for axial SpA, Modified NY criteria for AS	Sens.: 0.779 (0.679, 0.854) Spec.: 0.342 (0.288, 0.399)	PPV: 0.268 (0.217, 0.326) NPV: 0.833 (0.753, 0.891)	LR+: 1.184 (1.028, 1.363) LR-: 0.647 (0.421, 0.993)
PERIPHERAL									
no data									
MIXED AXIAL AND PERIPHERAL									
no data									

[a] *Some tests only performed in subset of participants*

IBP (Calin criteria)

Table 3: IBP (Calin criteria) – evidence table

Study	Population	Risk of bias	N		Prevalence	Reference standard	Sensitivity & specificity	Predictive values	Likelihood ratios
			Cases	Non-cases					
AXIAL									
Hermann 2009	Diagnosis of SpA in people with unspecified chronic back pain of limited duration	Not serious	30	62	0.326 (0.238, 0.428)	AS: modified NY; PsA: McGonagle; Ent-SpA: no standard used; Undiff-SpA: signs suggestive of SpA but criteria not fully met	Sens.: 0.900 (0.732, 0.967) Spec.: 0.371 (0.261, 0.497)	PPV: 0.409 (0.298, 0.531) NPV: 0.885 (0.697, 0.962)	LR+: 1.431 (1.142, 1.792) LR-: 0.270 (0.088, 0.827)
Rudwaleit 2009 (ASAS)	Diagnosing axial SpA among people with chronic back pain	Serious[a]	391	258	0.602 (0.564, 0.639)	Rheumatologist diagnosis	Sens.: 0.859 (0.821, 0.890) Spec.: 0.403 (0.345, 0.464)	PPV: 0.686 (0.643, 0.725) NPV: 0.654 (0.577, 0.724)	LR+: 1.440 (1.292, 1.604) LR-: 0.349 (0.262, 0.465)
van Hoeven 2014	Diagnosis of axial SpA among people with chronic lower back pain	Not serious	86	278	0.236 (0.195, 0.283)	ASAS criteria for axial SpA, Modified NY criteria for AS	Sens.: 0.872 (0.784, 0.928) Spec.: 0.281 (0.231, 0.336)	PPV: 0.273 (0.223, 0.328) NPV: 0.876 (0.790, 0.930)	LR+: 1.212 (1.087, 1.352) LR-: 0.456 (0.254, 0.817)
PERIPHERAL									
Sadek 2007	Diagnosis of PsA in people with Psoriasis	Serious[b,c]	59	22	0.728 (0.622, 0.814)	Clinician and 5 criteria sets	Sens.: 0.508 (0.383, 0.633) Spec.: 0.955 (0.739, 0.994)	PPV: 0.968 (0.804, 0.995) NPV: 0.420 (0.292, 0.559)	LR+: 11.186 (1.622, 77.167) LR-: 0.515 (0.391, 0.678)
MIXED AXIAL AND PERIPHERAL									
D'Agostino 2011	Diagnosis of SpA in people with suspected SpA	Not serious	51	48	0.515 (0.417, 0.612)	Rheumatologist diagnosis	Sens.: 0.706 (0.568, 0.814) Spec.: 0.271 (0.164, 0.412)	PPV: 0.507 (0.392, 0.621) NPV: 0.464 (0.292, 0.646)	LR+: 0.968 (0.756, 1.240) LR-: 1.086 (0.579, 2.038)

[a] *Some tests only performed in subset of participants*
[b] *Retrospective study*
[c] *Testers not blinded to final diagnosis*

IBP (ad hoc or unspecified definitions)

Table 4: IBP (ad hoc or unspecified definitions) – evidence table

Study	Population	Risk of bias	N		Prevalence	Reference standard	Sensitivity & specificity	Predictive values	Likelihood ratios
			Cases	Non-cases					
AXIAL									
Poddubnyy 2011	Diagnosis of axial SpA in people with low back pain	Serious[a]	222	338	0.396 (0.357, 0.438)	Rheumatologist diagnosis	Sens.: 0.793 (0.734, 0.841) Spec.: 0.172 (0.135, 0.216)	PPV: 0.386 (0.342, 0.431) NPV: 0.558 (0.461, 0.650)	LR+: 0.957 (0.881, 1.040) LR-: 1.208 (0.853, 1.710)
Rudwaleit 2009 (ASAS)	Diagnosing axial SpA among people with chronic back pain	Serious[b]	391	258	0.602 (0.564, 0.639)	Rheumatologist diagnosis	Sens.: 0.734 (0.688, 0.775) Spec.: 0.554 (0.493, 0.614)	PPV: 0.714 (0.668, 0.756) NPV: 0.579 (0.516, 0.639)	LR+: 1.647 (1.419, 1.911) LR-: 0.480 (0.394, 0.585)
Sieper 2013	Diagnosis of axial SpA among people with chronic back pain	Serious[c,d]	388	510	0.432 (0.400, 0.465)	Rheumatologist diagnosis	Sens.: 0.943 (0.915, 0.962) Spec.: 0.249 (0.213, 0.288)	PPV: 0.489 (0.453, 0.524) NPV: 0.852 (0.786, 0.901)	LR+: 1.256 (1.188, 1.328) LR-: 0.228 (0.148, 0.351)
PERIPHERAL									
Rudwaleit 2011	Diagnosing peripheral SpA among people with peripheral manifestation	Not serious	176	90	0.662 (0.603, 0.716)	Rheumatologist diagnosis	Sens.: 0.142 (0.098, 0.202) Spec.: 0.900 (0.819, 0.947)	PPV: 0.735 (0.565, 0.856) NPV: 0.349 (0.291, 0.413)	LR+: 1.420 (0.693, 2.913) LR-: 0.953 (0.870, 1.045)
MIXED AXIAL AND PERIPHERAL									
Althoff 2009	Diagnosis of SpA among people with suspected SpA	Serious[c]	72	33	0.686 (0.591, 0.767)	Unclear (treated in this analysis as 'published criteria')	Sens.: 0.694 (0.579, 0.790) Spec.: 0.636 (0.463, 0.781)	PPV: 0.806 (0.689, 0.887) NPV: 0.488 (0.344, 0.634)	LR+: 1.910 (1.186, 3.076) LR-: 0.480 (0.311, 0.741)
Tomero 2014	Diagnosis of SpA among people with suspected early SpA	Not serious	538	237	0.694 (0.661, 0.726)	Rheumatologist diagnosis	Sens.: 0.675 (0.634, 0.713) Spec.: 0.481 (0.418, 0.545)	PPV: 0.747 (0.706, 0.784) NPV: 0.394 (0.340, 0.452)	LR+: 1.300 (1.135, 1.489) LR-: 0.676 (0.565, 0.809)

[a] *Participants not consecutively recruited*
[b] *Some tests only performed in subset of participants*
[c] *Retrospective study*
[d] *Testers not blinded to final diagnosis*

Back pain (in people with other presenting complaints)

Table 5: Back pain (in people with other presenting complaints) – evidence table

Study	Population	Risk of bias	N		Prevalence	Reference standard	Sensitivity & specificity	Predictive values	Likelihood ratios
			Cases	Non-cases					
AXIAL									
no data									
PERIPHERAL									
Kvien 1994	Diagnosis of ReA in people with suspected ReA	Not serious	52	320	0.140 (0.108, 0.179)	Investigator defined criteria	Sens.: 0.288 (0.182, 0.425) Spec.: 0.797 (0.749, 0.837)	PPV: 0.188 (0.116, 0.288) NPV: 0.873 (0.830, 0.907)	LR+: 1.420 (0.880, 2.292) LR-: 0.893 (0.745, 1.071)
MIXED AXIAL AND PERIPHERAL									
Haroon 2015	Diagnosis of SpA in people with acute anterior uveitis	Not serious	42	59	0.416 (0.324, 0.514)	Rheumatologist diagnosis	Sens.: 0.988 (0.840, 0.999) Spec.: 0.042 (0.012, 0.134)	PPV: 0.425 (0.332, 0.524) NPV: 0.833 (0.194, 0.990)	LR+: 1.031 (0.969, 1.097) LR-: 0.279 (0.014, 5.667)
Tomero 2014	Diagnosis of SpA among people with suspected early SpA	Not serious	538	237	0.694 (0.661, 0.726)	Rheumatologist diagnosis	Sens.: 0.749 (0.711, 0.784) Spec.: 0.194 (0.149, 0.249)	PPV: 0.678 (0.640, 0.715) NPV: 0.254 (0.196, 0.323)	LR+: 0.929 (0.859, 1.006) LR-: 1.293 (0.960, 1.741)

E.1.1.2 Age

Age <45 at onset of back pain

Table 6: Age <45 at onset of back pain – evidence table

Study	Population	Risk of bias	N		Prevalence	Reference standard	Sensitivity & specificity	Predictive values	Likelihood ratios
			Cases	Non-cases					
AXIAL									
no data									
PERIPHERAL									
no data									
MIXED AXIAL AND PERIPHERAL									
Liao 2009	Diagnosis of SpA among people with lower back pain	Serious[a]	92	695	0.117 (0.095, 0.140)	ESSG for diagnosing SpA, modified NY criteria for AS, CASPAR for PsA, ReA according to criteria from Kingsley and Sieper	Sens.: 0.739 (0.645, 0.823) Spec.: 0.776 (0.744, 0.806)	PPV: 0.304 (0.245, 0.365) NPV: 0.957 (0.939, 0.972)	LR+: 3.293 (2.740, 3.958) LR-: 0.336 (0.238, 0.476)

[a] *Population not comprised of people with suspected SpA*

Age <35 at onset of back pain (in people aged <45 at onset of back pain)

Table 7: Age <35 at onset of back pain (in people aged <45 at onset of back pain) – evidence table

Study	Population	Risk of bias	N		Prevalence	Reference standard	Sensitivity & specificity	Predictive values	Likelihood ratios
			Cases	Non-cases					
AXIAL									
Braun 2011	Diagnosis of axial SpA among people with chronic back pain	Not serious	113	209	0.351 (0.300, 0.404)	Rheumatologist diagnosis	Sens.: 0.770 (0.688, 0.842) Spec.: 0.435 (0.369, 0.503)	PPV: 0.424 (0.358, 0.493) NPV: 0.778 (0.699, 0.848)	LR+: 1.364 (1.167, 1.594) LR-: 0.528 (0.365, 0.766)
PERIPHERAL									
no data									
MIXED AXIAL AND PERIPHERAL									
no data									

Age <40 at onset of back pain (in people aged <45 at onset of back pain)

Table 8: Age <40 at onset of back pain (in people aged <45 at onset of back pain) – evidence table

Study	Population	Risk of bias	N		Prevalence	Reference standard	Sensitivity & specificity	Predictive values	Likelihood ratios
			Cases	Non-cases					
AXIAL									
Rudwaleit 2009 (ASAS)	Diagnosing axial SpA among people with chronic back pain	Not serious	391	258	0.602 (0.565, 0.640)	Rheumatologist diagnosis	Sens.: 0.931 (0.904, 0.954) Spec.: 0.128 (0.090, 0.171)	PPV: 0.618 (0.578, 0.657) NPV: 0.550 (0.424, 0.673)	LR+: 1.067 (1.011, 1.127) LR-: 0.540 (0.333, 0.876)
PERIPHERAL									
no data									
MIXED AXIAL AND PERIPHERAL									
no data									

Back pain with age of onset <45 (in people with acute anterior uveitis)

Table 9: Back pain with age of onset <45 (in people with acute anterior uveitis) – evidence table

Study	Population	Risk of bias	N		Prevalence	Reference standard	Sensitivity & specificity	Predictive values	Likelihood ratios
			Cases	Non-cases					
AXIAL									
no data									
PERIPHERAL									
no data									
MIXED AXIAL AND PERIPHERAL									
Haroon 2015	Diagnosis of SpA in people with acute anterior uveitis	Not serious	42	59	0.416 (0.324, 0.514)	Rheumatologist diagnosis	Sens.: 0.988 (0.840, 0.999) Spec.: 0.342 (0.233, 0.469)	PPV: 0.518 (0.411, 0.624) NPV: 0.976 (0.713, 0.999)	LR+: 1.501 (1.248, 1.807) LR-: 0.034 (0.002, 0.547)

E.1.1.3 Morning stiffness

Table 10: Morning stiffness – evidence table

Study	Population	Risk of bias	N		Prevalence	Reference standard	Sensitivity & specificity	Predictive values	Likelihood ratios
			Cases	Non-cases					
AXIAL									
Braun 2011	Diagnosis of axial SpA among people with chronic back pain	Not serious	113	209	0.351 (0.301, 0.405)	Rheumatologist diagnosis	Sens.: 0.354 (0.271, 0.446) Spec.: 0.665 (0.598, 0.726)	PPV: 0.364 (0.279, 0.457) NPV: 0.656 (0.589, 0.717)	LR+: 1.057 (0.772, 1.447) LR-: 0.971 (0.822, 1.148)
PERIPHERAL									
no data									
MIXED AXIAL AND PERIPHERAL									
Liao 2009	Diagnosis of SpA among people with lower back pain	Serious[a]	92	695	0.117 (0.096, 0.141)	ESSG for diagnosing SpA, modified NY criteria for AS, CASPAR for PsA, ReA according to criteria from Kingsley and Sieper	Sens.: 0.717 (0.617, 0.800) Spec.: 0.863 (0.836, 0.887)	PPV: 0.410 (0.337, 0.487) NPV: 0.958 (0.940, 0.972)	LR+: 5.248 (4.184, 6.583) LR-: 0.327 (0.236, 0.454)

[a] *Population not comprised of people with suspected SpA*

E.1.1.4 Neck pain

Table 11: Neck pain – evidence table

Study	Population	Risk of bias	N		Prevalence	Reference standard	Sensitivity & specificity	Predictive values	Likelihood ratios
			Cases	Non-cases					
AXIAL									
Hermann 2009	Diagnosis of SpA in people with unspecified chronic back pain of limited duration	Serious[a]	30	62	0.326 (0.238, 0.428)	AS: modified NY; PsA: McGonagle; Ent-SpA: no standard used; Undiff-SpA: signs suggestive of SpA but criteria not fully met	Sens.: 0.067 (0.017, 0.231) Spec.: 0.532 (0.409, 0.652)	PPV: 0.065 (0.016, 0.224) NPV: 0.541 (0.416, 0.661)	LR+: 0.143 (0.036, 0.558) LR-: 1.754 (1.363, 2.256)
PERIPHERAL									
no data									
MIXED AXIAL AND PERIPHERAL									
no data									

[a] *Participants not consecutively recruited*

E.1.1.5 Response to NSAIDs

Table 12: Response to NSAIDs evidence table

Study	Population	Risk of bias	N		Prevalence	Reference standard	Sensitivity & specificity	Predictive values	Likelihood ratios
			Cases	Non-cases					
AXIAL									
Braun 2011	Diagnosis of axial SpA among people with chronic back pain	Not serious	113	209	0.351 (0.301, 0.405)	Rheumatologist diagnosis	Sens.: 0.938 (0.876, 0.970) Spec.: 0.478 (0.412, 0.546)	PPV: 0.493 (0.427, 0.560) NPV: 0.935 (0.869, 0.968)	LR+: 1.799 (1.566, 2.065) LR-: 0.129 (0.062, 0.269)
Poddubnyy 2011	Diagnosis of axial SpA in people with low back pain	Not serious	89	153	0.368 (0.309, 0.430)	Rheumatologist diagnosis	Sens.: 0.607 (0.502, 0.702) Spec.: 0.333 (0.263, 0.412)	PPV: 0.346 (0.276, 0.424) NPV: 0.593 (0.487, 0.691)	LR+: 0.910 (0.744, 1.113) LR-: 1.180 (0.838, 1.660)
Sieper 2013	Diagnosis of axial SpA among people with chronic back pain	Not serious	350	446	0.440 (0.406, 0.474)	Rheumatologist diagnosis	Sens.: 0.686 (0.635, 0.732) Spec.: 0.516 (0.469, 0.562)	PPV: 0.526 (0.480, 0.572) NPV: 0.676 (0.625, 0.724)	LR+: 1.416 (1.257, 1.595) LR-: 0.609 (0.510, 0.729)
van den Berg 2013b (ASAS)	Diagnosis of axial SpA in people with undiagnosed chronic back pain	Not serious	421	264	0.615 (0.578, 0.650)	Rheumatologist diagnosis	Sens.: 0.615 (0.568, 0.661) Spec.: 0.723 (0.666, 0.774)	PPV: 0.780 (0.732, 0.821) NPV: 0.541 (0.489, 0.592)	LR+: 2.225 (1.805, 2.743) LR-: 0.532 (0.461, 0.613)
van den Berg 2013b (SPACE)	Diagnosis of axial SpA in people with back pain of between 3 months and 2 years	Not serious	65	92	0.414 (0.340, 0.493)	Rheumatologist diagnosis	Sens.: 0.415 (0.303, 0.538) Spec.: 0.707 (0.606, 0.790)	PPV: 0.500 (0.370, 0.630) NPV: 0.631 (0.534, 0.719)	LR+: 1.415 (0.922, 2.173) LR-: 0.827 (0.649, 1.056)
van Hoeven 2014	Diagnosis of axial SpA among people with chronic lower back pain	Not serious	86	278	0.236 (0.195, 0.283)	ASAS criteria for axial SpA, Modified NY criteria for AS	Sens.: 0.605 (0.498, 0.702) Spec.: 0.622 (0.564, 0.677)	PPV: 0.331 (0.262, 0.408) NPV: 0.836 (0.779, 0.880)	LR+: 1.601 (1.275, 2.011) LR-: 0.635 (0.482, 0.838)
van Hoeven 2015	Diagnosis of axial SpA in people with chronic low back pain	Not serious	95	484	0.164 (0.136, 0.197)	ASAS criteria for axial	Sens.: 0.653 (0.552, 0.741) Spec.: 0.585 (0.540, 0.628)	PPV: 0.236 (0.188, 0.291) NPV: 0.896 (0.857, 0.925)	LR+: 1.572 (1.312, 1.883) LR-: 0.594 (0.446, 0.791)
PERIPHERAL									
no data									
MIXED AXIAL AND PERIPHERAL									
D'Agostino 2011	Diagnosis of SpA in people with suspected SpA	Not serious	51	48	0.515 (0.417, 0.612)	Rheumatologist diagnosis	Sens.: 0.706 (0.568, 0.814) Spec.: 0.542 (0.401, 0.676)	PPV: 0.621 (0.491, 0.736) NPV: 0.634 (0.479, 0.766)	LR+: 1.540 (1.080, 2.196) LR-: 0.543 (0.330, 0.894)

Study	Population	Risk of bias	N		Prevalence	Reference standard	Sensitivity & specificity	Predictive values	Likelihood ratios
			Cases	Non-cases					
Tomero 2014	Diagnosis of SpA among people with suspected early SpA	Not serious	538	237	0.694 (0.661, 0.726)	Rheumatologist diagnosis	Sens.: 0.636 (0.594, 0.675) Spec.: 0.557 (0.493, 0.619)	PPV: 0.765 (0.724, 0.802) NPV: 0.402 (0.351, 0.456)	LR+: 1.435 (1.227, 1.678) LR-: 0.654 (0.558, 0.767)

E.1.1.6 Enthesitis

Table 13 Enthesitis – evidence table

Study	Population	Risk of bias	N		Prevalence	Reference standard	Sensitivity & specificity	Predictive values	Likelihood ratios
			Cases	Non-cases					
AXIAL									
Braun 2011	Diagnosis of axial SpA among people with chronic back pain	Not serious	113	209	0.351 (0.301, 0.405)	Rheumatologist diagnosis	Sens.: 0.150 (0.096, 0.229) Spec.: 0.919 (0.873, 0.949)	PPV: 0.500 (0.338, 0.662) NPV: 0.667 (0.610, 0.719)	LR+: 1.850 (0.983, 3.480) LR-: 0.925 (0.847, 1.009)
Dougados 2011 (DESIR)	Diagnosis of SpA in people with early inflammatory back pain	Not serious	475	233	0.671 (0.635, 0.705)	ASAS criteria for axial	Sens.: 0.478 (0.433, 0.523) Spec.: 0.485 (0.421, 0.549)	PPV: 0.654 (0.603, 0.702) NPV: 0.313 (0.267, 0.363)	LR+: 0.928 (0.794, 1.085) LR-: 1.077 (0.919, 1.261)
Hulsemann 1995	Diagnosis of AS in people with suspected inflammatory rheumatic diseases seen at an early synovitis clinic	Serious[a]	41	167	0.197 (0.149, 0.257)	Clinician diagnosis	Sens.: 0.220 (0.118, 0.371) Spec.: 0.802 (0.735, 0.856)	PPV: 0.214 (0.115, 0.363) NPV: 0.807 (0.740, 0.860)	LR+: 1.111 (0.578, 2.135) LR-: 0.973 (0.813, 1.163)
van den Berg 2013b (ASAS)	Diagnosis of axial SpA in people with undiagnosed chronic back pain	Not serious	421	264	0.615 (0.578, 0.650)	Rheumatologist diagnosis	Sens.: 0.204 (0.168, 0.245) Spec.: 0.856 (0.808, 0.893)	PPV: 0.694 (0.607, 0.768) NPV: 0.403 (0.363, 0.444)	LR+: 1.419 (1.001, 2.013) LR-: 0.930 (0.867, 0.996)
van den Berg 2013b (SPACE)	Diagnosis of axial SpA in people with back pain of between 3 months and 2 years	Not serious	65	92	0.414 (0.340, 0.493)	Rheumatologist diagnosis	Sens.: 0.154 (0.085, 0.263) Spec.: 0.837 (0.747, 0.899)	PPV: 0.400 (0.230, 0.597) NPV: 0.583 (0.498, 0.664)	LR+: 0.944 (0.453, 1.967) LR-: 1.011 (0.881, 1.160)
van Hoeven 2014	Diagnosis of axial SpA among people with chronic lower back pain	Not serious	86	278	0.236 (0.195, 0.283)	ASAS criteria for axial SpA, Modified NY criteria for AS	Sens.: 0.093 (0.047, 0.175) Spec.: 0.845 (0.798, 0.883)	PPV: 0.157 (0.080, 0.284) NPV: 0.751 (0.700, 0.796)	LR+: 0.601 (0.294, 1.229) LR-: 1.073 (0.986, 1.167)
van Hoeven 2015	Diagnosis of axial SpA in people with chronic low back pain	Not serious	95	484	0.164 (0.136, 0.197)	ASAS criteria for axial	Sens.: 0.032 (0.010, 0.093) Spec.: 0.940 (0.915, 0.958)	PPV: 0.094 (0.031, 0.254) NPV: 0.832 (0.798, 0.861)	LR+: 0.527 (0.164, 1.695) LR-: 1.030 (0.987, 1.075)
PERIPHERAL									
Kvien 1994	Diagnosis of ReA in people with suspected ReA	Not serious	52	320	0.140 (0.108, 0.179)	Investigator defined criteria	Sens.: 0.019 (0.003, 0.124) Spec.: 0.909 (0.873, 0.936)	PPV: 0.033 (0.005, 0.202) NPV: 0.851 (0.809, 0.885)	LR+: 0.212 (0.030, 1.524) LR-: 1.079 (1.024, 1.135)
Rudwaleit 2011	Diagnosing peripheral SpA among people with peripheral manifestation	Not serious	176	90	0.662 (0.603, 0.716)	Rheumatologist diagnosis	Sens.: 0.568 (0.494, 0.639) Spec.: 0.756 (0.656, 0.833)	PPV: 0.820 (0.741, 0.878) NPV: 0.472 (0.392, 0.554)	LR+: 2.324 (1.581, 3.417) LR-: 0.572 (0.465, 0.702)

Study	Population	Risk of bias	N		Prevalence	Reference standard	Sensitivity & specificity	Predictive values	Likelihood ratios
			Cases	Non-cases					
Sadek 2007	Diagnosis of PsA in people with Psoriasis	Not serious	59	22	0.728 (0.622, 0.814)	Clinician and 5 criteria sets	Sens.: 0.608 (0.480, 0.723) Spec.: 0.978 (0.732, 0.999)	PPV: 0.986 (0.818, 0.999) NPV: 0.489 (0.349, 0.631)	LR+: 27.983 (1.791, 437.305) LR-: 0.400 (0.290, 0.552)
You 2015	Diagnosis of PsA in people with Psoriasis	Serious[b]	18	130	0.122 (0.078, 0.185)	CASPAR	Sens.: 0.132 (0.039, 0.364) Spec.: 0.996 (0.942, 1.000)	PPV: 0.833 (0.194, 0.990) NPV: 0.888 (0.826, 0.930)	LR+: 34.474 (1.720, 691.038) LR-: 0.872 (0.732, 1.039)
MIXED AXIAL AND PERIPHERAL									
D'Agostino 2011	Diagnosis of SpA in people with suspected SpA	Not serious	51	48	0.515 (0.417, 0.612)	Rheumatologist diagnosis	Sens.: 0.490 (0.357, 0.625) Spec.: 0.625 (0.482, 0.749)	PPV: 0.581 (0.431, 0.718) NPV: 0.536 (0.406, 0.661)	LR+: 1.307 (0.825, 2.071) LR-: 0.816 (0.577, 1.154)
Godfrin 2004	Diagnosis of SpA in people with entheseal pain	Not serious	13	20	0.394 (0.244, 0.566)[c]	Criteria specified by study authors (plus Amor and ESSG criteria)	Sens.: 0.692 (0.409, 0.880) Spec.: 0.600 (0.380, 0.786)	PPV: 0.529 (0.303, 0.745) NPV: 0.750 (0.492, 0.903)	LR+: 1.731 (0.906, 3.308) LR-: 0.513 (0.210, 1.249)
Tomero 2014	Diagnosis of SpA among people with suspected early SpA	Not serious	538	237	0.694 (0.661, 0.726)[d]	Rheumatologist diagnosis	Sens.: 0.296 (0.258, 0.335) Spec.: 0.890 (0.844, 0.924)	PPV: 0.859 (0.802, 0.903) NPV: 0.358 (0.320, 0.397)	LR+: 2.694 (1.832, 3.961) LR-: 0.791 (0.737, 0.849)

[a] *Majority of people end as undifferentiated arthritis*
[b] *Participants not consecutively recruited*
[c] *cases classified as nonspecific 'entheseal spondyloarthropathy' treated as negative for spondyloarthritis*
[d] *combines 'heel pain' and 'other enthesitis', assuming these are mutually exclusive categories*

Enthesitis (heel)

Table 14: Enthesitis (heel) – evidence table

Study	Population	Risk of bias	N		Prevalence	Reference standard	Sensitivity & specificity	Predictive values	Likelihood ratios
			Cases	Non-cases					
AXIAL									
Dougados 2011 (DESIR)	Diagnosis of SpA in people with early inflammatory back pain	Not serious	475	233	0.671 (0.635, 0.705)	ASAS criteria for axial	Sens.: 0.385 (0.343, 0.430) Spec.: 0.524 (0.459, 0.587)	PPV: 0.622 (0.566, 0.676) NPV: 0.295 (0.253, 0.340)	LR+: 0.809 (0.678, 0.964) LR-: 1.174 (1.019, 1.353)
Rudwaleit 2009 (ASAS)	Diagnosing axial SpA among people with chronic back pain	Not serious	391	258	0.602 (0.564, 0.639)	Rheumatologist diagnosis	Sens.: 0.169 (0.135, 0.209) Spec.: 0.822 (0.770, 0.864)	PPV: 0.589 (0.496, 0.676) NPV: 0.395 (0.354, 0.437)	LR+: 0.947 (0.672, 1.333) LR-: 1.012 (0.941, 1.087)
PERIPHERAL									
Rudwaleit 2011	Diagnosing peripheral SpA among people with peripheral manifestation	Not serious	176	90	0.662 (0.603, 0.716)	Rheumatologist diagnosis	Sens.: 0.313 (0.248, 0.385) Spec.: 0.867 (0.780, 0.923)	PPV: 0.821 (0.711, 0.895) NPV: 0.392 (0.327, 0.461)	LR+: 2.344 (1.325, 4.146) LR-: 0.793 (0.698, 0.902)
MIXED AXIAL AND PERIPHERAL									
Liao 2009	Diagnosis of SpA among people with lower back pain	Serious[a]	92	695	0.117 (0.096, 0.141)	ESSG for diagnosing SpA, modified NY criteria for AS, CASPAR for PsA, ReA according to criteria from Kingsley and Sieper	Sens.: 0.054 (0.023, 0.124) Spec.: 0.991 (0.981, 0.996)	PPV: 0.455 (0.203, 0.732) NPV: 0.888 (0.864, 0.908)	LR+: 6.295 (1.960, 20.217) LR-: 0.954 (0.908, 1.002)
Tomero 2014	Diagnosis of SpA among people with suspected early SpA	Not serious	538	237	0.694 (0.661, 0.726)	Rheumatologist diagnosis	Sens.: 0.229 (0.195, 0.266) Spec.: 0.916 (0.873, 0.945)	PPV: 0.860 (0.793, 0.908) NPV: 0.343 (0.307, 0.381)	LR+: 2.709 (1.732, 4.237) LR-: 0.842 (0.793, 0.895)

[a] *Population not comprised of people with suspected SpA*

E.1.1.7 Psoriasis

Table 15: Psoriasis – evidence table

Study	Population	Risk of bias	N		Prevalence	Reference standard	Sensitivity & specificity	Predictive values	Likelihood ratios
			Cases	Non-cases					
AXIAL									
Dougados 2011 (DESIR)	Diagnosis of SpA in people with early inflammatory back pain	Not serious	475	233	0.671 (0.635, 0.705)	ASAS criteria for axial	Sens.: 0.160 (0.130, 0.196) Spec.: 0.841 (0.788, 0.883)	PPV: 0.673 (0.581, 0.753) NPV: 0.329 (0.293, 0.368)	LR+: 1.008 (0.703, 1.445) LR-: 0.999 (0.933, 1.069)
van den Berg 2013b (ASAS)	Diagnosis of axial SpA in people with undiagnosed chronic back pain	Not serious	421	264	0.615 (0.578, 0.650)	Rheumatologist diagnosis	Sens.: 0.086 (0.062, 0.116) Spec.: 0.951 (0.917, 0.971)	PPV: 0.735 (0.595, 0.839) NPV: 0.395 (0.357, 0.433)	LR+: 1.737 (0.939, 3.213) LR-: 0.962 (0.924, 1.001)
van den Berg 2013b (SPACE)	Diagnosis of axial SpA in people with back pain of between 3 months and 2 years	Not serious	65	92	0.414 (0.340, 0.493)	Rheumatologist diagnosis	Sens.: 0.154 (0.085, 0.263) Spec.: 0.935 (0.862, 0.970)	PPV: 0.625 (0.377, 0.821) NPV: 0.610 (0.527, 0.687)	LR+: 2.359 (0.902, 6.167) LR-: 0.905 (0.805, 1.017)
van Hoeven 2014	Diagnosis of axial SpA among people with chronic lower back pain	Not serious	86	278	0.236 (0.195, 0.283)	ASAS criteria for axial SpA, Modified NY criteria for AS	Sens.: 0.058 (0.024, 0.132) Spec.: 0.953 (0.921, 0.973)	PPV: 0.278 (0.121, 0.519) NPV: 0.766 (0.718, 0.808)	LR+: 1.243 (0.456, 3.389) LR-: 0.988 (0.932, 1.048)
van Hoeven 2015	Diagnosis of axial SpA in people with chronic low back pain	Not serious	95	484	0.164 (0.136, 0.197)	ASAS criteria for axial	Sens.: 0.032 (0.010, 0.093) Spec.: 0.952 (0.930, 0.968)	PPV: 0.115 (0.038, 0.303) NPV: 0.834 (0.800, 0.862)	LR+: 0.665 (0.204, 2.169) LR-: 1.017 (0.975, 1.060)
PERIPHERAL									
no data									
MIXED AXIAL AND PERIPHERAL									
D'Agostino 2011	Diagnosis of SpA in people with suspected SpA	Not serious	51	48	0.515 (0.417, 0.612)	Rheumatologist diagnosis	Sens.: 0.333 (0.218, 0.472) Spec.: 0.833 (0.701, 0.914)	PPV: 0.680 (0.478, 0.831) NPV: 0.541 (0.427, 0.650)	LR+: 2.000 (0.952, 4.201) LR-: 0.800 (0.635, 1.009)
Godfrin 2004	Diagnosis of SpA in people with entheseal pain	Not serious	13	20	0.394 (0.244, 0.566)[a]	Criteria specified by study authors (plus Amor and ESSG criteria)	Sens.: 0.462 (0.224, 0.718) Spec.: 0.750 (0.522, 0.892)	PPV: 0.545 (0.268, 0.797) NPV: 0.682 (0.466, 0.840)	LR+: 1.846 (0.707, 4.820) LR-: 0.718 (0.409, 1.261)
Liao 2009	Diagnosis of SpA among people with lower back pain	Serious[b]	92	695	0.117 (0.096, 0.141)	ESSG for diagnosing SpA, modified NY criteria for AS, CASPAR for PsA, ReA according to criteria from Kingsley and Sieper	Sens.: 0.033 (0.011, 0.096) Spec.: 0.999 (0.990, 1.000)	PPV: 0.750 (0.238, 0.966) NPV: 0.886 (0.862, 0.907)	LR+: 22.663 (2.382, 215.603) LR-: 0.969 (0.933, 1.006)

Study	Population	Risk of bias	N		Prevalence	Reference standard	Sensitivity & specificity	Predictive values	Likelihood ratios
			Cases	Non-cases					
Tomero 2014	Diagnosis of SpA among people with suspected early SpA	Not serious	538	237	0.694 (0.661, 0.726)	Rheumatologist diagnosis	Sens.: 0.139 (0.113, 0.171) Spec.: 0.954 (0.918, 0.974)	PPV: 0.872 (0.784, 0.928) NPV: 0.328 (0.294, 0.364)	LR+: 3.004 (1.625, 5.550) LR-: 0.902 (0.864, 0.943)

[a] *cases classified as nonspecific 'entheseal spondyloarthropathy' treated as negative for spondyloarthritis*

[b] *Population not comprised of people with suspected SpA*

E.1.1.8 Uveitis

Table 16: Uveitis – evidence table

Study	Population	Risk of bias	N		Prevalence	Reference standard	Sensitivity & specificity	Predictive values	Likelihood ratios
			Cases	Non-cases					
AXIAL									
Dougados 2011 (DESIR)	Diagnosis of SpA in people with early inflammatory back pain	Not serious	475	233	0.671 (0.635, 0.705)	ASAS criteria for axial	Sens.: 0.097 (0.073, 0.127) Spec.: 0.940 (0.901, 0.964)	PPV: 0.767 (0.644, 0.857) NPV: 0.338 (0.303, 0.375)	LR+: 1.612 (0.905, 2.871) LR-: 0.961 (0.920, 1.004)
van den Berg 2013b (ASAS)	Diagnosis of axial SpA in people with undiagnosed chronic back pain	Not serious	421	264	0.615 (0.578, 0.650)	Rheumatologist diagnosis	Sens.: 0.102 (0.077, 0.135) Spec.: 0.920 (0.881, 0.948)	PPV: 0.672 (0.549, 0.775) NPV: 0.391 (0.354, 0.430)	LR+: 1.284 (0.780, 2.114) LR-: 0.975 (0.930, 1.023)
van den Berg 2013b (SPACE)	Diagnosis of axial SpA in people with back pain of between 3 months and 2 years	Not serious	65	92	0.414 (0.340, 0.493)	Rheumatologist diagnosis	Sens.: 0.154 (0.085, 0.263) Spec.: 0.946 (0.876, 0.977)	PPV: 0.667 (0.406, 0.854) NPV: 0.613 (0.530, 0.689)	LR+: 2.831 (1.015, 7.893) LR-: 0.895 (0.798, 1.003)
van Hoeven 2014	Diagnosis of axial SpA among people with chronic lower back pain	Not serious	86	278	0.236 (0.195, 0.283)	ASAS criteria for axial SpA, Modified NY criteria for AS	Sens.: 0.035 (0.011, 0.103) Spec.: 0.986 (0.962, 0.995)	PPV: 0.429 (0.144, 0.770) NPV: 0.768 (0.721, 0.808)	LR+: 2.424 (0.553, 10.621) LR-: 0.979 (0.938, 1.022)
PERIPHERAL									
Kvien 1994	Diagnosis of ReA in people with suspected ReA	Not serious	52	320	0.140 (0.108, 0.179)	Investigator defined criteria	Sens.: 0.231 (0.136, 0.364) Spec.: 0.875 (0.834, 0.907)	PPV: 0.231 (0.136, 0.364) NPV: 0.875 (0.834, 0.907)	LR+: 1.846 (1.039, 3.280) LR-: 0.879 (0.753, 1.026)
Mäki-Ikola 1991	Diagnosis of ReA among people with suspected ReA following Salmonella infection	Serious[a]	39	58	0.402 (0.309, 0.502)	Criteria specified by authors	Sens.: 0.077 (0.025, 0.213) Spec.: 0.983 (0.888, 0.998)	PPV: 0.750 (0.238, 0.966) NPV: 0.613 (0.511, 0.706)	LR+: 4.462 (0.481, 41.346) LR-: 0.939 (0.853, 1.035)
Mattila 1998	Diagnosis of ReA among people with suspected ReA following a Salmonella outbreak	Serious[b]	22	169	0.115 (0.077, 0.169)	Rheumatologist diagnosis	Sens.: 0.022 (0.001, 0.268) Spec.: 0.950 (0.905, 0.974)	PPV: 0.056 (0.003, 0.505) NPV: 0.878 (0.822, 0.918)	LR+: 0.435 (0.026, 7.285) LR-: 1.030 (0.960, 1.104)
Munch 1985	Diagnosis of AS among people with Crohn's disease	Not serious	15	152	0.090 (0.055, 0.144)	Clinician diagnosis	Sens.: 0.067 (0.009, 0.352) Spec.: 0.980 (0.941, 0.994)	PPV: 0.250 (0.034, 0.762) NPV: 0.914 (0.860, 0.948)	LR+: 3.378 (0.374, 30.488) LR-: 0.952 (0.830, 1.092)
Rigby 1993	Diagnosis of AS in people attending a rheumatology clinic	Serious[c,d]	30	181	0.142 (0.101, 0.196)	Clinician diagnosis	Sens.: 0.267 (0.139, 0.450) Spec.: 0.994 (0.962, 0.999)	PPV: 0.889 (0.500, 0.985) NPV: 0.891 (0.840, 0.927)	LR+: 48.267 (6.260, 372.180) LR-: 0.737 (0.594, 0.915)
MIXED AXIAL AND PERIPHERAL									

Study	Population	Risk of bias	N		Prevalence	Reference standard	Sensitivity & specificity	Predictive values	Likelihood ratios
			Cases	Non-cases					
Salvarini 2001	Diagnosis of SpA in people with inflammatory bowel disease	Serious[b]	29	131	0.181 (0.129, 0.249)	ESSG criteria	Sens.: 0.138 (0.053, 0.315) Spec.: 0.985 (0.941, 0.996)	PPV: 0.667 (0.268, 0.916) NPV: 0.838 (0.771, 0.888)	LR+: 9.034 (1.737, 46.997) LR-: 0.875 (0.756, 1.014)
Tomero 2014	Diagnosis of SpA among people with suspected early SpA	Not serious	538	237	0.694 (0.661, 0.726)	Rheumatologist diagnosis	Sens.: 0.052 (0.036, 0.074) Spec.: 0.979 (0.950, 0.991)	PPV: 0.848 (0.684, 0.935) NPV: 0.313 (0.280, 0.347)	LR+: 2.467 (0.964, 6.310) LR-: 0.968 (0.942, 0.995)

[a] *Participants not consecutively recruited*
[b] *Some tests only performed in subset of participants*
[c] *Retrospective study*
[d] *Testers not blinded to final diagnosis*

History of uveitis

Table 17: History of uveitis – evidence table

Study	Population	Risk of bias	N		Prevalence	Reference standard	Sensitivity & specificity	Predictive values	Likelihood ratios
			Cases	Non-cases					
AXIAL									
van Hoeven 2015	Diagnosis of axial SpA in people with chronic low back pain	Not serious	95	484	0.164 (0.136, 0.197)	ASAS criteria for axial	Sens.: 0.053 (0.022, 0.120) Spec.: 0.963 (0.942, 0.976)	PPV: 0.217 (0.093, 0.428) NPV: 0.838 (0.805, 0.866)	LR+: 1.415 (0.539, 3.719) LR-: 0.984 (0.935, 1.035)
PERIPHERAL									
no data									
MIXED AXIAL AND PERIPHERAL									
no data									

E.1.1.9 Inflammatory bowel disease

Table 18: Inflammatory bowel disease – evidence table

Study	Population	Risk of bias	N		Prevalence	Reference standard	Sensitivity & specificity	Predictive values	Likelihood ratios
			Cases	Non-cases					
AXIAL									
Dougados 2011 (DESIR)	Diagnosis of SpA in people with early inflammatory back pain	Not serious	475	233	0.671 (0.635, 0.705)	ASAS criteria for axial	Sens.: 0.042 (0.027, 0.064) Spec.: 0.957 (0.922, 0.977)	PPV: 0.667 (0.484, 0.810) NPV: 0.329 (0.295, 0.365)	LR+: 0.981 (0.467, 2.062) LR-: 1.001 (0.968, 1.035)
van den Berg 2013b (ASAS)	Diagnosis of axial SpA in people with undiagnosed chronic back pain	Not serious	421	264	0.615 (0.578, 0.650)	Rheumatologist diagnosis	Sens.: 0.033 (0.020, 0.055) Spec.: 0.985 (0.960, 0.994)	PPV: 0.778 (0.535, 0.914) NPV: 0.390 (0.353, 0.427)	LR+: 2.195 (0.730, 6.597) LR-: 0.982 (0.959, 1.005)
van den Berg 2013b (SPACE)	Diagnosis of axial SpA in people with back pain of between 3 months and 2 years	Not serious	65	92	0.414 (0.340, 0.493)	Rheumatologist diagnosis	Sens.: 0.062 (0.023, 0.153) Spec.: 0.946 (0.876, 0.977)	PPV: 0.444 (0.177, 0.749) NPV: 0.588 (0.507, 0.664)	LR+: 1.132 (0.316, 4.056) LR-: 0.992 (0.917, 1.074)
van Hoeven 2015	Diagnosis of axial SpA in people with chronic low back pain	Not serious	95	484	0.164 (0.136, 0.197)	ASAS criteria for axial	Sens.: 0.011 (0.001, 0.071) Spec.: 0.977 (0.959, 0.987)	PPV: 0.083 (0.012, 0.413) NPV: 0.834 (0.801, 0.863)	LR+: 0.463 (0.061, 3.545) LR-: 1.012 (0.988, 1.038)
PERIPHERAL									
no data									
MIXED AXIAL AND PERIPHERAL									
D'Agostino 2011	Diagnosis of SpA in people with suspected SpA	Not serious	51	48	0.515 (0.417, 0.612)	Rheumatologist diagnosis	Sens.: 0.078 (0.030, 0.191) Spec.: 0.979 (0.866, 0.997)	PPV: 0.800 (0.309, 0.973) NPV: 0.500 (0.400, 0.600)	LR+: 3.765 (0.436, 32.500) LR-: 0.941 (0.860, 1.030)
Liao 2009	Diagnosis of SpA among people with lower back pain	Serious[a]	92	695	0.117 (0.096, 0.141)	ESSG for diagnosing SpA, modified NY criteria for AS, CASPAR for PsA, ReA according to criteria from Kingsley and Sieper	Sens.: 0.005 (0.000, 0.080) Spec.: 0.998 (0.989, 1.000)	PPV: 0.250 (0.013, 0.891) NPV: 0.882 (0.858, 0.903)	LR+: 2.495 (0.102, 60.790) LR-: 0.997 (0.982, 1.012)
Tomero 2014	Diagnosis of SpA among people with suspected early SpA	Not serious	538	237	0.694 (0.661, 0.726)	Rheumatologist diagnosis	Sens.: 0.050 (0.035, 0.072) Spec.: 0.966 (0.934, 0.983)	PPV: 0.771 (0.605, 0.881) NPV: 0.309 (0.277, 0.344)	LR+: 1.487 (0.686, 3.224) LR-: 0.983 (0.953, 1.014)

[a] *Population not comprised of people with suspected SpA*

E.1.1.10 Dactylitis

Table 19: Dactylitis – evidence table

Study	Population	Risk of bias	N		Prevalence	Reference standard	Sensitivity & specificity	Predictive values	Likelihood ratios
			Cases	Non-cases					
AXIAL									
van den Berg 2013b (ASAS)	Diagnosis of axial SpA in people with undiagnosed chronic back pain	Not serious	421	264	0.615 (0.578, 0.650)	Rheumatologist diagnosis	Sens.: 0.067 (0.046, 0.095) Spec.: 0.981 (0.955, 0.992)	PPV: 0.848 (0.684, 0.935) NPV: 0.397 (0.360, 0.435)	LR+: 3.512 (1.373, 8.981) LR-: 0.952 (0.923, 0.981)
van den Berg 2013b (SPACE)	Diagnosis of axial SpA in people with back pain of between 3 months and 2 years	Not serious	65	92	0.414 (0.340, 0.493)	Rheumatologist diagnosis	Sens.: 0.062 (0.023, 0.153) Spec.: 0.978 (0.917, 0.995)	PPV: 0.667 (0.268, 0.916) NPV: 0.596 (0.516, 0.671)	LR+: 2.831 (0.534, 14.999) LR-: 0.959 (0.895, 1.028)
van Hoeven 2014	Diagnosis of axial SpA among people with chronic lower back pain	Not serious	86	278	0.236 (0.195, 0.283)	ASAS criteria for axial SpA, Modified NY criteria for AS	Sens.: 0.047 (0.018, 0.117) Spec.: 0.968 (0.939, 0.983)	PPV: 0.308 (0.120, 0.591) NPV: 0.766 (0.719, 0.808)	LR+: 1.437 (0.454, 4.550) LR-: 0.985 (0.936, 1.037)
van Hoeven 2015	Diagnosis of axial SpA in people with chronic low back pain	Not serious	95	484	0.164 (0.136, 0.197)	ASAS criteria for axial	Sens.: 0.053 (0.022, 0.120) Spec.: 0.971 (0.952, 0.983)	PPV: 0.263 (0.114, 0.498) NPV: 0.839 (0.806, 0.867)	LR+: 1.820 (0.671, 4.932) LR-: 0.976 (0.928, 1.025)
PERIPHERAL									
Sadek 2007	Diagnosis of PsA in people with Psoriasis	Not serious	59	22	0.728 (0.622, 0.814)	Clinician and 5 criteria sets	Sens.: 0.042 (0.012, 0.134) Spec.: 0.978 (0.732, 0.999)	PPV: 0.833 (0.194, 0.990) NPV: 0.281 (0.194, 0.389)	LR+: 1.917 (0.096, 38.423) LR-: 0.980 (0.904, 1.062)
You 2015	Diagnosis of PsA in people with Psoriasis	Serious[a]	18	130	0.122 (0.078, 0.185)	CASPAR	Sens.: 0.611 (0.379, 0.802) Spec.: 0.969 (0.921, 0.988)	PPV: 0.733 (0.467, 0.896) NPV: 0.947 (0.894, 0.975)	LR+: 19.861 (7.071, 55.787) LR-: 0.401 (0.225, 0.717)
MIXED AXIAL AND PERIPHERAL									
D'Agostino 2011	Diagnosis of SpA in people with suspected SpA	Not serious	51	48	0.515 (0.417, 0.612)	Rheumatologist diagnosis	Sens.: 0.087 (0.035, 0.199) Spec.: 0.990 (0.857, 0.999)	PPV: 0.900 (0.326, 0.994) NPV: 0.505 (0.406, 0.604)	LR+: 8.481 (0.469, 153.449) LR-: 0.923 (0.845, 1.008)
Tomero 2014	Diagnosis of SpA among people with suspected early SpA	Not serious	538	237	0.694 (0.661, 0.726)	Rheumatologist diagnosis	Sens.: 0.080 (0.060, 0.106) Spec.: 0.996 (0.971, 0.999)	PPV: 0.977 (0.856, 0.997) NPV: 0.323 (0.290, 0.358)	LR+: 18.942 (2.624, 136.746) LR-: 0.924 (0.900, 0.949)

[a] *Participants not consecutively recruited*

E.1.1.11 Arthritis

Arthritis / peripheral arthritis

Table 20: Arthritis / peripheral arthritis – evidence table

Study	Population	Risk of bias	N		Prevalence	Reference standard	Sensitivity & specificity	Predictive values	Likelihood ratios
			Cases	Non-cases					
AXIAL									
Dougados 2011 (DESIR)	Diagnosis of SpA in people with early inflammatory back pain	Not serious	475	233	0.671 (0.635, 0.705)	ASAS criteria for axial	Sens.: 0.549 (0.504, 0.594) Spec.: 0.391 (0.330, 0.455)	PPV: 0.648 (0.600, 0.693) NPV: 0.298 (0.250, 0.352)	LR+: 0.902 (0.791, 1.028) LR-: 1.154 (0.955, 1.393)
Hulsemann 1995	Diagnosis of AS in people with suspected inflammatory rheumatic diseases seen at an early synovitis clinic	Serious[a]	10	167	0.056 (0.031, 0.102)	Clinician diagnosis	Sens.: 0.700 (0.376, 0.900) Spec.: 0.509 (0.434, 0.584)	PPV: 0.079 (0.038, 0.156) NPV: 0.966 (0.900, 0.989)	LR+: 1.426 (0.924, 2.201) LR-: 0.589 (0.226, 1.537)
van den Berg 2013b (ASAS)	Diagnosis of axial SpA in people with undiagnosed chronic back pain	Not serious	421	264	0.615 (0.578, 0.650)	Rheumatologist diagnosis	Sens.: 0.169 (0.136, 0.207) Spec.: 0.777 (0.722, 0.823)	PPV: 0.546 (0.460, 0.630) NPV: 0.369 (0.330, 0.410)	LR+: 0.755 (0.554, 1.028) LR-: 1.071 (0.991, 1.157)
van den Berg 2013b (SPACE)	Diagnosis of axial SpA in people with back pain of between 3 months and 2 years	Not serious	65	92	0.414 (0.340, 0.493)	Rheumatologist diagnosis	Sens.: 0.200 (0.120, 0.315) Spec.: 0.891 (0.810, 0.941)	PPV: 0.565 (0.363, 0.748) NPV: 0.612 (0.527, 0.691)	LR+: 1.840 (0.860, 3.938) LR-: 0.898 (0.780, 1.033)
van Hoeven 2014	Diagnosis of axial SpA among people with chronic lower back pain	Not serious	86	278	0.236 (0.195, 0.283)	ASAS criteria for axial SpA, Modified NY criteria for AS	Sens.: 0.116 (0.064, 0.203) Spec.: 0.935 (0.900, 0.959)	PPV: 0.357 (0.204, 0.546) NPV: 0.774 (0.726, 0.815)	LR+: 1.796 (0.862, 3.742) LR-: 0.945 (0.870, 1.026)
van Hoeven 2015	Diagnosis of axial SpA in people with chronic low back pain	Not serious	95	484	0.164 (0.136, 0.197)	ASAS criteria for axial	Sens.: 0.137 (0.081, 0.222) Spec.: 0.870 (0.837, 0.897)	PPV: 0.171 (0.102, 0.273) NPV: 0.837 (0.802, 0.867)	LR+: 1.051 (0.603, 1.831) LR-: 0.992 (0.909, 1.083)
PERIPHERAL									
Mattila 1998	Diagnosis of ReA among people with suspected ReA following a Salmonella outbreak	Serious[b]	22	169	0.115 (0.077, 0.169)	Rheumatologist diagnosis	Sens.: 0.978 (0.732, 0.999) Spec.: 0.738 (0.667, 0.799)	PPV: 0.336 (0.233, 0.456) NPV: 0.996 (0.940, 1.000)	LR+: 3.737 (2.882, 4.845) LR-: 0.029 (0.002, 0.457)
MIXED AXIAL AND PERIPHERAL									
D'Agostino 2011	Diagnosis of SpA in people with suspected SpA	Not serious	51	48	0.515 (0.417, 0.612)	Rheumatologist diagnosis	Sens.: 0.314 (0.202, 0.452) Spec.: 0.750 (0.610, 0.852)	PPV: 0.571 (0.387, 0.738) NPV: 0.507 (0.392, 0.621)	LR+: 1.255 (0.664, 2.371) LR-: 0.915 (0.715, 1.172)
Tomero 2014	Diagnosis of SpA among people with suspected early SpA	Not serious	538	237	0.694 (0.661, 0.726)	Rheumatologist diagnosis	Sens.: 0.180 (0.150, 0.215) Spec.: 0.958 (0.923, 0.977)	PPV: 0.907 (0.835, 0.949) NPV: 0.340 (0.305, 0.377)	LR+: 4.273 (2.269, 8.045) LR-: 0.856 (0.816, 0.898)

[a] *Majority of people end as undifferentiated arthritis*
[b] *Some tests only performed in subset of participants*

Oligoarthritis (in people with symptoms of peripheral arthritis)

Table 21: Oligoarthritis (in people with symptoms of peripheral arthritis) – evidence table

Study	Population	Risk of bias	N		Prevalence	Reference standard	Sensitivity & specificity	Predictive values	Likelihood ratios
			Cases	Non-cases					
AXIAL									
no data									
PERIPHERAL									
Sadek 2007	Diagnosis of PsA in people with Psoriasis	Not serious	59	22	0.728 (0.622, 0.814)	Clinician and 5 criteria sets	Sens.: 0.192 (0.111, 0.311) Spec.: 0.978 (0.732, 0.999)	PPV: 0.958 (0.575, 0.997) NPV: 0.317 (0.220, 0.433)	LR+: 8.817 (0.541, 143.591) LR-: 0.826 (0.720, 0.948)
Tinazzi 2012	Diagnosis of PsA in people with Psoriasis	Serious[a]	71	147	0.326 (0.267, 0.391)	CASPAR	Sens.: 0.313 (0.216, 0.428) Spec.: 0.997 (0.948, 1.000)	PPV: 0.978 (0.732, 0.999) NPV: 0.749 (0.684, 0.804)	LR+: 92.500 (5.691, 1503.362) LR-: 0.690 (0.590, 0.806)
MIXED AXIAL AND PERIPHERAL									
no data									

[a] *Participants not consecutively recruited*

E.1.1.12 Nail disease

Table 22: Nail disease – evidence table

Study	Population	Risk of bias	N		Prevalence	Reference standard	Sensitivity & specificity	Predictive values	Likelihood ratios
			Cases	Non-cases					
AXIAL									
no data									
PERIPHERAL									
Haroon 2013	Diagnosis of PsA in people with Psoriasis	Not serious	29	71	0.290 (0.210, 0.386)	CASPAR	Sens.: 0.690 (0.503, 0.830) Spec.: 0.324 (0.226, 0.441)	PPV: 0.294 (0.198, 0.412) NPV: 0.719 (0.542, 0.847)	LR+: 1.020 (0.761, 1.367) LR-: 0.958 (0.506, 1.814)
Tinazzi 2012	Diagnosis of PsA in people with Psoriasis	Serious[a]	71	147	0.326 (0.267, 0.391)	CASPAR	Sens.: 0.577 (0.460, 0.686) Spec.: 0.558 (0.477, 0.636)	PPV: 0.387 (0.299, 0.483) NPV: 0.732 (0.643, 0.806)	LR+: 1.306 (0.998, 1.710) LR-: 0.757 (0.557, 1.030)
Wilson 2009	(Retrospective) onset of PsA in cohort of people with psoriasis	Serious[b,c]	57	1536	0.036 (0.028, 0.046)	CASPAR	Sens.: 0.421 (0.301, 0.552) Spec.: 0.870 (0.852, 0.886)	PPV: 0.107 (0.073, 0.155) NPV: 0.976 (0.966, 0.983)	LR+: 3.234 (2.323, 4.501) LR-: 0.666 (0.533, 0.831)
Yang 2011	Diagnosis of PsA in people with Psoriasis	Serious[a]	112	1397	0.074 (0.062, 0.089)	CASPAR	Sens.: 0.464 (0.374, 0.557) Spec.: 0.790 (0.767, 0.810)	PPV: 0.150 (0.116, 0.192) NPV: 0.948 (0.934, 0.960)	LR+: 2.206 (1.765, 2.758) LR-: 0.679 (0.570, 0.808)
You 2015	Diagnosis of PsA in people with Psoriasis	Serious[a]	18	130	0.122 (0.078, 0.185)	CASPAR	Sens.: 0.278 (0.121, 0.519) Spec.: 0.685 (0.600, 0.759)	PPV: 0.109 (0.046, 0.236) NPV: 0.873 (0.793, 0.925)	LR+: 0.881 (0.401, 1.934) LR-: 1.055 (0.774, 1.437)
MIXED AXIAL AND PERIPHERAL									
no data									

[a] *Participants not consecutively recruited*
[b] *Retrospective study*
[c] *Testers not blinded to final diagnosis*

E.1.1.13 Fatigue / malaise

Table 23: Fatigue / malaise – evidence table

Study	Population	Risk of bias	N		Prevalence	Reference standard	Sensitivity & specificity	Predictive values	Likelihood ratios
			Cases	Non-cases					
AXIAL									
no data									
PERIPHERAL									
Kvien 1996	Diagnostic classification in people with unexplained oligoarthritis	Not serious	46	92	0.333 (0.260, 0.416)	ReA: positive culture and/or positive antibody titre plus arthritis	Sens.: 0.543 (0.400, 0.680) Spec.: 0.457 (0.358, 0.559)	PPV: 0.333 (0.236, 0.447) NPV: 0.667 (0.542, 0.772)	LR+: 1.000 (0.723, 1.383) LR-: 1.000 (0.680, 1.471)
Mattila 1998	Diagnosis of ReA among people with suspected ReA following a Salmonella outbreak	Serious[a]	22	169	0.115 (0.077, 0.169)	Rheumatologist diagnosis	Sens.: 0.318 (0.160, 0.534) Spec.: 0.550 (0.475, 0.624)	PPV: 0.084 (0.041, 0.166) NPV: 0.861 (0.782, 0.915)	LR+: 0.708 (0.375, 1.334) LR-: 1.239 (0.903, 1.700)
MIXED AXIAL AND PERIPHERAL									
no data									

[a] *Some tests only performed in subset of participants*

E.1.1.14 Family history

Family history of spondyloarthritis

Table 24: Family history of spondyloarthritis – evidence table

Study	Population	Risk of bias	N		Prevalence	Reference standard	Sensitivity & specificity	Predictive values	Likelihood ratios
			Cases	Non-cases					
AXIAL									
Poddubnyy 2011	Diagnosis of axial SpA in people with low back pain	Not serious	89	153	0.368 (0.309, 0.430)	Rheumatologist diagnosis	Sens.: 0.236 (0.159, 0.335) Spec.: 0.837 (0.769, 0.887)	PPV: 0.457 (0.320, 0.600) NPV: 0.653 (0.584, 0.716)	LR+: 1.444 (0.860, 2.424) LR-: 0.913 (0.798, 1.045)
Sieper 2013	Diagnosis of axial SpA among people with chronic back pain	Not serious	372	509	0.422 (0.390, 0.455)	Rheumatologist diagnosis	Sens.: 0.129 (0.099, 0.167) Spec.: 0.912 (0.884, 0.933)	PPV: 0.516 (0.415, 0.616) NPV: 0.589 (0.554, 0.623)	LR+: 1.459 (0.994, 2.143) LR-: 0.955 (0.911, 1.002)
van den Berg 2013b (ASAS)	Diagnosis of axial SpA in people with undiagnosed chronic back pain	Not serious	421	264	0.615 (0.578, 0.650)	Rheumatologist diagnosis	Sens.: 0.252 (0.213, 0.295) Spec.: 0.803 (0.751, 0.847)	PPV: 0.671 (0.594, 0.740) NPV: 0.402 (0.361, 0.445)	LR+: 1.278 (0.953, 1.715) LR-: 0.932 (0.859, 1.011)
van den Berg 2013b (SPACE)	Diagnosis of axial SpA in people with back pain of between 3 months and 2 years	Not serious	65	92	0.414 (0.340, 0.493)	Rheumatologist diagnosis	Sens.: 0.477 (0.359, 0.597) Spec.: 0.728 (0.629, 0.809)	PPV: 0.554 (0.423, 0.677) NPV: 0.663 (0.566, 0.749)	LR+: 1.755 (1.153, 2.672) LR-: 0.718 (0.552, 0.935)
van Hoeven 2014	Diagnosis of axial SpA among people with chronic lower back pain	Not serious	86	278	0.236 (0.195, 0.283)	ASAS criteria for axial SpA, Modified NY criteria for AS	Sens.: 0.198 (0.127, 0.295) Spec.: 0.917 (0.879, 0.944)	PPV: 0.425 (0.283, 0.580) NPV: 0.787 (0.739, 0.828)	LR+: 2.389 (1.340, 4.260) LR-: 0.875 (0.783, 0.977)
van Hoeven 2015	Diagnosis of axial SpA in people with chronic low back pain	Not serious	95	484	0.164 (0.136, 0.197)	ASAS criteria for axial	Sens.: 0.253 (0.175, 0.349) Spec.: 0.884 (0.853, 0.910)	PPV: 0.300 (0.210, 0.409) NPV: 0.858 (0.824, 0.886)	LR+: 2.183 (1.428, 3.338) LR-: 0.845 (0.749, 0.954)
PERIPHERAL									
Rudwaleit 2011	Diagnosing peripheral SpA among people with peripheral manifestation	Not serious	176	90	0.662 (0.603, 0.716)	Rheumatologist diagnosis	Sens.: 0.205 (0.151, 0.271) Spec.: 0.922 (0.846, 0.962)	PPV: 0.837 (0.696, 0.920) NPV: 0.372 (0.311, 0.438)	LR+: 2.630 (1.219, 5.673) LR-: 0.863 (0.784, 0.949)
Tey 2010	Diagnosis of PsA in people with Psoriasis	Serious[a]	134	266	0.335 (0.290, 0.383)	Clinician diagnosis	Sens.: 0.067 (0.035, 0.124) Spec.: 0.996 (0.974, 0.999)	PPV: 0.900 (0.533, 0.986) NPV: 0.679 (0.632, 0.724)	LR+: 17.866 (2.287, 139.547) LR-: 0.936 (0.894, 0.980)
MIXED AXIAL AND PERIPHERAL									
D'Agostino 2011	Diagnosis of SpA in people with suspected SpA	Not serious	51	48	0.515 (0.417, 0.612)	Rheumatologist diagnosis	Sens.: 0.353 (0.235, 0.492) Spec.: 0.896 (0.773, 0.956)	PPV: 0.783 (0.572, 0.907) NPV: 0.566 (0.453, 0.672)	LR+: 3.388 (1.365, 8.409) LR-: 0.722 (0.577, 0.904)

Study	Population	Risk of bias	N		Prevalence	Reference standard	Sensitivity & specificity	Predictive values	Likelihood ratios
			Cases	Non-cases					
Liao 2009	Diagnosis of SpA among people with lower back pain	Serious[b]	92	695	0.117 (0.096, 0.141)	ESSG for diagnosing SpA, modified NY criteria for AS, CASPAR for PsA, ReA according to criteria from Kingsley and Sieper	Sens.: 0.027 (0.008, 0.088) Spec.: 0.999 (0.989, 1.000)	PPV: 0.833 (0.194, 0.990) NPV: 0.885 (0.861, 0.905)	LR+: 37.419 (1.810, 773.427) LR-: 0.974 (0.941, 1.007)
Salvarini 2001	Diagnosis of SpA in people with inflammatory bowel disease	Serious[c]	29	131	0.181 (0.129, 0.249)	ESSG criteria	Sens.: 0.172 (0.074, 0.353) Spec.: 0.870 (0.801, 0.918)	PPV: 0.227 (0.098, 0.444) NPV: 0.826 (0.754, 0.881)	LR+: 1.329 (0.534, 3.309) LR-: 0.951 (0.795, 1.137)
Tomero 2014	Diagnosis of SpA among people with suspected early SpA	Not serious	538	237	0.694 (0.661, 0.726)	Rheumatologist diagnosis	Sens.: 0.309 (0.271, 0.349) Spec.: 0.814 (0.760, 0.859)	PPV: 0.790 (0.730, 0.840) NPV: 0.342 (0.304, 0.382)	LR+: 1.662 (1.237, 2.233) LR-: 0.849 (0.781, 0.923)

[a] *Retrospective study*
[b] *Population not comprised of people with suspected SpA*
[c] *Some tests only performed in subset of participants*

Family history of psoriasis

Table 25: Family history of psoriasis – evidence table

Study	Population	Risk of bias	N		Prevalence	Reference standard	Sensitivity & specificity	Predictive values	Likelihood ratios
			Cases	Non-cases					
AXIAL									
no data									
PERIPHERAL									
Tey 2010	Diagnosis of PsA in people with Psoriasis	Serious[a]	134	266	0.335 (0.290, 0.383)	Clinician diagnosis	Sens.: 0.231 (0.168, 0.310) Spec.: 0.838 (0.789, 0.878)	PPV: 0.419 (0.312, 0.534) NPV: 0.684 (0.632, 0.732)	LR+: 1.431 (0.947, 2.162) LR-: 0.917 (0.824, 1.020)
Yang 2011	Diagnosis of PsA in people with Psoriasis	Serious[b]	112	1397	0.074 (0.062, 0.089)	CASPAR	Sens.: 0.313 (0.234, 0.404) Spec.: 0.759 (0.736, 0.780)	PPV: 0.094 (0.068, 0.128) NPV: 0.932 (0.916, 0.946)	LR+: 1.295 (0.969, 1.731) LR-: 0.906 (0.797, 1.030)
MIXED AXIAL AND PERIPHERAL									
no data									

[a] *Retrospective study*
[b] *Participants not consecutively recruited*

E.1.1.15 Preceding infection

Table 26: Preceding infection – evidence table

Study	Population	Risk of bias	N		Prevalence	Reference standard	Sensitivity & specificity	Predictive values	Likelihood ratios
			Cases	Non-cases					
AXIAL									
van den Berg 2013b (ASAS)	Diagnosis of axial SpA in people with undiagnosed chronic back pain	Not serious	421	264	0.615 (0.578, 0.650)	Rheumatologist diagnosis	Sens.: 0.029 (0.016, 0.050) Spec.: 0.981 (0.955, 0.992)	PPV: 0.706 (0.458, 0.872) NPV: 0.388 (0.351, 0.425)	LR+: 1.505 (0.536, 4.223) LR-: 0.990 (0.967, 1.014)
van den Berg 2013b (SPACE)	Diagnosis of axial SpA in people with back pain of between 3 months and 2 years	Not serious	65	92	0.414 (0.340, 0.493)	Rheumatologist diagnosis	Sens.: 0.038 (0.011, 0.122) Spec.: 0.995 (0.920, 1.000)	PPV: 0.833 (0.194, 0.990) NPV: 0.593 (0.514, 0.667)	LR+: 7.045 (0.344, 144.361) LR-: 0.967 (0.920, 1.017)
PERIPHERAL									
Kvien 1994	Diagnosis of ReA in people with suspected ReA	Not serious	52	320	0.140 (0.108, 0.179)	Investigator defined criteria	Sens.: 0.654 (0.516, 0.770) Spec.: 0.897 (0.858, 0.926)	PPV: 0.507 (0.390, 0.625) NPV: 0.941 (0.908, 0.963)	LR+: 6.340 (4.341, 9.261) LR-: 0.386 (0.265, 0.562)
Rudwaleit 2011	Diagnosing peripheral SpA among people with peripheral manifestation	Not serious	176	90	0.662 (0.603, 0.716)	Rheumatologist diagnosis	Sens.: 0.057 (0.031, 0.102) Spec.: 0.967 (0.902, 0.989)	PPV: 0.769 (0.478, 0.924) NPV: 0.344 (0.288, 0.405)	LR+: 1.705 (0.481, 6.039) LR-: 0.976 (0.926, 1.029)
MIXED AXIAL AND PERIPHERAL									
Granfors 1983	Diagnosis of SpA and measurement of Yersinia antibodies in people with recent inflammatory joint disease	Not serious	62	292	0.175 (0.139, 0.218)	Clinician diagnosis	Sens.: 0.194 (0.113, 0.311) Spec.: 0.932 (0.896, 0.955)	PPV: 0.375 (0.227, 0.551) NPV: 0.845 (0.801, 0.880)	LR+: 2.826 (1.459, 5.473) LR-: 0.866 (0.763, 0.982)
Hulsemann 1995	Diagnosis of SpA in people with suspected inflammatory rheumatic diseases seen at an early synovitis clinic	Serious[a]	41	167	0.197 (0.149, 0.257)	Clinician diagnosis	Sens.: 0.244 (0.137, 0.397) Spec.: 0.814 (0.748, 0.866)	PPV: 0.244 (0.137, 0.397) NPV: 0.814 (0.748, 0.866)	LR+: 1.314 (0.703, 2.456) LR-: 0.928 (0.769, 1.121)
Tomero 2014	Diagnosis of SpA among people with suspected early SpA	Not serious	538	237	0.694 (0.661, 0.726)	Rheumatologist diagnosis	Sens.: 0.019 (0.011, 0.035) Spec.: 0.998 (0.967, 1.000)	PPV: 0.955 (0.552, 0.997) NPV: 0.310 (0.278, 0.344)	LR+: 9.273 (0.546, 157.592) LR-: 0.983 (0.970, 0.996)

[a] *Majority of people end as undifferentiated arthritis*

E.1.2 Indicators for referral

Review Question 12

- What are the indications (signs, risk factors, test or scan findings) for referral for specialist advice at initial diagnosis?

Table 27: Braun et al., 2011

Paper title	Braun, A., Saracbasi, E., Grifka, J., Schnitker, J., Braun, J., Identifying patients with axial spondyloarthritis in primary care: how useful are items indicative of inflammatory back pain?, Annals of the Rheumatic Diseases, 70, 1782-1787, 2011
Population	People aged under 45 with back pain of at least 2 months duration
Setting	Initial presentation to orthopaedic surgeons, referral to rheumatologists. Study conducted in Germany
Referral strategy	Eligible participants were stratified on the following criteria and a randomised selection were referred onwards: Morning stiffness >30 mins Improvement by movement not rest Waking up in the second half of the night because of back pain Improvement with NSAIDs within 48 hours
N participants	1074 people were approached; 950 were available for analysis; 670 were referred to a rheumatologist of whom 334 attended and 322 had complete data for final analysis. 113 were diagnosed as having SpA and 209 were classified as non-SpA.
Sensitivity (%)	Number of criteria met: ≥2: 96.5 ≥3: 78.8 ≥4: 47.8
Specificity (%)	Number of criteria met: ≥2: 17.0 ≥3: 46.4 ≥4: 86.1
Positive likelihood ratio	Number of criteria met: ≥2: 1.16 ≥3: 1.47

Paper title	Braun, A., Saracbasi, E., Grifka, J., Schnitker, J., Braun, J., Identifying patients with axial spondyloarthritis in primary care: how useful are items indicative of inflammatory back pain?, Annals of the Rheumatic Diseases, 70, 1782-1787, 2011
	≥4: 3.44
Negative likelihood ratio	Number of criteria met: ≥2: 0.21 ≥3: 0.46 ≥4: 0.61
Positive predictive value (%)	Number of criteria met: ≥2: 38.6 ≥3: 44.3 ≥4: 65.0
Negative predictive value (%)	Number of criteria met: ≥2: 89.9 ≥3: 80.2 ≥4: 75.3

Table 28: Braun et al., 2013

Paper title	Braun, A., Gnann, H., Saracbasi, E., Grifka, J., Kiltz, U., Letschert, K., Braun, J., Optimizing the identification of patients with axial spondyloarthritis in primary care – the case for a two-step strategy combining the most relevant clinical items with HLA B27., Rheumatology, 52, 1418-1424, 2013
Population	People aged under 45 with back pain of at least 2 months duration
Setting	Initial presentation to orthopaedic surgeons, referral to rheumatologists. Study conducted in Germany
Referral strategy	Three different strategies were validated: Strategy 1: Buttock pain and HLA-B27 positive Strategy 2: • age at onset of chronic BP ≤35 years • waking during the second half of the night • buttock pain

Paper title	Braun, A., Gnann, H., Saracbasi, E., Grifka, J., Kiltz, U., Letschert, K., Braun, J., Optimizing the identification of patients with axial spondyloarthritis in primary care – the case for a two-step strategy combining the most relevant clinical items with HLA B27., Rheumatology, 52, 1418-1424, 2013
	• improvement by movement • improvement by NSAIDs within 48 h or no NSAIDs • first-grade relatives with AS • history of arthritis • history of enthesitis • history of psoriasis • HLA-B27 positive Strategy 3: HLA-B27 positive plus any two of • Improvement by movement • Buttock pain (both sides) • History of psoriasis
N participants	1074 people were approached; 950 were available for analysis; 670 were referred to a rheumatologist of whom 334 attended and 322 had complete data for final analysis. 113 were diagnosed as having SpA and 209 were classified as non-SpA.
Strategy 1	
Sensitivity (%)	Number of criteria met: 0: 100 ≥1: 89.7 ≥2: 45.8
Specificity (%)	Number of criteria met: 0: 0.0 ≥1: 40.3 ≥2: 93.7
Positive likelihood ratio	Number of criteria met: 0: 1.00 ≥1: 1.50 ≥2: 7.29

Paper title	Braun, A., Gnann, H., Saracbasi, E., Grifka, J., Kiltz, U., Letschert, K., Braun, J., Optimizing the identification of patients with axial spondyloarthritis in primary care – the case for a two-step strategy combining the most relevant clinical items with HLA B27., Rheumatology, 52, 1418-1424, 2013
Negative likelihood ratio	Number of criteria met: 0: N/A ≥1: 0.26 ≥2: 0.58
Strategy 2	
Sensitivity (%)	Number of criteria met: 0: 100 ≥1: 99.1 ≥2: 97.2 ≥3: 93.5 ≥4: 86.0 ≥5: 53.3 ≥6: 23.4 ≥7: 4.7 ≥8: 0.0 ≥9: 0.0 ≥10: 0.0
Specificity (%)	Number of criteria met: 0: 0.0 ≥1: 2.6 ≥2: 7.3 ≥3: 26.7 ≥4: 63.4 ≥5: 95.3 ≥6: 99.5 ≥7: 99.5 ≥8: 100 ≥9: 100 ≥10: 100
Positive likelihood ratio	Number of criteria met: 0: 1.00

Paper title	Braun, A., Gnann, H., Saracbasi, E., Grifka, J., Kiltz, U., Letschert, K., Braun, J., Optimizing the identification of patients with axial spondyloarthritis in primary care – the case for a two-step strategy combining the most relevant clinical items with HLA B27., Rheumatology, 52, 1418-1424, 2013
	≥1: 1.02 ≥2: 1.05 ≥3: 1.28 ≥4: 2.35 ≥5: 11.31 ≥6: 44.63 ≥7: 8.93 ≥8: n/a ≥9: n/a ≥10: n/a
Negative likelihood ratio	Number of criteria met: 0: n/a ≥1: 0.36 ≥2: 0.38 ≥3: 0.25 ≥4: 0.22 ≥5: 0.49 ≥6: 0.77 ≥7: 0.96 ≥8: 1.00 ≥9: 1.00 ≥10: 1.00
Strategy 3	
Sensitivity (%)	80.4%
Specificity (%)	75.4%
Positive likelihood ratio	3.27
Negative likelihood ratio	0.26

Table 29: van Hoeven et al., 2015 (CaFaSpA referral rule)

Paper title	van Hoeven, L., Vergouwe, Y., de Buck, P.D.M., Luime, J.J., Hazes, J.M.W., Weel, A.E.A. M., External validation of a referral rule for axial spondyloarthritis in primary care patients with chronic low back pain., PLOS ONE, 10, e0131963, 2015
Population	People aged 18-45 with chronic low back pain of at least three months, with onset of back pain before the age of 45 years
Setting	Dutch primary care practices
Referral strategy	Referral criteria are met when any 2 of the 4 criteria below are positive: Inflammatory back pain* (scores 0 or 1) Good response to NSAIDs (scores 0 or 1) Family history of spondyloarthritis (scores 0 or 1) Back pain duration longer than 5 years (scores 0 or 0.5) *ASAS criteria were used in this study
N participants	Validation cohort: 579 participants of whom 95 received diagnosis of axial spondyloarthritis according to ASAS diagnostic criteria (Rudwaleit 2009)
Sensitivity (%)	Total score according to referral rule: ≥1.0: 92.3 ≥1.5: 74.6 ≥2.0: 40.9 ≥2.5: 28.7
Specificity (%)	Total score according to referral rule: ≥1.0: 39.1 ≥1.5: 57.6 ≥2.0: 82.4 ≥2.5: 88.3
Positive likelihood ratio	Total score according to referral rule: ≥1.0: 1.52 ≥1.5: 1.76 ≥2.0: 2.32 ≥2.5: 2.45
Negative likelihood ratio	Total score according to referral rule: ≥1.0: 0.20

Paper title	van Hoeven, L., Vergouwe, Y., de Buck, P.D.M., Luime, J.J., Hazes, J.M.W., Weel, A.E.A. M., External validation of a referral rule for axial spondyloarthritis in primary care patients with chronic low back pain., PLOS ONE, 10, e0131963, 2015
	≥1.5: 0.44 ≥2.0: 0.72 ≥2.5: 0.81
Positive predictive value (%)	Total score according to referral rule: ≥1.0: 22.9 ≥1.5: 25.7 ≥2.0: 31.3 ≥2.5: 32.4
Negative predictive value (%)	Total score according to referral rule: ≥1.0: 96.3 ≥1.5: 92.0 ≥2.0: 87.7 ≥2.5: 86.3

Table 30: van Hoeven et al., 2015b (ASAS referral rule validated in CaFaSpA cohort)

Paper title	van Hoeven, L., Koes, B.W., Hazes, J.M.W., Weel, A.E.A.M, External validation of a referral rule for axial spondyloarthritis in primary care patients with chronic low back pain, Annals of the Rheumatic Diseases, 74, e68-69, 2015.
Population	People aged 18-45 with chronic low back pain of at least three months, with onset of back pain before the age of 45 years
Setting	Dutch primary care practices
Referral strategy	Referral criteria are met when any 2 of the 4 criteria below are positive: Inflammatory back pain* (scores 0 or 1) Good response to NSAIDs (scores 0 or 1) Family history of spondyloarthritis (scores 0 or 1) Back pain duration longer than 5 years (scores 0 or 0.5) *ASAS criteria were used in this study
N participants	Validation cohort: 579 participants of whom 95 received diagnosis of axial spondyloarthritis according to ASAS diagnostic criteria (Rudwaleit 2009)

Paper title	van Hoeven, L., Koes, B.W., Hazes, J.M.W., Weel, A.E.A.M, External validation of a referral rule for axial spondyloarthritis in primary care patients with chronic low back pain, Annals of the Rheumatic Diseases, 74, e68-69, 2015.
Sensitivity (%)	Total score according to referral rule: ≥1.0: 92.3 ≥1.5: 74.6 ≥2.0: 40.9 ≥2.5: 28.7
Specificity (%)	Total score according to referral rule: ≥1.0: 39.1 ≥1.5: 57.6 ≥2.0: 82.4 ≥2.5: 88.3
Positive likelihood ratio	Total score according to referral rule: ≥1.0: 1.52 ≥1.5: 1.76 ≥2.0: 2.32 ≥2.5: 2.45
Negative likelihood ratio	Total score according to referral rule: ≥1.0: 0.20 ≥1.5: 0.44 ≥2.0: 0.72 ≥2.5: 0.81
Positive predictive value (%)	Total score according to referral rule: ≥1.0: 22.9 ≥1.5: 25.7 ≥2.0: 31.3 ≥2.5: 32.4
Negative predictive value (%)	Total score according to referral rule: ≥1.0: 96.3 ≥1.5: 92.0 ≥2.0: 87.7 ≥2.5: 86.3

E.1.3 Comparative effectiveness of referral strategies

Review Question 6

- What is the comparative effectiveness of different referral strategies in diagnosing spondyloarthritis?

Table 31: Poddubnyy 2011

	Poddubnyy, D., Vahldiek, J., Spiller, I., Buss, B., Listing, J., Rudwaleit, M., Sieper, J., Evaluation of 2 screening strategies for early identification of patients with axial spondyloarthritis in primary care, Journal of Rheumatology, 38, 2452-60, 2011
Population	People with suspected axial spondyloarthritis, with chronic back pain of at least 3 months duration, aged under 45 at time of onset.
Setting	Multicentre study in Germany. 43 participating rheumatologists designated 1035 referring physicians (orthopaedists and general practitioners). Each referring physician was randomised to a referral strategy.
Referral strategy 1	At least one of the following 3 criteria • inflammatory back pain • HLA-B27 positivity • sacroiliitis detected by imaging (any imaging technique)
Referral strategy 2	Strategy 2: At least two of the following 5 criteria • inflammatory back pain • HLA-B27 positivity • sacroiliitis detected by imaging (any imaging technique) • positive family history for AS • good response to NSAIDs
N participants	Referral strategy 1: 318 of whom 133 were diagnosed with axial SpA, 43 received diagnosis of 'possible SpA' and 142 were determined not to have SpA. Referral strategy 2: 242 of whom 89 were diagnosed with axial SpA, 38 received diagnosis of 'possible SpA' and 115 were determined not to have SpA.
Percentage of referrals correctly diagnosed as spondyloarthritis	Strategy 1: Axial SpA: 41.8% Ankylosing spondylitis: 25.8% Non-radiographic SpA: 16.0% Possible axial SpA: 13.5%

	Poddubnyy, D., Vahldiek, J., Spiller, I., Buss, B., Listing, J., Rudwaleit, M., Sieper, J., Evaluation of 2 screening strategies for early identification of patients with axial spondyloarthritis in primary care, Journal of Rheumatology, 38, 2452-60, 2011
	No SpA: 44.7% Strategy 2: Axial SpA: 36.8% Ankylosing spondylitis: 22.7% Non-radiographic SpA: 14.1% Possible axial SpA: 15.7% No axial SpA: 47.5%
Time taken from symptoms to diagnosis (not time from referral)	Not reported
Resource use and costs	No economic evidence was presented.
Health-related quality of life	No quality of life evidence was presented.
Improvement in disease-specific outcomes	Not reported
Reduced long term complications and/or skeletal damage	Not reported

Table 32: Sieper 2013

Paper title	**Sieper, J., Srinivasan, S., Zamani, O., Mielants, H., Choquette, D., Pavelka, K., Loft, A.G., Géher, P., Danda, D., Reitblat, T., Cantini, F., Ancuta, C., Erdes, S., Raffayová, H., Keat, A., Gaston, J.S., Praprotnik, S., Vastesaeger, N., Comparison of two referral strategies for diagnosis of axial spondyloarthritis: the Recognising and Diagnosing Ankylosing Spondylitis Reliably (RADAR) study, Annals of the Rheumatic Diseases, 72, 1621-1627, 2013**
Population	People with suspected axial spondyloarthritis, with chronic back pain of at least 3 months duration, aged under 45 at time of onset.
Setting	Multinational multicentre study in which local primary care doctors were selected by the lead rheumatologist. Each local site was randomised in a 1:1 ratio to the participating rheumatologist for diagnosis.
Referral strategy 1	Presence of any of the following three criteria: Inflammatory back pain (IBP)* positive HLA-B27 sacroiliitis demonstrated by imaging

Paper title	Sieper, J., Srinivasan, S., Zamani, O., Mielants, H., Choquette, D., Pavelka, K., Loft, A.G., Géher, P., Danda, D., Reitblat, T., Cantini, F., Ancuta, C., Erdes, S., Raffayová, H., Keat, A., Gaston, J.S., Praprotnik, S., Vastesaeger, N., Comparison of two referral strategies for diagnosis of axial spondyloarthritis: the Recognising and Diagnosing Ankylosing Spondylitis Reliably (RADAR) study, Annals of the Rheumatic Diseases, 72, 1621-1627, 2013
	*The presence of IBP was determined by referring physician opinion.
Referral strategy 2	Presence of at least two of the following six criteria: • IBP* • HLA-B27 • sacroiliitis on imaging • family history of axial SpA • good response of back pain to non-steroidal anti-inflammatory drugs (NSAIDs) • known extra-articular manifestations (EAMs) (i.e., uveitis, iridocyclitis, psoriasis or inflammatory bowel disease). *The presence of IBP was determined by referring physician opinion.
N participants	Referral strategy 1: 504 of whom 10 withdrew, 176 were diagnosed with axial SpA, 39 received diagnosis of 'possible SpA' and 279 were determined not to have axial SpA. Referral strategy 2: 568 of whom 13 withdrew, 221 were diagnosed with axial SpA, 42 received diagnosis of 'possible SpA' and 292 were determined not to have axial SpA.
Percentage of referrals correctly diagnosed as spondyloarthritis	Strategy 1: Axial SpA: 35.6% Radiographic SpA: 27.3% Non-radiographic SpA: 8.3% Possible axial SpA: 7.9% No axial SpA: 56.5% Strategy 2: Axial SpA: 39.8% Radiographic SpA: 31.0% Non-radiographic SpA: 8.8% Possible axial SpA: 7.6% No axial SpA: 52.6%

Paper title	Sieper, J., Srinivasan, S., Zamani, O., Mielants, H., Choquette, D., Pavelka, K., Loft, A.G., Géher, P., Danda, D., Reitblat, T., Cantini, F., Ancuta, C., Erdes, S., Raffayová, H., Keat, A., Gaston, J.S., Praprotnik, S., Vastesaeger, N., Comparison of two referral strategies for diagnosis of axial spondyloarthritis: the Recognising and Diagnosing Ankylosing Spondylitis Reliably (RADAR) study, Annals of the Rheumatic Diseases, 72, 1621-1627, 2013
Time taken from symptoms to diagnosis (not time from referral)	Not reported
Resource use and costs	No economic evidence was presented.
Health-related quality of life	No quality of life evidence was presented.
Improvement in disease-specific outcomes	Not reported
Reduced long term complications and/or skeletal damage	Not reported

E.1.4 Obstacles to prompt diagnosis

Review Question 3

- What are the obstacles to a prompt diagnosis of spondyloarthritis?

Table 33: Aggarwal et al., 2009

Bibliographic reference	Aggarwal,R., Malaviya,A.N., 20090430, Diagnosis delay in patients with ankylosing spondylitis: factors and outcomes--an Indian perspective, Clinical Rheumatology 28, 327-331, 2009
Country/ies where the study was carried out	USA
Study type	Cross sectional survey
Aim of the study	To identify the factors that lead to a delay in diagnosis
Study dates	Not reported
Source of funding	Not reported
Sample size	N=70
Inclusion criteria	Inclusion; AS diagnosed by modified New York criteria
Details	Consecutively diagnosed patients at a rheumatology clinic in New Delhi Baseline; • male 84.3% (N=59) • age at symptom onset 23.6±8.8yrs • age at diagnosis 32.5±9.7yrs • duration of symptoms 9.3±6.5yrs
Interventions	Investigator administered questionnaire
Results	Diagnosis delay defined as the interval between a patient's first spondyloarthritic symptom and a correct diagnosis of AS Results

Bibliographic reference	**Aggarwal,R., Malaviya,A.N., 20090430, Diagnosis delay in patients with ankylosing spondylitis: factors and outcomes--an Indian perspective, Clinical Rheumatology 28, 327-331, 2009**

Delay in diagnosis by clinical characteristics

Clinical feature	Number of patients	Delay, mean years (SD)	P value
male	59/70	6.5 (4.7)	
female	11/70	8.6 (6.6)	0.23
HLA B27 (+ve)	64/68	6.9 (5.1)	
HLA B27 (-ve)	4/68	6.6 (5.4)	0.90
peripheral joint involvement	46/64	6.8 (4.3)	
no peripheral joint involvement	18/64	6.4 (6.1)	0.80
inflammatory back pain	48/70	7.3 (5.2)	
no inflammatory back pain	22/70	5.9 (4.6)	0.30
family history	36/68	7.1 (5.9)	
no family history	32/68	6.6 (3.8)	0.68
adult onset (>16yrs)	55/70	6.1 (4.5)	
juvenile onset (<16yrs)	15/70	9.1 (5.3)	0.03
extra-articular	23/70	8.7 (6.0)	
no extra-articular	47/70	5.9 (4.2)	0.03

Prior to referral to rheumatology clinic;
N=41, 58.5% had correct diagnosis of AS
Incorrect diagnoses;
101 wrong diagnoses in N=54/70, 77% who were subsequently diagnosed with AS
non-specific back pain in N=19/54, 35.1%
degenerative disc disease in N=14/54, 25.9%
RA in N=11/54, 20.4%
spinal TB in N=9/54, 16.6%

Table 34: Dincer et al., 2008a

Bibliographic reference	Dincer,U., Cakar,E., Kiralp,M.Z., Dursun,H., 20080617, Diagnosis delay in patients with ankylosing spondylitis: possible reasons and proposals for new diagnostic criteria, Clinical Rheumatology, 27, 457-462, 2008
Country/ies where the study was carried out	Turkey
Study type	Mixed methods
Aim of the study	To investigate diagnostic delay and possible reasons in ankylosing spondylitis
Study dates	Not reported
Source of funding	Not reported
Sample size	N=111
Inclusion criteria	Inclusion: diagnosis of AS by modified New York criteria
Exclusion criteria	None
Details	Baseline; average age at disease onset, mean, SD, 23.18±9.59 mean age, male 32.49±11.15, female 47.63±13.90 male, N=103 (92.7%) peripheral joint involvement, N=29 first symptom, back pain (N=49), hip pain (N=31), heel pain (N=9), knee pain (N=7), wrist pain (N=9), uveitis (N=3), diarrhoea (N=3)
Interventions	Face-to-face interview of medical history and clinical knowledge using questionnaire Measured anterior spinal flexion and lateral spinal flexion
Results	Diagnostic delay; the gap between first spondiloarthritic symptom (inflammatory back pain, hip pain, knee pain, heel pain, decreased chest expansion, peripheral arthritis, uveitis) and correct diagnosis of AS

Clinical feature	Number of participants	Average diagnostic delay, yrs (SD)	P value

Bibliographic reference	Dincer,U., Cakar,E., Kiralp,M.Z., Dursun,H., 20080617, Diagnosis delay in patients with ankylosing spondylitis: possible reasons and proposals for new diagnostic criteria, Clinical Rheumatology, 27, 457-462, 2008			
	male	103	5.32±5.69	0.061
	female	8	14.42±14.24	
	HLA B27 (-ve)	20	9.20±2.40	0.037
	HLA B27 (+ve)	61	5.33±5.50	
	peripheral joint involvement	29	4.78±6.80	0.291
	no peripheral joint involvement	82	6.55±6.80	
	inflammatory back pain at onset	42	3.28±3.32	0.001
	no inflammatory back pain at onset	46	8.57±8.54	
	seronegative SpA in first degree relative	16	4.60±4.44	0.003
	no seronegative SpA in first degree relative	88	10.00±2.30	
	onset ≤16 yrs	14	8.89±8.78	0.027
	onset >16yrs	97	5.51±6.63	
	morning stiffness at onset	36	7.29±8.51	0.174
	no morning stiffness at onset	50	5.16±5.90	
	radiologic sacroiliitis at onset	46	6.63±8.23	0.407
	no radiologic sacroiliitis at onset	24	5.53±5.61	

Table 35: Hajialilo et al., 2014a

Bibliographic reference	Hajialilo,M., Ghorbanihaghjo,A., Khabbazi,A., Kolahi,S., Rashtchizadeh,N., 20140609, Ankylosing spondylitis in Iran; late diagnosis and its causes, Iranian Red Crescent Medical Journal, 16, e11798-, 2014
Country/ies where the study was carried out	Iran
Study type	Cross-sectional survey

Bibliographic reference	**Hajialilo,M., Ghorbanihaghjo,A., Khabbazi,A., Kolahi,S., Rashtchizadeh,N., 20140609, Ankylosing spondylitis in Iran; late diagnosis and its causes, Iranian Red Crescent Medical Journal, 16, e11798-, 2014**
Aim of the study	To evaluate and identify factors leading to a delayed diagnosis of AS in Iranian patients
Study dates	Not reported
Source of funding	Not reported
Sample size	N=60
Inclusion criteria	Participants selected from rheumatology clinics Inclusion; AS diagnosed using modified New York criteria
Exclusion criteria	None
Details	Diagnosis delay defined as the interval between first spondyloarthritic symptoms (IBP, inflammatory arthritis, enthesopathy, uveitis) Baseline; female, 11.7% mean age at time of diagnosis, mean, SD, 36.4±4.5, diagnosis delay 6.2±3.5
Interventions	Questions about aspects of the condition
Results	Comparison of diagnosis delay and clinical manifestations

clinical feature	N (%)	mean diagnosis delay (±SD)	P value
IBP	39 (65)	4.81.9	0.001
no IBP	21 (35)	8.7±4.4	
buttock pain	30 (50)	5.3±3.8	0.07
no buttock pain	30 (50)	7.0±3.1	

Bibliographic reference	Hajialilo,M., Ghorbanihaghjo,A., Khabbazi,A., Kolahi,S., Rashtchizadeh,N., 20140609, Ankylosing spondylitis in Iran; late diagnosis and its causes, Iranian Red Crescent Medical Journal, 16, e11798-, 2014

peripheral arthritis involvement	10 (16.7)	11.3±1.8	0.0001
no peripheral arthritis involvement	50 (83.3)	5.1±2.8	
morning stiffness	43 (71.7)	4.6±2.2	0.0001
no morning stiffness	17 (28.3)	10.1±3.2	
anterior uveitis	4 (6.7)	2.4±0.3	0.02
no anterior uveitis	56 (93.3)	6.4±3.5	
heel pain	2 (3.3)	13.0±0.0	0.004
no heel pain	58 (96.7)	5.9±3.4	
female	7 (11.7)	8.0±4.7	0.14
male	53 (88.3)	5.9±3.3	
family history	18 (30)	6.5±3.4	0.64
no family history	42 (70)	6.0±3.6	

Comparison of diagnosis delay and HLA-B27, ESR, CRP

	N (%)	mean diagnosis delay (±SD)	P value
HLA-B27 positive	43	4.6±2.2	0.0001
HLA-B27 negative	17	10.1±3.2	
ESR >30mm/hr	34	4.8±2.7	0.0001
ESR <30mm/hr	26	7.9±3.8	
CRP >6 mg/L	45	5.6±3.3	0.036
CRP <6 mg/L	15	7.8±3.7	

Table 36: Jois et al., 2008

Bibliographic reference	Jois,R.N., Macgregor,A.J., Gaffney,K., 20081014, Recognition of inflammatory back pain and ankylosing spondylitis in primary care, Rheumatology, 47, 1364-1366, 2008
Country/ies where the study was carried out	UK
Study type	Postal survey
Aim of the study	To assess current practice in terms of the way in which GPs use clinical, radiological, and lab investigations to assess patients with inflammatory back pain
Study dates	Not reported
Source of funding	Wyeth Pharmaceuticals funded the research post
Sample size	N=300 questionnaires sent, N=186 (62%) response rate
Inclusion criteria	Inclusion; urban and rural GPs in Norfolk
Exclusion criteria	None
Interventions	Questionnaire; designed to test ability to identify symptoms of IBP in patients <40years presenting with low back pain enquired whether GPs considered other known features of SpA approach to initial management
Results	Proportion of GPs who identified individual symptoms of IBP and associated SpA features

symptoms of IBP	% (from N=186)
morning stiffness >30min	90
insidious onset	80
pain relieved by NSAID	75
symptom duration >3mths	73

Bibliographic reference	Jois,R.N., Macgregor,A.J., Gaffney,K., 20081014, Recognition of inflammatory back pain and ankylosing spondylitis in primary care, Rheumatology, 47, 1364-1366, 2008

nocturnal pain	67
pain improved with exercise	50
pain not relieved by rest	45
alternating buttock pain	13

associated SpA symptoms	% (from N=186)
psoriasis	96
IBD	68
uveitis	60
GU/GI infection in the last month	41
enthesitis	17
dactylitis	17

Free-text responses;
22% felt diagnosis to be the main unmet need
16% felt education (patient and doctor) to be the main unmet need
9% felt that delayed hospital appointment with a rheumatologist to be the main unmet need

Table 37: Martindale et al., 2014

Bibliographic reference	Martindale,J., Goodacre,L., 20150831, The journey to diagnosis in AS/axial SpA: the impact of delay, Musculoskeletal Care, 12, 221-231, 2014
Country/ies where the study was carried out	UK
Study type	Qualitative, interviews (embedded within a larger prospective longitudinal, cohort study)
Aim of the study	An in-depth exploration of the journey to diagnosis of those with AS/SPA to gain insights into the experience, potential barriers and facilitators in the process

Bibliographic reference	Martindale,J., Goodacre,L., 20150831, The journey to diagnosis in AS/axial SpA: the impact of delay, Musculoskeletal Care, 12, 221-231, 2014
Study dates	December 2011 to July 2012
Source of funding	NIHR/CNO Clinical Lectureship
Sample size	N=10
Inclusion criteria	Inclusion; >18years, referred to physiotherapy within the previous year recent diagnosis of early sacroiliitis on x-ray and/or inflammatory spinal changes on MRI, meeting ASAS inflammatory back pain criteria
Exclusion criteria	Exclusion; recent serious illness
Details	Two rheumatology departments in the NW England Baseline; average age 40.2years, 30% female concomitant conditions, N=5 (N=2 iritis, N=2 psoriasis, N=1 Crohn's disease)
Interventions	Subgroup of participants from the larger prospective cohort study, completed questionnaires and participated in interviews in years 1 and 2 First interview; schedule to guide but not constrain discussion, approach adopted during interviews was iterative and flexible broad areas explored - journey to diagnosis, and the broad impact of the impairment on participants' lives (Second interview, not reported in this paper, explores how the experience of newly diagnosed may change and evolve over 12months)
Results	4 themes were identified in the analysis; what's going on?

Bibliographic reference	Martindale,J., Goodacre,L., 20150831, The journey to diagnosis in AS/axial SpA: the impact of delay, Musculoskeletal Care, 12, 221-231, 2014
	initially tended to attribute back pain to one-off incident, recurrent nature changed this and caused confusion about what was happening - with a lack of definitive diagnosis tended to attribute symptoms to a past event (e.g. injury, weight loss etc.) fighting for a diagnosis 'push' to get something done, prepared to undergo multiple investigations to get a definitive answer, described experiencing negativity and reluctance from GPs, described having to be persistent and 'fighting' to be referred for investigations strong thread through the narratives sense that HCP had repeatedly missed the diagnosis and got it wrong on a number of occasions described feeling that they were not being believed, too young to have back problems, being non-compliant where they saw someone who they perceived as having relevant knowledge, sense of relief and confidence in the diagnosis and management being adrift the delay in diagnosis was described as upsetting, distressing and disheartening - described feelings of anger, frustration and anger described a lack of knowledge and control, and feelings of depression described difficulties with employment repeat visits to doctors participants described as feeling like they were simply giving medications which from previous experience they found ineffective - trying to explain hard-to-describe symptoms could led to depression and annoyance the start of a journey sense of relief at diagnosis felt empowered by the knowledge they could do something to help themselves, that it was not life threatening, that HCPs believed them following diagnosis sought to acquire as much knowledge as they could, symptoms became less worrying when they understood what they were dealing with
Other information	Analysed using an interpretative phenomenological approach

Table 38: Seo et al., 2015

Bibliographic reference	Seo,M.R., Baek,H.L., Yoon,H.H., Ryu,H.J., Choi,H.J., Baek,H.J., Ko,K.P., Delayed diagnosis is linked to worse outcomes and unfavourable treatment responses in patients with axial spondyloarthritis, Clinical Rheumatology, 34, 1397-1405, 2015
Country/ies where the study was carried out	Republic of Korea
Study type	Cross-sectional study (mixed methods)

<table>
<tr><th>Bibliographic reference</th><th>Seo,M.R., Baek,H.L., Yoon,H.H., Ryu,H.J., Choi,H.J., Baek,H.J., Ko,K.P., Delayed diagnosis is linked to worse outcomes and unfavourable treatment responses in patients with axial spondyloarthritis, Clinical Rheumatology, 34, 1397-1405, 2015</th></tr>
<tr><td></td><td></td></tr>
<tr><td>Aim of the study</td><td>To compare between early and late diagnosis groups to identify factors related to delayed diagnosis in SpA</td></tr>
<tr><td>Study dates</td><td>November 2012 to February 2013</td></tr>
<tr><td>Source of funding</td><td>Unfunded study</td></tr>
<tr><td>Sample size</td><td>N=105</td></tr>
<tr><td>Inclusion criteria</td><td>Consecutively enrolled patients at a rheumatology clinic
Inclusion;
diagnosed with SpA, met ASAS criteria for axial or peripheral SpA</td></tr>
<tr><td>Exclusion criteria</td><td>None</td></tr>
<tr><td>Details</td><td>Classified into two groups depending on the median duration of diagnostic delay
Baseline;
female 22.9%
current age, median (IQR) 40(30 to 48), age at onset 23 (17 to 31), age at diagnosis 35 (24 to 43)
disease duration, median (IQR) 12 (6 to 20), diagnostic delay 8 (3 to 14)
history of (%), IBP (92.4), arthritis or arthralgia (86.7), enthesopathy (43.8), psoriasis (6.7), IBD (1.0), uveitis (25.7)</td></tr>
<tr><td>Interventions</td><td>Pre-designed data collection form using face-to-face interviews, reviews of medical records and physician assessment of disease status</td></tr>
<tr><td>Results</td><td>Alternative diagnosis
<table>
<tr><td>alternative diagnosis
N (%)</td><td>axial SpA (N=54)</td><td>peripheral SpA (N=6)</td><td>total</td></tr>
<tr><td>mechanical back pain</td><td>37 (68.5)</td><td>0</td><td>37 (61.7)</td></tr>
<tr><td>intervertebral disc herniation</td><td>19 (35.2)</td><td>0</td><td>19 (31.7)</td></tr>
</table></td></tr>
</table>

Bibliographic reference	Seo,M.R., Baek,H.L., Yoon,H.H., Ryu,H.J., Choi,H.J., Baek,H.J., Ko,K.P., Delayed diagnosis is linked to worse outcomes and unfavourable treatment responses in patients with axial spondyloarthritis, Clinical Rheumatology, 34, 1397-1405, 2015

osteoarthritis of the spine	4 (7.4)	0	4 (6.7)
others	14 (25.9)	0	14 (23.3)
gout	5 (9.3)	3 (50.0)	8 (13.3)
RA	4 (7.4)	2 (33.3)	6 (10.0)
arthritis	6 (11.1)	0	6 (10.0)
ischialgia	4 (7.4)	0	4 (2.7)
trauma	1 (1.9)	1 (16.7)	2 (3.3)
other (single cases of other diagnoses)	6 (11.1)	1 (16.7)	7 (11.7)

Factors related to delayed diagnosis (univariate analysis)

factors (%)	early diagnosis ≤8yrs (N=48)	late diagnosis >8yrs (N=46)	OR (95%CI)	P value
non-radiographic SpA	22.9	10.9	0.41 (0.13 to 1.29)	0.12
female	20.8	21.7	1.06 (0.39 to 2.84)	0.92
absence of HLA-B27	6.3	13.3	2.31 (0.54 to 9.85)	0.31
onset <17yrs	27.1	17.4	0.57 (0.21 to 1.53)	0.26
absence of family history in first degree relatives	82.5	91.9	2.40 (0.57 to 10.09)	0.31
absence of peripheral of any musculoskeletal symptoms	43.8	63.0	2.19 (0.96 to 5.01)	0.06

Bibliographic reference	Seo,M.R., Baek,H.L., Yoon,H.H., Ryu,H.J., Choi,H.J., Baek,H.J., Ko,K.P., Delayed diagnosis is linked to worse outcomes and unfavourable treatment responses in patients with axial spondyloarthritis, Clinical Rheumatology, 34, 1397-1405, 2015

extra-articular disease	25.0	39.1	1.93 (0.80 to 4.66)	0.14
history of smoking	54.8	63.2	1.42 (0.58 to 3.47)	0.45
late patient visit (>1yr after onset of symptoms)	22.9	39.1	2.16 (0.88 to 5.30)	0.09
prior diagnosis of mechanical back pain	22.9	45.7	2.83 (1.16 to 6.87)	0.02
history of surgery	12.5	23.9	2.20 (0.74 to 6.55)	0.15

Factors related to delayed diagnosis of axial spondyloarthritis (multivariate analysis)
prior diagnosis of mechanical back pain, OR 2.83 (1.16 to 6.87), p=0.02

Table 39: Slobodin et al., 2011a

Bibliographic reference	Slobodin,G., Reyhan,I., Avshovich,N., Balbir-Gurman,A., Boulman,N., Elias,M., Feld,J., Mader,R., Markovitz,D., Rimar,D., Rosner,I., Rozenbaum,M., Zisman,D., Odeh,M., 20111129, Recently diagnosed axial spondyloarthritis: gender differences and factors related to delay in diagnosis, Clinical Rheumatology, 30, 1075-1080, 2011
Country/ies where the study was carried out	Israel
Study type	Cross-sectional survey
Aim of the study	To characterise patients with recently diagnosed axial SpA, with emphasis on gender differences and factors leading to delay in diagnosis
Study dates	July 2009 to January 2010
Source of funding	Not reported

<table>
<tr><th>Bibliographic reference</th><td>Slobodin,G., Reyhan,I., Avshovich,N., Balbir-Gurman,A., Boulman,N., Elias,M., Feld,J., Mader,R., Markovitz,D., Rimar,D., Rosner,I., Rozenbaum,M., Zisman,D., Odeh,M., 20111129, Recently diagnosed axial spondyloarthritis: gender differences and factors related to delay in diagnosis, Clinical Rheumatology, 30, 1075-1080, 2011</td></tr>
<tr><td>Sample size</td><td>N=151</td></tr>
<tr><td>Inclusion criteria</td><td>Inclusion;
AS or undifferentiated SpA, sacroiliitis on imaging plus ≥1 SpA features satisfying the ASAS classification criteria for axial SpA</td></tr>
<tr><td>Exclusion criteria</td><td>Exclusion;
did not meet ASAS criteria
psoriasis or IBD and predominantly peripheral rather than axial involvement</td></tr>
<tr><td>Details</td><td>Baseline;
N=79 male, N=72 female</td></tr>
<tr><td>Interventions</td><td>Data collected during recruitment visit or retrospectively from chart review</td></tr>
<tr><td>Results</td><td>Gender-dependent features of axial SpA
<table>
<tr><td></td><td>male (N=79)</td><td>female (N=72)</td><td>P value</td></tr>
<tr><td>age at diagnosis</td><td>35.6±11.7</td><td>38.5±12.3</td><td>0.13</td></tr>
<tr><td>delay time to diagnosis</td><td>5.9±6.4</td><td>5.7±6.0</td><td>0.87</td></tr>
<tr><td>follow-up time</td><td>2.1±1.5</td><td>1.9±1.2</td><td>0.3</td></tr>
<tr><td>presenting symptoms;</td><td></td><td></td><td></td></tr>
<tr><td>inflammatory low back pain</td><td>70 (89%)</td><td>52 (73%)</td><td>0.02</td></tr>
<tr><td>neck pain</td><td>4 (5%)</td><td>8 (11%)</td><td>0.23</td></tr>
<tr><td>arthritis, knee</td><td>11 (14%)</td><td>8 (11%)</td><td>0.6</td></tr>
<tr><td>arthritis, hip</td><td>4 (5%)</td><td>1 (1.4%)</td><td>0.36</td></tr>
<tr><td>heel pain</td><td>1 (1.3%)</td><td>5 (7%)</td><td>0.23</td></tr>
</table></td></tr>
</table>

Bibliographic reference	Slobodin,G., Reyhan,I., Avshovich,N., Balbir-Gurman,A., Boulman,N., Elias,M., Feld,J., Mader,R., Markovitz,D., Rimar,D., Rosner,I., Rozenbaum,M., Zisman,D., Odeh,M., 20111129, Recently diagnosed axial spondyloarthritis: gender differences and factors related to delay in diagnosis, Clinical Rheumatology, 30, 1075-1080, 2011

uveitis	4 (5%)	5 (7%)	0.74
symptoms at time of diagnosis;			
inflammatory low back pain	74 (94%)	70 (97%)	0.45
musculoskeletal chest/rib pain	5 (6.3%)	12 (17%)	0.07
neck pain	21 (26%)	27 (37%)	0.16
arthritis or arthralgia	40 (51%)	42 (58%)	0.4
heel pain	18 (23%)	33 (46%)	0.003
dactylitis	2 (2.5%)	3 (4.2%)	0.67
uveitis	9 (12%)	8 (11%)	0.8
widespread pain	5 (6.3%)	28 (39%)	<0.0001

Disease features with different delay time to diagnosis

	≤1year (N=36)	1-5years (N=59)	≥5years (N=53)	P value
mean delay time	0.7±0.3	3.2±1.1	12.3±6.4	
age at diagnosis	33.2±12.3	35.4±11.6	40.8±11.5	0.004
male/female	17/19	34/25	27/26	NS
presenting symptoms;				
low back pain	29 (81%)	40 (68%)	41 (77%)	NS
neck pain	5 (14%)	3 (5%)	5 (9%)	NS
arthritis	5 (14%)	14 (24%)	7 (13%)	NS
heel pain	1 (3%)	1 (2%)	4 (8%)	NS

Bibliographic reference	Slobodin,G., Reyhan,I., Avshovich,N., Balbir-Gurman,A., Boulman,N., Elias,M., Feld,J., Mader,R., Markovitz,D., Rimar,D., Rosner,I., Rozenbaum,M., Zisman,D., Odeh,M., 20111129, Recently diagnosed axial spondyloarthritis: gender differences and factors related to delay in diagnosis, Clinical Rheumatology, 30, 1075-1080, 2011				
	uveitis	0	5 (8%)	2 (4%)	NS

Table 40: van Onna et al., 2014a

Bibliographic reference	van Onna, M., Gorter,S., van,Meerendonk A., van,Tubergen A., 20150204, General practitioners' perceptions of their ability to identify and refer patients with suspected axial spondyloarthritis: a qualitative study, Journal of Rheumatology, 41, 897-901, 2014
Country/ies where the study was carried out	The Netherlands
Study type	Qualitative study
Aim of the study	To explore the knowledge, beliefs, and experiences of GPs about inflammatory back pain and axial SpA, and the potential barriers for referral of those suspected of having axial SpA
Study dates	2012
Source of funding	Not reported
Sample size	N=10
Inclusion criteria	Inclusion; GPs without known specific interest or knowledge of musculoskeletal diseases
Exclusion criteria	None
Details	Baseline; all male, mean age 49yrs (range 37 to 58yrs) mean years as a GP 20 (range 10 to 29, SD 6) N=3 had a specific interest in musculoskeletal disorders
Interventions	Semi-structured interviews with GPs, duration approx. 1hr

Bibliographic reference	van Onna, M., Gorter,S., van,Meerendonk A., van,Tubergen A., 20150204, General practitioners' perceptions of their ability to identify and refer patients with suspected axial spondyloarthritis: a qualitative study, Journal of Rheumatology, 41, 897-901, 2014
	Grounded theory approach used, transcripts independently analysed by 2 readers, themes and patterns identified across interviews
Results	Results; Themes and patterns identified across the interviews ability to differentiate MBP from IBP? 4 GPs were not familiar with the terms MBP and IBP 6 GPs could recall a limited number of typical variables to differentiate MBP from IBP knowledge about "classic" AS and axSpA and awareness of diagnostic delay all were familiar with AS and mentioned prominent features none could adequately describe axSpA all considered that symptoms first appear in early adulthood and the AS is almost exclusively diagnosed in men delay in diagnosis considered to be due to patients' and doctors' delay knowledge about the clinical manifestations of axSpA fighting for a diagnosis most could describe a limited number of features of axSpA asked about extra articular manifestations; 5 mentioned anterior uveitis, 1 "eye complaints", 2 IBD, 3 psoriasis use of diagnostic tests in the primary care setting none would order an HLA B27 for those presenting with chronic back pain most - would only use x-ray for chronic back pain perceptions about management of axSpA most important treatment goals considered to be a decrease in pain and stiffness of the back and maintaining function all considered NSAIDs to be an adequate treatment option most mentioned physical therapy or home based exercises 5 GPs mentioned that anti-TNF-α therapy can be prescribed for axSpA preferences for educational programmes about axSpA most said that referral measures to decrease delay in diagnosis would be useful in clinical practice most wanted to know more about treatment options

E.1.5 Blood tests for spondyloarthritis

Review questions 7-9

- What is the diagnostic utility of a HLA B27 test for investigating suspected spondyloarthritis?
- What is the diagnostic utility of an erythrocyte sedimentation rate test for investigating suspected spondyloarthritis?
- What is the diagnostic utility of a C-reactive protein test for investigating suspected spondyloarthritis?

Table 41: HLA-B27

Study	Population	Risk of bias	N		Prevalence	Reference standard	Sensitivity & specificity	Predictive values	Likelihood ratios
			Cases	Non-cases					
AXIAL									
Braun 2011	Diagnosis of axial SpA among people with chronic back pain	Not serious	106	184	0.366 (0.312, 0.423)	Rheumatologist diagnosis	Sens.: 0.623 (0.527, 0.710) Spec.: 0.880 (0.825, 0.920)	PPV: 0.750 (0.649, 0.829) NPV: 0.802 (0.741, 0.851)	LR+: 5.208 (3.424, 7.919) LR-: 0.429 (0.334, 0.550)
Davis 1978	Diagnosis of ankylosing spondylitis in people with Crohn's disease	Not serious	3	57	0.050 (0.016, 0.144)	New York criteria (NB. Study pre-dates modified NY criteria)	Sens.: 0.875 (0.266, 0.993) Spec.: 0.802 (0.680, 0.885)	PPV: 0.233 (0.084, 0.502) NPV: 0.989 (0.851, 0.999)	LR+: 4.413 (2.335, 8.339) LR-: 0.156 (0.012, 2.091)
Dougados 2011 (DESIR)	Diagnosis of SpA in people with early inflammatory back pain	Not serious	475	233	0.671 (0.635, 0.705)	ASAS criteria for axial	Sens.: 0.832 (0.795, 0.863) Spec.: 0.957 (0.922, 0.977)	PPV: 0.975 (0.955, 0.987) NPV: 0.736 (0.683, 0.783)	LR+: 19.376 (10.552, 35.578) LR-: 0.176 (0.144, 0.215)
Goie The 1985	Diagnosis of AS among people with inflammatory back pain	Serious[a]	124	26	0.827 (0.758, 0.879)	Modified NY criteria	Sens.: 0.823 (0.745, 0.880) Spec.: 0.769 (0.572, 0.892)	PPV: 0.944 (0.882, 0.975) NPV: 0.476 (0.332, 0.625)	LR+: 3.565 (1.759, 7.225) LR-: 0.231 (0.150, 0.356)
Hermann 2009	Diagnosis of SpA in people with unspecified chronic back	Serious[a]	30	62	0.326 (0.238, 0.428)	AS: modified NY; PsA: McGonagle; Ent-SpA: no standard used;	Sens.: 0.800 (0.621, 0.907) Spec.: 0.742 (0.619, 0.835)	PPV: 0.600 (0.443, 0.738) NPV: 0.885 (0.766, 0.947)	LR+: 3.100 (1.960, 4.903) LR-: 0.270 (0.130, 0.560)

Study	Population	Risk of bias	N		Prevalence	Reference standard	Sensitivity & specificity	Predictive values	Likelihood ratios
			Cases	Non-cases					
	pain of limited duration					Undiff-SpA: signs suggestive of SpA but criteria not fully met			
Linssen 1983	Diagnosis of AS among people with acute anterior uveitis	Serious[a]	29	74	0.282 (0.203, 0.376)	New York criteria (NB. Study pre-dates modified NY criteria)	Sens.: 0.931 (0.762, 0.983) Spec.: 0.703 (0.589, 0.796)	PPV: 0.551 (0.411, 0.683) NPV: 0.963 (0.864, 0.991)	LR+: 3.132 (2.176, 4.507) LR-: 0.098 (0.026, 0.377)
Poddubnyy 2011	Diagnosis of axial SpA in people with low back pain	Not serious	222	338	0.396 (0.357, 0.438)	Rheumatologist diagnosis	Sens.: 0.784 (0.725, 0.833) Spec.: 0.595 (0.541, 0.646)	PPV: 0.559 (0.504, 0.614) NPV: 0.807 (0.753, 0.852)	LR+: 1.934 (1.670, 2.239) LR-: 0.364 (0.279, 0.474)
Sieper 2013	Diagnosis of axial SpA among people with chronic back pain	Not serious	280	423	0.398 (0.363, 0.435)	Rheumatologist diagnosis	Sens.: 0.661 (0.603, 0.714) Spec.: 0.799 (0.758, 0.835)	PPV: 0.685 (0.627, 0.738) NPV: 0.781 (0.739, 0.817)	LR+: 3.288 (2.671, 4.047) LR-: 0.425 (0.358, 0.503)
Song 2010	Diagnosis of axial SpA in people evaluated with chronic low back pain	Serious[b]	97	97	0.500 (0.430, 0.570)	Clinician diagnosis	Sens.: 0.804 (0.713, 0.871) Spec.: 0.660 (0.560, 0.747)	PPV: 0.703 (0.611, 0.780) NPV: 0.771 (0.669, 0.849)	LR+: 2.364 (1.762, 3.172) LR-: 0.297 (0.194, 0.455)
van den Berg 2013b (ASAS)	Diagnosis of axial SpA in people with undiagnosed chronic back pain	Not serious	421	264	0.615 (0.578, 0.650)	Rheumatologist diagnosis	Sens.: 0.641 (0.594, 0.686) Spec.: 0.723 (0.666, 0.774)	PPV: 0.787 (0.741, 0.827) NPV: 0.558 (0.505, 0.610)	LR+: 2.319 (1.884, 2.855) LR-: 0.496 (0.428, 0.575)
van den Berg 2013b (SPACE)	Diagnosis of axial SpA in people with back pain of between 3	Not serious	65	92	0.414 (0.340, 0.493)	Rheumatologist diagnosis	Sens.: 0.677 (0.555, 0.779) Spec.: 0.902 (0.823, 0.948)	PPV: 0.830 (0.705, 0.909) NPV: 0.798 (0.710, 0.864)	LR+: 6.920 (3.638, 13.161) LR-: 0.358 (0.250, 0.512)

Study	Population	Risk of bias	N		Prevalence	Reference standard	Sensitivity & specificity	Predictive values	Likelihood ratios
			Cases	Non-cases					
	months and 2 years								
van Hoeven 2014	Diagnosis of axial SpA among people with chronic lower back pain	Not serious	86	278	0.236 (0.195, 0.283)	ASAS criteria for axial SpA, Modified NY criteria for AS	Sens.: 0.198 (0.127, 0.295) Spec.: 0.989 (0.967, 0.997)	PPV: 0.850 (0.624, 0.951) NPV: 0.799 (0.754, 0.838)	LR+: 18.318 (5.499, 61.019) LR-: 0.811 (0.730, 0.901)
van Hoeven 2015	Diagnosis of axial SpA in people with chronic low back pain	Not serious	95	484	0.164 (0.136, 0.197)	ASAS criteria for axial	Sens.: 0.221 (0.149, 0.315) Spec.: 0.969 (0.949, 0.981)	PPV: 0.583 (0.419, 0.731) NPV: 0.864 (0.832, 0.890)	LR+: 7.133 (3.818, 13.326) LR-: 0.804 (0.721, 0.896)
PERIPHERAL									
Esdaile 1997	Diagnosis of peripheral arthritis in people with rheumatoid-factor negative polyarthritis	Not serious	25	58	0.301 (0.212, 0.408)	Pre-specified investigator-defined criteria	Sens.: 0.440 (0.263, 0.634) Spec.: 0.914 (0.809, 0.964)	PPV: 0.688 (0.433, 0.864) NPV: 0.791 (0.677, 0.872)	LR+: 5.104 (1.979, 13.164) LR-: 0.613 (0.429, 0.875)
Kvien 1994	Diagnosis of ReA in people with suspected ReA	Not serious	52	134	0.280 (0.220, 0.348)	Investigator defined criteria	Sens.: 0.577 (0.440, 0.703) Spec.: 0.843 (0.772, 0.896)	PPV: 0.588 (0.450, 0.714) NPV: 0.837 (0.765, 0.890)	LR+: 3.681 (2.332, 5.811) LR-: 0.502 (0.362, 0.695)
Kvien 1996	Diagnostic classification in people with unexplained oligoarthritis	Not serious	46	100	0.315 (0.245, 0.395)	ReA: positive culture and/or positive antibody titre plus arthritis	Sens.: 0.609 (0.462, 0.738) Spec.: 0.900 (0.824, 0.945)	PPV: 0.737 (0.576, 0.852) NPV: 0.833 (0.751, 0.892)	LR+: 6.087 (3.235, 11.452) LR-: 0.435 (0.301, 0.627)
Mattila 1998	Diagnosis of ReA among people with suspected ReA following a	Serious[c]	22	23	0.489 (0.348, 0.632)	Rheumatologist diagnosis	Sens.: 0.457 (0.270, 0.656) Spec.: 0.979 (0.741, 0.999)	PPV: 0.955 (0.552, 0.997) NPV: 0.653 (0.486, 0.789)	LR+: 21.913 (1.361, 352.791) LR-: 0.555 (0.380, 0.811)

Study	Population	Risk of bias	N		Prevalence	Reference standard	Sensitivity & specificity	Predictive values	Likelihood ratios
			Cases	Non-cases					
	Salmonella outbreak								
McColl 2000	Diagnosis of ReA in people exposed to Salmonella Typhimurium	Serious[c]	19	186	0.093 (0.060, 0.141)	Investigator defined criteria	Sens.: 0.105 (0.026, 0.337) Spec.: 0.909 (0.858, 0.942)	PPV: 0.105 (0.026, 0.337) NPV: 0.909 (0.858, 0.942)	LR+: 1.152 (0.288, 4.610) LR-: 0.985 (0.838, 1.157)
Rohekar 2008	Diagnosis of ReA among people exposed to a Salmonella outbreak	Serious[c]	46	28	0.622 (0.507, 0.724)	Questionnaire (QUEST-2 with modified instrument (Acute Reactive Arthritis (AReA) questionnaire)	Sens.: 0.109 (0.046, 0.236) Spec.: 0.786 (0.598, 0.900)	PPV: 0.455 (0.203, 0.732) NPV: 0.349 (0.242, 0.474)	LR+: 0.507 (0.171, 1.509) LR-: 1.134 (0.912, 1.411)
Rudwaleit 2011	Diagnosing peripheral SpA among people with peripheral manifestation	Not serious	176	90	0.662 (0.603, 0.716)	Rheumatologist diagnosis	Sens.: 0.472 (0.399, 0.545) Spec.: 0.944 (0.873, 0.977)	PPV: 0.943 (0.871, 0.976) NPV: 0.478 (0.405, 0.551)	LR+: 8.489 (3.570, 20.182) LR-: 0.559 (0.482, 0.649)
MIXED AXIAL AND PERIPHERAL									
Althoff 2009	Diagnosis of SpA among people with suspected SpA	Serious[b]	72	33	0.686 (0.591, 0.767)	Unclear (treated in this analysis as 'published criteria')	Sens.: 0.694 (0.579, 0.790) Spec.: 0.636 (0.463, 0.781)	PPV: 0.806 (0.689, 0.887) NPV: 0.488 (0.344, 0.634)	LR+: 1.910 (1.186, 3.076) LR-: 0.480 (0.311, 0.741)
Brandt 1999	Diagnosis of SpA among people with inflammatory back pain or peripheral oligoarthritis of the lower limbs	Serious[c]	111	40	0.735 (0.659, 0.799)	ESSG, modified NY	Sens.: 0.712 (0.621, 0.788) Spec.: 0.650 (0.492, 0.781)	PPV: 0.849 (0.762, 0.909) NPV: 0.448 (0.326, 0.577)	LR+: 2.033 (1.311, 3.153) LR-: 0.444 (0.306, 0.642)
D'Agostino 2011	Diagnosis of SpA in people	Not serious	51	47	0.520 (0.422, 0.617)	Rheumatologist diagnosis	Sens.: 0.510 (0.375, 0.643)	PPV: 0.703 (0.539, 0.827)	LR+: 2.178 (1.216, 3.902)

Study	Population	Risk of bias	N		Prevalence	Reference standard	Sensitivity & specificity	Predictive values	Likelihood ratios
			Cases	Non-cases					
	with suspected SpA						Spec.: 0.766 (0.625, 0.865)	NPV: 0.590 (0.464, 0.706)	LR-: 0.640 (0.464, 0.883)
Godfrin 2004	Diagnosis of SpA in people with entheseal pain	Not serious	13	20	0.394 (0.244, 0.566)	Criteria specified by study authors (plus Amor and ESSG criteria)	Sens.: 0.462 (0.224, 0.718) Spec.: 0.900 (0.676, 0.975)	PPV: 0.750 (0.377, 0.937) NPV: 0.720 (0.518, 0.860)	LR+: 4.615 (1.094, 19.479) LR-: 0.598 (0.354, 1.010)
Granfors 1983	Diagnosis of SpA and measurement of Yersinia antibodies in people with recent inflammatory joint disease	Not serious	62	292	0.175 (0.139, 0.218)	Clinician diagnosis	Sens.: 0.726 (0.602, 0.822) Spec.: 0.705 (0.651, 0.755)	PPV: 0.344 (0.267, 0.429) NPV: 0.924 (0.881, 0.952)	LR+: 2.464 (1.950, 3.115) LR-: 0.389 (0.257, 0.587)
Hulsemann 1995	Diagnosis of SpA in people with suspected inflammatory rheumatic diseases seen at an early synovitis clinic	Serious[d]	10	167	0.056 (0.031, 0.102)	Clinician diagnosis	Sens.: 0.955 (0.552, 0.997) Spec.: 0.789 (0.720, 0.844)	PPV: 0.228 (0.129, 0.371) NPV: 0.996 (0.943, 1.000)	LR+: 4.517 (3.282, 6.217) LR-: 0.058 (0.004, 0.865)
Hulsemann 1995	Diagnosis of SpA in people with suspected inflammatory rheumatic diseases seen at an early synovitis clinic	Serious[d]	31	167	0.157 (0.112, 0.214)	Clinician diagnosis	Sens.: 0.484 (0.317, 0.655) Spec.: 0.790 (0.722, 0.846)	PPV: 0.300 (0.190, 0.440) NPV: 0.892 (0.831, 0.933)	LR+: 2.309 (1.446, 3.686) LR-: 0.653 (0.460, 0.926)
Liao 2009	Diagnosis of SpA among	Serious[e]	75	369	0.169 (0.137, 0.207)	ESSG for diagnosing SpA, modified NY	Sens.: 0.827 (0.724, 0.897)	PPV: 0.590 (0.494, 0.680)	LR+: 7.094 (5.258, 9.570)

Study	Population	Risk of bias	N		Prevalence	Reference standard	Sensitivity & specificity	Predictive values	Likelihood ratios
			Cases	Non-cases					
	people with lower back pain					criteria for AS, CASPAR for PsA, ReA according to criteria from Kingsley and Sieper	Spec.: 0.883 (0.847, 0.912)	NPV: 0.962 (0.935, 0.978)	LR-: 0.196 (0.120, 0.322)
Salvarini 2001	Diagnosis of SpA in people with inflammatory bowel disease	Serious[c]	26	114	0.186 (0.130, 0.259)	ESSG criteria	Sens.: 0.038 (0.005, 0.228) Spec.: 0.965 (0.910, 0.987)	PPV: 0.200 (0.027, 0.691) NPV: 0.815 (0.740, 0.872)	LR+: 1.096 (0.128, 9.406) LR-: 0.997 (0.916, 1.084)
Tomero 2014	Diagnosis of SpA among people with suspected early SpA	Not serious	538	237	0.694 (0.661, 0.726)	Rheumatologist diagnosis	Sens.: 0.556 (0.513, 0.597) Spec.: 0.835 (0.783, 0.877)	PPV: 0.885 (0.846, 0.915) NPV: 0.453 (0.407, 0.500)	LR+: 3.377 (2.510, 4.544) LR-: 0.532 (0.476, 0.594)

[a] *Participants not consecutively recruited*
[b] *Retrospective study*
[c] *Some tests only performed in subset of participants*
[d] *Majority of people end as undifferentiated arthritis*
[e] *Population not comprised of people with suspected SpA*

Table 42: ESR

Study	Population	Risk of bias	N		Prevalence	Reference standard	Sensitivity & specificity	Predictive values	Likelihood ratios
			Cases	Non-cases					
AXIAL									
Hermann 2009	Diagnosis of SpA in people with unspecified chronic back pain of limited duration	Seriousa	30	62	0.326 (0.238, 0.428)	AS: modified NY; PsA: McGonagle; Ent-SpA: no standard used; Undiff-SpA: signs suggestive of SpA but criteria not fully met	Sens.: 0.333 (0.190, 0.516) Spec.: 0.806 (0.689, 0.887)	PPV: 0.455 (0.265, 0.659) NPV: 0.714 (0.598, 0.808)	LR+: 1.722 (0.841, 3.528) LR-: 0.827 (0.624, 1.095)
PERIPHERAL									

Study	Population	Risk of bias	N		Prevalence	Reference standard	Sensitivity & specificity	Predictive values	Likelihood ratios
			Cases	Non-cases					
no data									
MIXED AXIAL AND PERIPHERAL									
Tomero 2014	Diagnosis of SpA among people with suspected early SpA	Not serious	538	237	0.694 (0.661, 0.726)	Rheumatologist diagnosis	Sens.: 0.208 (0.176, 0.245) Spec.: 0.941 (0.903, 0.965)	PPV: 0.889 (0.821, 0.933) NPV: 0.344 (0.308, 0.381)	LR+: 3.524 (2.066, 6.012) LR-: 0.842 (0.797, 0.888)

(a) Participants not consecutively recruited

Table 43: CRP

Study	Population	Risk of bias	N		Prevalence	Reference standard	Sensitivity & specificity	Predictive values	Likelihood ratios
			Cases	Non-cases					
AXIAL									
Dougados 2011 (DESIR)	Diagnosis of SpA in people with early inflammatory back pain	Not serious	475	233	0.671 (0.635, 0.705)	ASAS criteria for axial	Sens.: 0.627 (0.583, 0.670) Spec.: 0.219 (0.170, 0.277)	PPV: 0.621 (0.577, 0.663) NPV: 0.224 (0.174, 0.282)	LR+: 0.803 (0.729, 0.885) LR-: 1.702 (1.301, 2.228)
Hermann 2009	Diagnosis of SpA in people with unspecified chronic back pain of limited duration	Serious[a]	30	62	0.326 (0.238, 0.428)	AS: modified NY; PsA: McGonagle; Ent-SpA: no standard used; Undiff-SpA: signs suggestive of SpA but criteria not fully met	Sens.: 0.333 (0.190, 0.516) Spec.: 0.871 (0.763, 0.934)	PPV: 0.556 (0.330, 0.760) NPV: 0.730 (0.618, 0.819)	LR+: 2.583 (1.136, 5.872) LR-: 0.765 (0.584, 1.003)
Rudwaleit 2009 (ASAS)	Diagnosing axial SpA among people with chronic back pain	Not serious	391	258	0.602 (0.564, 0.639)	Rheumatologist diagnosis	Sens.: 0.381 (0.334, 0.430) Spec.: 0.853 (0.804, 0.891)	PPV: 0.797 (0.733, 0.848) NPV: 0.476 (0.431, 0.522)	LR+: 2.587 (1.879, 3.562) LR-: 0.726 (0.661, 0.796)
van Hoeven 2014	Diagnosis of axial SpA among people with chronic lower back pain	Not serious	86	278	0.236 (0.195, 0.283)	ASAS criteria for axial SpA, Modified NY criteria for AS	Sens.: 0.105 (0.055, 0.189) Spec.: 0.957 (0.926, 0.975)	PPV: 0.429 (0.240, 0.640) NPV: 0.776 (0.728, 0.817)	LR+: 2.424 (1.057, 5.559) LR-: 0.936 (0.867, 1.010)
van Hoeven 2015	Diagnosis of axial SpA in people with chronic low back pain	Not serious	95	481	0.165 (0.137, 0.198)	ASAS criteria for axial	Sens.: 0.105 (0.058, 0.185) Spec.: 0.950 (0.927, 0.966)	PPV: 0.294 (0.166, 0.466) NPV: 0.843 (0.810, 0.871)	LR+: 2.110 (1.043, 4.266) LR-: 0.942 (0.876, 1.012)
PERIPHERAL									
Kvien 1996	Diagnostic classification in people with unexplained oligoarthritis	Not serious	46	100	0.315 (0.245, 0.395)	ReA: positive culture and/or positive antibody titre plus arthritis	Sens.: 0.696 (0.549, 0.811) Spec.: 0.600 (0.501, 0.691)	PPV: 0.444 (0.334, 0.560) NPV: 0.811 (0.705, 0.885)	LR+: 1.739 (1.280, 2.364) LR-: 0.507 (0.319, 0.808)
Rudwaleit 2011	Diagnosing peripheral SpA among people with peripheral manifestation	Not serious	176	90	0.662 (0.603, 0.716)	Rheumatologist diagnosis	Sens.: 0.580 (0.505, 0.650) Spec.: 0.567 (0.463, 0.665)	PPV: 0.723 (0.644, 0.791) NPV: 0.408 (0.325, 0.496)	LR+: 1.337 (1.023, 1.748) LR-: 0.742 (0.578, 0.953)
MIXED AXIAL AND PERIPHERAL									
Tomero 2014	Diagnosis of SpA among people with suspected early SpA	Not serious	538	237	0.694 (0.661, 0.726)	Rheumatologist diagnosis	Sens.: 0.240 (0.206, 0.278) Spec.: 0.806 (0.751, 0.851)	PPV: 0.737 (0.667, 0.797) NPV: 0.318 (0.282, 0.357)	LR+: 1.235 (0.915, 1.667) LR-: 0.943 (0.872, 1.020)

[a] *Participants not consecutively recruited*

E.1.6 Imaging for diagnosis of spondyloarthritis

Review Question 10

- What is the diagnostic utility of imaging (alone or in sequence) for investigating suspected spondyloarthritis?

E.1.6.1 Sacroiliitis on x-ray

Study	Population	Risk of bias	N		Prevalence	Reference standard	Sensitivity & specificity	Predictive values	Likelihood ratios
			Cases	Non-cases					
AXIAL									
Dougados 2011 (DESIR)	Diagnosis of SpA in people with early inflammatory back pain	Not serious	475	233	0.671 (0.635, 0.705)	ASAS criteria for axial	Sens.: 0.381 (0.339, 0.426) Spec.: 0.998 (0.967, 1.000)	PPV: 0.997 (0.958, 1.000) NPV: 0.442 (0.400, 0.485)	LR+: 178.450 (11.169, 2851.255) LR-: 0.620 (0.578, 0.665)
van den Berg 2013b (ASAS)	Diagnosis of axial SpA in people with undiagnosed chronic back pain	Not serious	421	264	0.615 (0.578, 0.650)	Rheumatologist diagnosis	Sens.: 0.292 (0.251, 0.337) Spec.: 0.966 (0.936, 0.982)	PPV: 0.932 (0.874, 0.964) NPV: 0.461 (0.420, 0.503)	LR+: 8.570 (4.434, 16.566) LR-: 0.733 (0.686, 0.782)
van den Berg 2013b (SPACE)	Diagnosis of axial SpA in people with back pain of between 3 months and 2 years	Not serious	65	92	0.414 (0.340, 0.493)	Rheumatologist diagnosis	Sens.: 0.169 (0.096, 0.280) Spec.: 0.989 (0.927, 0.998)	PPV: 0.917 (0.587, 0.988) NPV: 0.628 (0.546, 0.702)	LR+: 15.569 (2.061, 117.640) LR-: 0.840 (0.751, 0.939)
PERIPHERAL									
Esdaile 1997	Diagnosis of peripheral arthritis in people with rheumatoid-factor negative polyarthritis	Not serious	25	58	0.301 (0.212, 0.408)	Pre-specified investigator-defined criteria	Sens.: 0.120 (0.039, 0.313) Spec.: 0.897 (0.788, 0.953)	PPV: 0.333 (0.111, 0.667) NPV: 0.703 (0.589, 0.796)	LR+: 1.160 (0.315, 4.274) LR-: 0.982 (0.829, 1.162)
Rigby 1993	Diagnosis of AS in people attending a rheumatology clinic	Serious[a,b]	30	182	0.142 (0.101, 0.195)	Clinician diagnosis	Sens.: 0.933 (0.769, 0.983) Spec.: 0.907 (0.855, 0.941)	PPV: 0.622 (0.474, 0.751) NPV: 0.988 (0.953, 0.997)	LR+: 9.992 (6.291, 15.870) LR-: 0.074 (0.019, 0.281)
Rudwaleit 2011	Diagnosing peripheral SpA among people with peripheral manifestation	Not serious	164	63	0.722 (0.661, 0.777)	Rheumatologist diagnosis	Sens.: 0.195 (0.141, 0.263) Spec.: 0.968 (0.882, 0.992)	PPV: 0.941 (0.793, 0.985) NPV: 0.316 (0.254, 0.385)	LR+: 6.146 (1.518, 24.892) LR-: 0.831 (0.762, 0.907)
Sadek 2007	Diagnosis of PsA in people with Psoriasis	Not serious	59	22	0.728 (0.622, 0.814)	Clinician and 5 criteria sets	Sens.: 0.392 (0.277, 0.520) Spec.: 0.978 (0.732, 0.999)	PPV: 0.979 (0.741, 0.999) NPV: 0.381 (0.267, 0.510)	LR+: 18.017 (1.141, 284.544) LR-: 0.622 (0.503, 0.769)
You 2015	Diagnosis of PsA in people with Psoriasis	Serious[c]	18	130	0.122 (0.078, 0.185)	CASPAR	Sens.: 0.222 (0.086, 0.465) Spec.: 0.992 (0.947, 0.999)	PPV: 0.800 (0.309, 0.973) NPV: 0.902 (0.841, 0.941)	LR+: 28.889 (3.415, 244.351) LR-: 0.784 (0.612, 1.004)
MIXED AXIAL AND PERIPHERAL									
Tomero 2014	Diagnosis of SpA among people with suspected early SpA	Not serious	538	237	0.694 (0.661, 0.726)	Rheumatologist diagnosis	Sens.: 0.188 (0.157, 0.224) Spec.: 0.998 (0.967, 1.000)	PPV: 0.995 (0.927, 1.000) NPV: 0.352 (0.317, 0.389)	LR+: 89.636 (5.592, 1436.834) LR-: 0.813 (0.781, 0.848)

[a] *Retrospective study*
[b] *Testers not blinded to final diagnosis*
[c] *Participants not consecutively recruited*

E.1.6.2 Finger or toe pathology on x-ray

Table 44: Finger or toe pathology on x-ray – evidence table

Study	Population	Risk of bias	N		Prevalence	Reference standard	Sensitivity & specificity	Predictive values	Likelihood ratios
			Cases	Non-cases					
AXIAL									
no data									
PERIPHERAL									
De Simone 2011	Diagnosis of psoriatic arthritis in people with psoriasis	Not serious	36	16	0.692 (0.555, 0.802)	rheumatologist diagnosis	Sens.: 0.311 (0.184, 0.475) Spec.: 0.971 (0.664, 0.998)	PPV: 0.958 (0.575, 0.997) NPV: 0.393 (0.258, 0.546)	LR+: 10.568 (0.660, 169.079) LR-: 0.710 (0.563, 0.895)
MIXED AXIAL AND PERIPHERAL									
no data									

E.1.6.3 Enthesitis on x-ray

Table 45: Enthesitis on x-ray – evidence table

Study	Population	Risk of bias	N		Prevalence	Reference standard	Sensitivity & specificity	Predictive values	Likelihood ratios
			Cases	Non-cases					
AXIAL									
no data									
PERIPHERAL									
Sadek 2007	Diagnosis of PsA in people with Psoriasis	Not serious	59	22	0.728 (0.622, 0.814)	Clinician and 5 criteria sets	Sens.: 0.644 (0.515, 0.755) Spec.: 0.591 (0.382, 0.772)	PPV: 0.809 (0.671, 0.897) NPV: 0.382 (0.237, 0.553)	LR+: 1.574 (0.920, 2.693) LR-: 0.602 (0.370, 0.982)
MIXED AXIAL AND PERIPHERAL									
Godfrin 2004	Diagnosis of SpA in people with entheseal pain	Not serious	13	20	0.394 (0.244, 0.566)[a]	Criteria specified by study authors (plus Amor and ESSG criteria)	Sens.: 0.607 (0.346, 0.819) Spec.: 0.976 (0.713, 0.999)	PPV: 0.944 (0.495, 0.997) NPV: 0.788 (0.593, 0.905)	LR+: 25.500 (1.597, 407.286) LR-: 0.402 (0.209, 0.774)

[a] *cases classified as nonspecific 'entheseal spondyloarthropathy' treated as negative for spondyloarthritis*

MRI

E.1.6.4 Sacroiliitis on MRI

Table 46: Sacroiliitis on MRI – evidence table

Study	Population	Risk of bias	N		Prevalence	Reference standard	Sensitivity & specificity	Predictive values	Likelihood ratios
			Cases	Non-cases					
AXIAL									
Dougados 2011 (DESIR)	Diagnosis of SpA in people with early inflammatory back pain	Not serious	475	233	0.671 (0.635, 0.705)	ASAS criteria for axial	Sens.: 0.474 (0.429, 0.519) Spec.: 0.998 (0.967, 1.000)	PPV: 0.998 (0.966, 1.000) NPV: 0.482 (0.438, 0.527)	LR+: 221.710 (13.886, 3539.829) LR-: 0.527 (0.484, 0.574)
van den Berg 2013b (ASAS)	Diagnosis of axial SpA in people with undiagnosed chronic back pain	Not serious	421	264	0.615 (0.578, 0.650)	Rheumatologist diagnosis	Sens.: 0.480 (0.432, 0.528) Spec.: 0.970 (0.941, 0.985)	PPV: 0.962 (0.926, 0.981) NPV: 0.539 (0.494, 0.583)	LR+: 15.834 (7.945, 31.555) LR-: 0.536 (0.488, 0.589)
van den Berg 2013b (SPACE)	Diagnosis of axial SpA in people with back pain of between 3 months and 2 years	Not serious	65	92	0.414 (0.340, 0.493)	Rheumatologist diagnosis	Sens.: 0.417 (0.305, 0.538) Spec.: 0.995 (0.920, 1.000)	PPV: 0.982 (0.770, 0.999) NPV: 0.706 (0.623, 0.778)	LR+: 77.500 (4.813, 1248.033) LR-: 0.586 (0.478, 0.720)
PERIPHERAL									
Rudwaleit 2011	Diagnosing peripheral SpA among people with peripheral manifestation	Not serious	50	10	0.833 (0.717, 0.908)	Rheumatologist diagnosis	Sens.: 0.441 (0.312, 0.578) Spec.: 0.955 (0.552, 0.997)	PPV: 0.978 (0.732, 0.999) NPV: 0.269 (0.154, 0.428)	LR+: 9.706 (0.636, 148.171) LR-: 0.585 (0.444, 0.771)
MIXED AXIAL AND PERIPHERAL									
D'Agostino 2011	Diagnosis of SpA in people with suspected SpA	Not serious	39	34	0.534 (0.420, 0.645)	Rheumatologist diagnosis	Sens.: 0.359 (0.225, 0.519) Spec.: 0.912 (0.760, 0.971)	PPV: 0.824 (0.573, 0.942) NPV: 0.554 (0.423, 0.677)	LR+: 4.068 (1.277, 12.966) LR-: 0.703 (0.544, 0.909)

E.1.6.5 Spinal features on MRI

Table 47: Spinal features on MRI – evidence table

Study	Population	Risk of bias	N		Prevalence	Reference standard	Sensitivity & specificity	Predictive values	Likelihood ratios
			Cases	Non-cases					
AXIAL									
Dougados 2011 (DESIR)	Diagnosis of SpA in people with early inflammatory back pain	Not serious	475	233	0.671 (0.635, 0.705)	ASAS criteria for axial	Sens.: 0.255 (0.218, 0.296) Spec.: 0.906 (0.861, 0.937)	PPV: 0.846 (0.777, 0.897) NPV: 0.373 (0.335, 0.414)	LR+: 2.698 (1.761, 4.132) LR-: 0.823 (0.770, 0.880)
PERIPHERAL									
no data									
MIXED AXIAL AND PERIPHERAL									
no data									

E.1.6.6 Enthesitis on MRI

Table 48: Enthesitis on MRI – evidence table

Study	Population	Risk of bias	N		Prevalence	Reference standard	Sensitivity & specificity	Predictive values	Likelihood ratios
			Cases	Non-cases					
AXIAL									
no data									
PERIPHERAL									
no data									
MIXED AXIAL AND PERIPHERAL									
Godfrin 2004	Diagnosis of SpA in people with entheseal pain	Not serious	13	20	0.394 (0.244, 0.566)[a]	Criteria specified by study authors (plus Amor and ESSG criteria)	Sens.: 0.692 (0.409, 0.880) Spec.: 0.850 (0.624, 0.951)	PPV: 0.750 (0.448, 0.917) NPV: 0.810 (0.588, 0.927)	LR+: 4.615 (1.530, 13.927) LR-: 0.362 (0.157, 0.835)

[a] *cases classified as nonspecific 'entheseal spondyloarthropathy' treated as negative for spondyloarthritis*

Ultrasound

E.1.6.7 Finger or toe pathology on ultrasound

Table 49: Finger or toe pathology on ultrasound – evidence table

Study	Population	Risk of bias	N		Prevalence	Reference standard	Sensitivity & specificity	Predictive values	Likelihood ratios
			Cases	Non-cases					
AXIAL									
no data									
PERIPHERAL									
De Simone 2011	Diagnosis of psoriatic arthritis in people with psoriasis	Not serious	36	16	0.692 (0.555, 0.802)	rheumatologist diagnosis	Sens.: 0.986 (0.818, 0.999) Spec.: 0.971 (0.664, 0.998)	PPV: 0.986 (0.818, 0.999) NPV: 0.971 (0.664, 0.998)	LR+: 33.541 (2.185, 514.789) LR-: 0.014 (0.001, 0.219)
MIXED AXIAL AND PERIPHERAL									
no data									

E.1.6.8 Finger or toe pathology on power Doppler ultrasound

Table 50: Finger or toe pathology on power Doppler ultrasound – evidence table

Study	Population	Risk of bias	N		Prevalence	Reference standard	Sensitivity & specificity	Predictive values	Likelihood ratios
			Cases	Non-cases					
AXIAL									
no data									
PERIPHERAL									
De Simone 2011	Diagnosis of psoriatic arthritis in people with psoriasis	Not serious	36	16	0.692 (0.555, 0.802)	rheumatologist diagnosis	Sens.: 0.806 (0.645, 0.904) Spec.: 0.625 (0.377, 0.821)	PPV: 0.829 (0.667, 0.921) NPV: 0.588 (0.352, 0.790)	LR+: 2.148 (1.119, 4.126) LR-: 0.311 (0.145, 0.669)
MIXED AXIAL AND PERIPHERAL									
no data									

E.1.6.9 Enthesitis on power Doppler ultrasound

Table 51: Enthesitis on power Doppler ultrasound – evidence table

Study	Population	Risk of bias	N		Prevalence	Reference standard	Sensitivity & specificity	Predictive values	Likelihood ratios
			Cases	Non-cases					
AXIAL									
no data									
PERIPHERAL									
no data									
MIXED AXIAL AND PERIPHERAL									
D'Agostino 2011	Diagnosis of SpA in people with suspected SpA	Not serious	51	48	0.515 (0.417, 0.612)	Rheumatologist diagnosis	Sens.: 0.863 (0.739, 0.933) Spec.: 0.396 (0.269, 0.539)	PPV: 0.603 (0.487, 0.708) NPV: 0.731 (0.533, 0.866)	LR+: 1.428 (1.108, 1.841) LR-: 0.347 (0.160, 0.750)

Scintigraphy

E.1.6.10 Sacroiliitis on scintigraphy

Table 52: Sacroiliitis on scintigraphy – evidence table

Study	Population	Risk of bias	N		Prevalence	Reference standard	Sensitivity & specificity	Predictive values	Likelihood ratios
			Cases	Non-cases					
AXIAL									
Song 2010	Diagnosis of axial SpA in people evaluated with chronic low back pain	Serious[a]	97	97	0.500 (0.430, 0.570)	Clinician diagnosis	Sens.: 0.649 (0.550, 0.738) Spec.: 0.505 (0.407, 0.603)	PPV: 0.568 (0.474, 0.656) NPV: 0.590 (0.482, 0.691)	LR+: 1.313 (1.024, 1.683) LR-: 0.694 (0.496, 0.970)
PERIPHERAL									
no data									
MIXED AXIAL AND PERIPHERAL									
no data									

[a] *Retrospective study*

E.1.7 Information gathering to improve early diagnosis

Review Question 5

- What is the usefulness of information gathering (for example family history, self-report questionnaires, and screening criteria) in improving early diagnosis of spondyloarthritis?

None

E.1.8 Diagnostic risk scores and models

Review Question 4

- What is the diagnostic utility of a risk assessment score for identifying spondyloarthritis?

E.1.8.1 Amor criteria

Original Amor criteria

Table 53: Original Amor criteria – evidence table

Study	Population	Risk of bias	N		Prevalence	Reference standard	Sensitivity & specificity	Predictive values	Likelihood ratios
			Cases	Non-cases					
AXIAL									
Dougados 2015 (DESIR)	Diagnosis of SpA in people with early inflammatory back pain	Serious[a]	319	389	0.451 (0.414, 0.487)	Rheumatologist diagnosis	Sens.: 0.884 (0.844, 0.915) Spec.: 0.293 (0.250, 0.340)	PPV: 0.506 (0.465, 0.548) NPV: 0.755 (0.680, 0.817)	LR+: 1.250 (1.160, 1.348) LR-: 0.396 (0.282, 0.556)
Rudwaleit 2009 (ASAS)	Diagnosing axial SpA among people with chronic back pain	Not serious	391	258	0.602 (0.564, 0.639)	Rheumatologist diagnosis	Sens.: 0.693 (0.646, 0.737) Spec.: 0.779 (0.724, 0.826)	PPV: 0.826 (0.781, 0.864) NPV: 0.626 (0.572, 0.677)	LR+: 3.137 (2.472, 3.982) LR-: 0.394 (0.335, 0.463)
PERIPHERAL									
Rudwaleit 2011	Diagnosing peripheral SpA among people with peripheral manifestation	Not serious	176	90	0.662 (0.603, 0.716)	Rheumatologist diagnosis	Sens.: 0.352 (0.285, 0.426) Spec.: 0.978 (0.915, 0.994)	PPV: 0.969 (0.883, 0.992) NPV: 0.436 (0.369, 0.505)	LR+: 15.852 (3.968, 63.326) LR-: 0.662 (0.591, 0.742)
MIXED AXIAL AND PERIPHERAL									
D'Agostino 2011	Diagnosis of SpA in people with suspected SpA	Not serious	51	48	0.515 (0.417, 0.612)	Rheumatologist diagnosis	Sens.: 0.608 (0.469, 0.731) Spec.: 0.875 (0.748, 0.943)	PPV: 0.838 (0.683, 0.925) NPV: 0.677 (0.552, 0.781)	LR+: 4.863 (2.229, 10.611) LR-: 0.448 (0.313, 0.641)
Godfrin 2004	Diagnosis of SpA in people with entheseal pain	Not serious	13	20[b]	0.394 (0.244, 0.566)	Criteria specified by study authors	Sens.: 0.964 (0.616, 0.998) Spec.: 0.357 (0.185, 0.576)	PPV: 0.500 (0.320, 0.680) NPV: 0.938 (0.461, 0.996)	LR+: 1.500 (1.074, 2.096) LR-: 0.100 (0.006, 1.615)
Tomero 2014	Diagnosis of SpA among people with suspected early SpA	Not serious	538	237	0.694 (0.661, 0.726)	Rheumatologist diagnosis	Sens.: 0.589 (0.547, 0.630) Spec.: 0.861 (0.811, 0.899)	PPV: 0.906 (0.870, 0.932) NPV: 0.480 (0.433, 0.528)	LR+: 4.232 (3.060, 5.853) LR-: 0.477 (0.426, 0.535)

[a] *Number of people with SpA as judged by rheumatologists is not clear form the report and has been estimated*
[b] *Cases classified as nonspecific 'entheseal spondyloarthropathy' treated as negative for spondyloarthritis*

Modified Amor criteria

Table 54: Modified Amor criteria – evidence table

Study	Population	Risk of bias	N		Prevalence	Reference standard	Sensitivity & specificity	Predictive values	Likelihood ratios
			Cases	Non-cases					
AXIAL									
Dougados 2015 (DESIR)	Diagnosis of SpA in people with early inflammatory back pain	Serious[a]	319	389	0.451 (0.414, 0.487)	Rheumatologist diagnosis	Sens.: 0.903 (0.865, 0.931) Spec.: 0.293 (0.250, 0.340)	PPV: 0.512 (0.470, 0.553) NPV: 0.786 (0.712, 0.845)	LR+: 1.277 (1.187, 1.374) LR-: 0.332 (0.229, 0.479)
Rudwaleit 2009 (ASAS)	Diagnosing axial SpA among people with chronic back pain	Not serious	391	258	0.602 (0.564, 0.639)	Rheumatologist diagnosis	Sens.: 0.829 (0.788, 0.863) Spec.: 0.775 (0.720, 0.822)	PPV: 0.848 (0.809, 0.881) NPV: 0.749 (0.694, 0.797)	LR+: 3.686 (2.926, 4.644) LR-: 0.221 (0.176, 0.278)
PERIPHERAL									
Rudwaleit 2011	Diagnosing peripheral SpA among people with peripheral manifestation	Not serious	176	90	0.662 (0.603, 0.716)	Rheumatologist diagnosis	Sens.: 0.398 (0.328, 0.472) Spec.: 0.978 (0.915, 0.994)	PPV: 0.972 (0.896, 0.993) NPV: 0.454 (0.385, 0.524)	LR+: 17.898 (4.492, 71.314) LR-: 0.616 (0.544, 0.697)
MIXED AXIAL AND PERIPHERAL									
no data									

[a] *Number of people with SpA as judged by rheumatologists is not clear form the report and has been estimated*

E.1.8.2 ASAS axial criteria

Table 55: ASAS axial criteria – evidence table

Study	Population	Risk of bias	N		Prevalence	Reference standard	Sensitivity & specificity	Predictive values	Likelihood ratios
			Cases	Non-cases					
AXIAL									
Dougados 2015 (DESIR)	Diagnosis of SpA in people with early inflammatory back pain	Serious[a]	319	389	0.451 (0.414, 0.487)	Rheumatologist diagnosis	Sens.: 0.812 (0.765, 0.851) Spec.: 0.416 (0.368, 0.466)	PPV: 0.533 (0.488, 0.577) NPV: 0.730 (0.668, 0.784)	LR+: 1.391 (1.260, 1.536) LR-: 0.452 (0.349, 0.584)
Rudwaleit 2009 (ASAS)	Diagnosing axial SpA among people with chronic back pain	Not serious	391	258	0.602 (0.564, 0.639)	Rheumatologist diagnosis	Sens.: 0.829 (0.788, 0.863) Spec.: 0.845 (0.796, 0.884)	PPV: 0.890 (0.854, 0.918) NPV: 0.765 (0.712, 0.811)	LR+: 5.345 (4.006, 7.132) LR-: 0.203 (0.162, 0.254)
PERIPHERAL									
no data									
MIXED AXIAL AND PERIPHERAL									
D'Agostino 2011	Diagnosis of SpA in people with suspected SpA	Not serious	23	20	0.535 (0.387, 0.677)	Rheumatologist diagnosis	Sens.: 0.652 (0.443, 0.816) Spec.: 0.800 (0.572, 0.923)	PPV: 0.789 (0.554, 0.919) NPV: 0.667 (0.461, 0.824)	LR+: 3.261 (1.292, 8.231) LR-: 0.435 (0.238, 0.793)

[a] *Number of people with SpA as judged by rheumatologists is not clear form the report and has been estimated*

ASAS axial criteria (imaging 'arm' only)

Table 56: ASAS axial criteria – evidence table

Study	Population	Risk of bias	N		Prevalence	Reference standard	Sensitivity & specificity	Predictive values	Likelihood ratios
			Cases	Non-cases					
AXIAL									
Dougados 2015 (DESIR)	Diagnosis of SpA in people with early inflammatory back pain	Serious[b]	319	389	0.451 (0.414, 0.487)	Rheumatologist diagnosis	Sens.: 0.812 (0.765, 0.851) Spec.: 0.416 (0.368, 0.466)	PPV: 0.533 (0.488, 0.577) NPV: 0.730 (0.668, 0.784)	LR+: 1.391 (1.260, 1.536) LR-: 0.452 (0.349, 0.584)
Rudwaleit 2009 (ASAS)	Diagnosing axial SpA among people with chronic back pain	Not serious	391	258	0.602 (0.564, 0.639)	Rheumatologist diagnosis	Sens.: 0.829 (0.788, 0.863) Spec.: 0.845 (0.796, 0.884)	PPV: 0.890 (0.854, 0.918) NPV: 0.765 (0.712, 0.811)	LR+: 5.345 (4.006, 7.132) LR-: 0.203 (0.162, 0.254)
PERIPHERAL									
no data									
MIXED AXIAL AND PERIPHERAL									
D'Agostino 2011	Diagnosis of SpA in people with suspected SpA	Not serious	23	20	0.535 (0.387, 0.677)	Rheumatologist diagnosis	Sens.: 0.652 (0.443, 0.816) Spec.: 0.800 (0.572, 0.923)	PPV: 0.789 (0.554, 0.919) NPV: 0.667 (0.461, 0.824)	LR+: 3.261 (1.292, 8.231) LR-: 0.435 (0.238, 0.793)

[a] *Number of people with SpA as judged by rheumatologists is not clear form the report and has been estimated*

ASAS axial criteria (imaging 'arm' only)

Table 57: ASAS axial criteria (imaging 'arm' only) – evidence table

Study	Population	Risk of bias	N		Prevalence	Reference standard	Sensitivity & specificity	Predictive values	Likelihood ratios
			Cases	Non-cases					
AXIAL									
Rudwaleit 2009 (ASAS)	Diagnosing axial SpA among people with chronic back pain	Not serious	391	258	0.602 (0.564, 0.639)	Rheumatologist diagnosis	Sens.: 0.662 (0.614, 0.708) Spec.: 0.973 (0.944, 0.987)	PPV: 0.974 (0.946, 0.987) NPV: 0.655 (0.606, 0.701)	LR+: 24.414 (11.717, 50.870) LR-: 0.347 (0.302, 0.399)
PERIPHERAL									
no data									
MIXED AXIAL AND PERIPHERAL									
no data									

E.1.8.3 Berlin algorithm

Original Berlin algorithm

Table 58: Original Berlin algorithm – evidence table

Study	Population	Risk of bias	N		Prevalence	Reference standard	Sensitivity & specificity	Predictive values	Likelihood ratios
			Cases	Non-cases					
AXIAL									
van den Berg 2013b (ASAS)	Diagnosis of axial SpA in people with undiagnosed chronic back pain	Not serious	421	264	0.615 (0.578, 0.650)	Rheumatologist diagnosis	Sens.: 0.653 (0.606, 0.697) Spec.: 0.792 (0.738, 0.836)	PPV: 0.833 (0.789, 0.870) NPV: 0.589 (0.537, 0.639)	LR+: 3.135 (2.454, 4.007) LR-: 0.438 (0.379, 0.506)
van den Berg 2013b (SPACE)	Diagnosis of axial SpA in people with back pain of between 3 months and 2 years	Not serious	65	92	0.414 (0.340, 0.493)	Rheumatologist diagnosis	Sens.: 0.662 (0.539, 0.766) Spec.: 0.837 (0.747, 0.899)	PPV: 0.741 (0.614, 0.838) NPV: 0.778 (0.685, 0.849)	LR+: 4.057 (2.474, 6.653) LR-: 0.404 (0.285, 0.575)
PERIPHERAL									
no data									
MIXED AXIAL AND PERIPHERAL									
D'Agostino 2011	Diagnosis of SpA in people with suspected SpA	Not serious	23	20	0.535 (0.387, 0.677)	Rheumatologist diagnosis	Sens.: 0.609 (0.402, 0.782) Spec.: 0.800 (0.572, 0.923)	PPV: 0.778 (0.535, 0.914) NPV: 0.640 (0.440, 0.801)	LR+: 3.043 (1.194, 7.758) LR-: 0.489 (0.281, 0.852)

Berlin algorithm -- modification #1

Table 59: Berlin algorithm -- modification #1 – evidence table

Study	Population	Risk of bias	N		Prevalence	Reference standard	Sensitivity & specificity	Predictive values	Likelihood ratios
			Cases	Non-cases					
AXIAL									
van den Berg 2013b (ASAS)	Diagnosis of axial SpA in people with undiagnosed chronic back pain	Not serious	421	264	0.615 (0.578, 0.650)	Rheumatologist diagnosis	Sens.: 0.779 (0.737, 0.816) Spec.: 0.723 (0.666, 0.774)	PPV: 0.818 (0.777, 0.853) NPV: 0.673 (0.616, 0.725)	LR+: 2.818 (2.303, 3.447) LR-: 0.305 (0.251, 0.371)
van den Berg 2013b (SPACE)	Diagnosis of axial SpA in people with back pain of between 3 months and 2 years	Not serious	65	92	0.414 (0.340, 0.493)	Rheumatologist diagnosis	Sens.: 0.723 (0.603, 0.818) Spec.: 0.783 (0.687, 0.855)	PPV: 0.701 (0.582, 0.799) NPV: 0.800 (0.705, 0.870)	LR+: 3.326 (2.194, 5.041) LR-: 0.354 (0.235, 0.532)
PERIPHERAL									
no data									
MIXED AXIAL AND PERIPHERAL									
no data									

Berlin algorithm -- modification #2

Table 60: Berlin algorithm -- modification #2 – evidence table

Study	Population	Risk of bias	N		Prevalence	Reference standard	Sensitivity & specificity	Predictive values	Likelihood ratios
			Cases	Non-cases					
AXIAL									
van den Berg 2013b (ASAS)	Diagnosis of axial SpA in people with undiagnosed chronic back pain	Not serious	421	264	0.615 (0.578, 0.650)	Rheumatologist diagnosis	Sens.: 0.796 (0.755, 0.832) Spec.: 0.758 (0.702, 0.805)	PPV: 0.840 (0.800, 0.872) NPV: 0.699 (0.644, 0.750)	LR+: 3.282 (2.638, 4.085) LR-: 0.270 (0.221, 0.330)
van den Berg 2013b (SPACE)	Diagnosis of axial SpA in people with back pain of between 3 months and 2 years	Not serious	65	92	0.414 (0.340, 0.493)	Rheumatologist diagnosis	Sens.: 0.785 (0.668, 0.868) Spec.: 0.804 (0.711, 0.873)	PPV: 0.739 (0.623, 0.829) NPV: 0.841 (0.749, 0.903)	LR+: 4.010 (2.600, 6.186) LR-: 0.268 (0.167, 0.431)
PERIPHERAL									
no data									
MIXED AXIAL AND PERIPHERAL									
no data									

E.1.8.4 ESSG criteria

Original ESSG criteria

Table 61: Original ESSG criteria – evidence table

Study	Population	Risk of bias	N		Prevalence	Reference standard	Sensitivity & specificity	Predictive values	Likelihood ratios
			Cases	Non-cases					
AXIAL									
Dougados 2015 (DESIR)	Diagnosis of SpA in people with early inflammatory back pain	Serious[a]	319	389	0.451 (0.414, 0.487)	Rheumatologist diagnosis	Sens.: 0.871 (0.830, 0.904) Spec.: 0.298 (0.255, 0.346)	PPV: 0.505 (0.463, 0.546) NPV: 0.739 (0.665, 0.802)	LR+: 1.242 (1.149, 1.342) LR-: 0.431 (0.312, 0.596)
Rudwaleit 2009 (ASAS)	Diagnosing axial SpA among people with chronic back pain	Not serious	391	258	0.602 (0.564, 0.639)	Rheumatologist diagnosis	Sens.: 0.724 (0.677, 0.766) Spec.: 0.663 (0.603, 0.718)	PPV: 0.765 (0.719, 0.805) NPV: 0.613 (0.554, 0.668)	LR+: 2.146 (1.790, 2.574) LR-: 0.417 (0.347, 0.500)
PERIPHERAL									
Rudwaleit 2011	Diagnosing peripheral SpA among people with peripheral manifestation	Not serious	176	90	0.662 (0.603, 0.716)	Rheumatologist diagnosis	Sens.: 0.551 (0.477, 0.623) Spec.: 0.811 (0.717, 0.879)	PPV: 0.851 (0.773, 0.905) NPV: 0.480 (0.402, 0.560)	LR+: 2.918 (1.863, 4.569) LR-: 0.553 (0.457, 0.670)
MIXED AXIAL AND PERIPHERAL									
D'Agostino 2011	Diagnosis of SpA in people with suspected SpA	Not serious	51	48	0.515 (0.417, 0.612)	Rheumatologist diagnosis	Sens.: 0.784 (0.651, 0.876) Spec.: 0.625 (0.482, 0.749)	PPV: 0.690 (0.560, 0.795) NPV: 0.732 (0.577, 0.845)	LR+: 2.092 (1.412, 3.097) LR-: 0.345 (0.196, 0.609)
Godfrin 2004	Diagnosis of SpA in people with entheseal pain	Not serious	13	20	0.394 (0.244, 0.566)	Criteria specified by study authors (plus Amor and ESSG criteria)	Sens.: 0.964 (0.616, 0.998) Spec.: 0.405 (0.221, 0.619)	PPV: 0.519 (0.334, 0.700) NPV: 0.944 (0.495, 0.997)	LR+: 1.620 (1.123, 2.338) LR-: 0.088 (0.006, 1.409)
Tomero 2014	Diagnosis of SpA among people with suspected early SpA	Not serious	538	237	0.694 (0.661, 0.726)	Rheumatologist diagnosis	Sens.: 0.580 (0.538, 0.621) Spec.: 0.899 (0.853, 0.931)	PPV: 0.929 (0.896, 0.952) NPV: 0.485 (0.439, 0.532)	LR+: 5.727 (3.893, 8.425) LR-: 0.467 (0.420, 0.521)

[a] *Number of people with SpA as judged by rheumatologists is not clear form the report and has been estimated*

Modified ESSG criteria

Table 62: Modified ESSG criteria – evidence table

Study	Population	Risk of bias	N		Prevalence	Reference standard	Sensitivity & specificity	Predictive values	Likelihood ratios
			Cases	Non-cases					
AXIAL									
Dougados 2015 (DESIR)	Diagnosis of SpA in people with early inflammatory back pain	Serious[a]	319	389	0.451 (0.414, 0.487)	Rheumatologist diagnosis	Sens.: 0.912 (0.876, 0.939) Spec.: 0.237 (0.197, 0.281)	PPV: 0.495 (0.455, 0.535) NPV: 0.767 (0.683, 0.834)	LR+: 1.195 (1.120, 1.275) LR-: 0.371 (0.250, 0.552)
Rudwaleit 2009 (ASAS)	Diagnosing axial SpA among people with chronic back pain	Not serious	391	258	0.602 (0.564, 0.639)	Rheumatologist diagnosis	Sens.: 0.852 (0.813, 0.884) Spec.: 0.651 (0.591, 0.707)	PPV: 0.787 (0.746, 0.824) NPV: 0.743 (0.682, 0.796)	LR+: 2.441 (2.056, 2.899) LR-: 0.228 (0.177, 0.294)
PERIPHERAL									
Rudwaleit 2011	Diagnosing peripheral SpA among people with peripheral manifestation	Not serious	176	90	0.662 (0.603, 0.716)	Rheumatologist diagnosis	Sens.: 0.625 (0.551, 0.693) Spec.: 0.811 (0.717, 0.879)	PPV: 0.866 (0.795, 0.915) NPV: 0.525 (0.442, 0.607)	LR+: 3.309 (2.124, 5.154) LR-: 0.462 (0.373, 0.573)
MIXED AXIAL AND PERIPHERAL									
no data									

[a] *Number of people with SpA as judged by rheumatologists is not clear form the report and has been estimated*

E.1.8.5 New York criteria

Original New York criteria

Table 63: Original New York criteria

Study	Population	Risk of bias	N		Prevalence	Reference standard	Sensitivity & specificity	Predictive values	Likelihood ratios
			Cases	Non-cases					
AXIAL									
Rigby 1993	Diagnosis of AS in people attending a rheumatology clinic	Serious[a,b]	30	182	0.142 (0.101, 0.195)	Clinician diagnosis	Sens.: 0.733 (0.550, 0.861) Spec.: 0.956 (0.915, 0.978)	PPV: 0.733 (0.550, 0.861) NPV: 0.956 (0.915, 0.978)	LR+: 16.683 (8.193, 33.971) LR-: 0.279 (0.154, 0.505)
PERIPHERAL									
no data									
MIXED AXIAL AND PERIPHERAL									
no data									

[a] *Retrospective study*
[b] *Testers not blinded to final diagnosis*

Modified New York criteria

Table 64: Modified New York criteria – evidence table

Study	Population	Risk of bias	N		Prevalence	Reference standard	Sensitivity & specificity	Predictive values	Likelihood ratios
			Cases	Non-cases					
AXIAL									
Dougados 2015 (DESIR)	Diagnosis of SpA in people with early inflammatory back pain	Serious[a]	319	389	0.451 (0.414, 0.487)	Rheumatologist diagnosis	Sens.: 0.401 (0.349, 0.456) Spec.: 0.848 (0.809, 0.881)	PPV: 0.684 (0.614, 0.747) NPV: 0.633 (0.591, 0.674)	LR+: 2.646 (2.018, 3.468) LR-: 0.706 (0.639, 0.779)
Rigby 1993	Diagnosis of AS in people attending a rheumatology clinic	Serious[b,c]	30	182	0.142 (0.101, 0.195)	Clinician diagnosis	Sens.: 0.800 (0.621, 0.907) Spec.: 0.967 (0.929, 0.985)	PPV: 0.800 (0.621, 0.907) NPV: 0.967 (0.929, 0.985)	LR+: 24.267 (10.828, 54.382) LR-: 0.207 (0.101, 0.423)
PERIPHERAL									
no data									
MIXED AXIAL AND PERIPHERAL									
no data									

[a] *Number of people with SpA as judged by rheumatologists is not clear form the report and has been estimated*
[b] *Retrospective study*
[c] *Testers not blinded to final diagnosis*

E.1.8.6 Rome criteria

Rome criteria (clinical)

Table 65: Rome criteria (clinical) – evidence table

Study	Population	Risk of bias	N		Prevalence	Reference standard	Sensitivity & specificity	Predictive values	Likelihood ratios
			Cases	Non-cases					
AXIAL									
Rigby 1993	Diagnosis of AS in people attending a rheumatology clinic	Serious[a,b]	30	182	0.142 (0.101, 0.195)	Clinician diagnosis	Sens.: 0.267 (0.139, 0.450) Spec.: 0.879 (0.823, 0.919)	PPV: 0.267 (0.139, 0.450) NPV: 0.879 (0.823, 0.919)	LR+: 2.206 (1.083, 4.492) LR-: 0.834 (0.668, 1.042)
PERIPHERAL									
no data									
MIXED AXIAL AND PERIPHERAL									
no data									

[a] *Retrospective study*
[b] *Testers not blinded to final diagnosis*

Rome criteria (radiographic)

Table 66: Rome criteria (radiographic) – evidence table

Study	Population	Risk of bias	N		Prevalence	Reference standard	Sensitivity & specificity	Predictive values	Likelihood ratios
			Cases	Non-cases					
AXIAL									
Rigby 1993	Diagnosis of AS in people attending a rheumatology clinic	Serious[a,b]	30	182	0.142 (0.101, 0.195)	Clinician diagnosis	Sens.: 0.867 (0.694, 0.949) Spec.: 0.978 (0.943, 0.992)	PPV: 0.867 (0.694, 0.949) NPV: 0.978 (0.943, 0.992)	LR+: 39.433 (14.811, 104.991) LR-: 0.136 (0.055, 0.340)
PERIPHERAL									
no data									
MIXED AXIAL AND PERIPHERAL									
no data									

[a] *Retrospective study*
[b] *Testers not blinded to final diagnosis*

E.1.8.7 ASAS peripheral criteria

Table 67: ASAS peripheral criteria – evidence table

Study	Population	Risk of bias	N		Prevalence	Reference standard	Sensitivity & specificity	Predictive values	Likelihood ratios
			Cases	Non-cases					
AXIAL									
no data									
PERIPHERAL									
Rudwaleit 2011	Diagnosing peripheral SpA among people with peripheral manifestation	Not serious	176	90	0.662 (0.603, 0.716)	Rheumatologist diagnosis	Sens.: 0.778 (0.711, 0.834) Spec.: 0.822 (0.729, 0.888)	PPV: 0.895 (0.836, 0.935) NPV: 0.655 (0.563, 0.737)	LR+: 4.379 (2.788, 6.875) LR-: 0.270 (0.201, 0.361)
MIXED AXIAL AND PERIPHERAL									
no data									

E.1.8.8 French Society for Rheumatology criteria for reactive arthritis

Table 68: French Society for Rheumatology criteria for reactive arthritis – evidence table

Study	Population	Risk of bias	N		Prevalence	Reference standard	Sensitivity & specificity	Predictive values	Likelihood ratios
			Cases	Non-cases					
AXIAL									
no data									
PERIPHERAL									
Hulsemann 1999	Diagnosis of ReA among people with suspected inflammatory rheumatological diseases	Serious[a]	24	193	0.111 (0.075, 0.160)	Clinician diagnosis	Sens.: 0.792 (0.587, 0.911) Spec.: 0.922 (0.875, 0.953)	PPV: 0.559 (0.392, 0.714) NPV: 0.973 (0.936, 0.989)	LR+: 10.186 (6.010, 17.263) LR-: 0.226 (0.103, 0.493)
MIXED AXIAL AND PERIPHERAL									
no data									

[a] *Majority of people end as undifferentiated arthritis*

E.1.8.9 Diagnosis of spondyloarthritis in people presenting with acute anterior uveitis

DUET algorithm for acute anterior uveitis

Table 69: DUET algorithm for acute anterior uveitis – evidence table

Study	Population	Risk of bias	N		Prevalence	Reference standard	Sensitivity & specificity	Predictive values	Likelihood ratios
			Cases	Non-cases					
AXIAL									
no data									
PERIPHERAL									
no data									
MIXED AXIAL AND PERIPHERAL									
Haroon 2015	Diagnosis of SpA in people with acute anterior uveitis	Not serious	42	59	0.416 (0.324, 0.514)	Rheumatologist diagnosis	Sens.: 0.952 (0.829, 0.988) Spec.: 0.983 (0.889, 0.998)	PPV: 0.976 (0.846, 0.997) NPV: 0.967 (0.876, 0.992)	LR+: 56.190 (8.039, 392.763) LR-: 0.048 (0.013, 0.187)
Haroon 2015	Diagnosis of SpA in people with acute anterior uveitis	Not serious	29	43	0.403 (0.296, 0.519)	Rheumatologist diagnosis	Sens.: 0.966 (0.792, 0.995) Spec.: 0.977 (0.853, 0.997)	PPV: 0.966 (0.792, 0.995) NPV: 0.977 (0.853, 0.997)	LR+: 41.517 (5.977, 288.406) LR-: 0.035 (0.005, 0.242)

E.1.9 Microbiology testing in Reactive Arthritis

Review Question 11

- What is the diagnostic utility of testing for infection such as salmonella, shigella, yersinia, campylobacter and chlamydia in cases of suspected reactive arthritis?

<table>
<tr><th>Full citation</th><th>Granfors K, Viljanen M, Tiilikainen A, et al. Persistence of IgM, IgG and IgA antibodies to Yersinia in Yersinia arthritis. Journal of Infectious Diseases 1980 141:424-9</th></tr>
<tr><td>Study details</td><td>Country/ies where the study was carried out: Finland
Study type: Prospective cohort study
Aim of the study: To investigate the persistence of IgM, IgG and IgA antibodies after Yerisnia infection in people who do/do not develop reactive arthritis
Study dates: Not reported
Sources of funding: Association of Finnish Life insurance Companies</td></tr>
<tr><td>Participants</td><td>Sample size: 37 people
Inclusion criteria
Acute infection with Y. enterocolitica serotype O:3, diagnosed by serological/bacteriological findings and clinical picture</td></tr>
<tr><td>Methods</td><td>Diagnostic definition of reactive arthritis
Joint symptoms and subjective pain
Infection tests
Blood culture (ELISA for IgM, IgG and IgA antibodies to Yersinia)</td></tr>
<tr><td>Results</td><td>Diagnostic accuracy results
<table>
<tr><td rowspan="2">ReA diagnosis</td><td colspan="3">1-2 months</td><td colspan="3">6-8 months</td><td colspan="3">14-16 months</td></tr>
<tr><td>IgM</td><td>IgG</td><td>IgA</td><td>IgM</td><td>IgG</td><td>IgA</td><td>IgM</td><td>IgG</td><td>IgA</td></tr>
<tr><td>Negative</td><td>10/12</td><td>12/12</td><td>12/12</td><td>0/12</td><td>7/12</td><td>1/12</td><td>0/9</td><td>2/9</td><td>1/9</td></tr>
<tr><td>Positive</td><td>21/25</td><td>25/25</td><td>25/25</td><td>0/25</td><td>23/25</td><td>21/25</td><td>0/15</td><td>11/15</td><td>14/15</td></tr>
</table></td></tr>
<tr><td>Comments</td><td>Risk of bias:
No rigorous method used for diagnosing reactive arthritis
Potentially informative dropout during study</td></tr>
</table>

<table>
<tr><th>Full citation</th><th>Locht H, Kihlstroem E, Lindstroem FD. ReA after Salmonella among medical doctors – study of an outbreak. Journal of Rheumatology 1993 20:845-8</th></tr>
<tr><td>Study details</td><td>Country/ies where the study was carried out: Sweden
Study type: Post-outbreak cross-sectional study
Aim of the study: To investigate an outbreak of S. enteritidis enterocolitis which occurred at a radiology symposium in Malmö, Sweden in March 1990
Study dates: 1990
Sources of funding: King Gustav V's 80-year foundation, the Swedish Association against Rheumatism and Professor Nanna Swartz' Foundation</td></tr>
<tr><td>Participants</td><td>Sample size: 29 people reporting joint symptoms (out of 126 people send questionnaires)
Inclusion criteria
Attendance at 1990 Swedish Society of Radiology conference
Joint symptoms</td></tr>
<tr><td>Methods</td><td>Diagnostic definition of reactive arthritis
Pain in a previously healthy joint at a well-defined anatomical location within the first 4 weeks after exposure
Infection tests
Stool culture
Blood samples taken but results not reported for suspected reactive arthritis population</td></tr>
<tr><td>Results</td><td>Diagnostic accuracy results
<table>
<tr><td></td><td>Reactive arthritis</td><td>No reactive arthritis</td><td>Total</td></tr>
<tr><td>Culture positive</td><td>16</td><td>9</td><td>25</td></tr>
<tr><td>Culture negative</td><td>1</td><td>3</td><td>4</td></tr>
<tr><td>Total</td><td>17</td><td>12</td><td>29</td></tr>
</table></td></tr>
<tr><td>Comments</td><td>Risk of bias:
No rigorous method used for diagnosing reactive arthritis
Only 113 of 126 people returned questionnaires</td></tr>
</table>

<table>
<tr><th>Full citation</th><th>Mattila L, Leirisalo-Repo M, Pelkonen P, et al. Reactive arthritis following an outbreak of Salmonella Bovismorbificans infection. Journal of Infection 1998 36:289-95</th></tr>
<tr><td>Study details</td><td>Country/ies where the study was carried out: Finland
Study type: Post-outbreak cross-sectional study
Aim of the study: To investigate reactive arthritis outcomes following an outbreak of S. bovismorbificans
Study dates: 1994</td></tr>
</table>

<table>
<tr><th>Full citation</th><td>Mattila L, Leirisalo-Repo M, Pelkonen P, et al. Reactive arthritis following an outbreak of Salmonella Bovismorbificans infection. Journal of Infection 1998 36:289-95</td></tr>
<tr><td></td><td>Sources of funding: Not reported</td></tr>
<tr><td>Participants</td><td>Sample size: 45 people reporting joint symptoms (out of 210 people send questionnaires)
Inclusion criteria
Positive stool culture
Joint symptoms</td></tr>
<tr><td>Methods</td><td>Diagnostic definition of reactive arthritis
Development of synovitis (both swelling and tenderness) in a previously asymptomatic joint within the first weeks after the exposure in patients without another diagnosis or current inflammatory rheumatological diagnosis
Infection tests
Blood culture (Salmonella-specific IgM, IgA and IgG antibodies)</td></tr>
<tr><td>Results</td><td>Diagnostic accuracy results (Any class)
<table>
<tr><td></td><td>Reactive arthritis</td><td>No reactive arthritis</td><td>Total</td></tr>
<tr><td>Antibody positive</td><td>18</td><td>12</td><td>30</td></tr>
<tr><td>Antibody negative</td><td>4</td><td>11</td><td>15</td></tr>
<tr><td>Total</td><td>22</td><td>23</td><td>45</td></tr>
</table>
Diagnostic accuracy results (IgA)
<table>
<tr><td></td><td>Reactive arthritis</td><td>No reactive arthritis</td><td>Total</td></tr>
<tr><td>Antibody positive</td><td>5</td><td>2</td><td>30</td></tr>
<tr><td>Antibody negative</td><td>17</td><td>21</td><td>15</td></tr>
<tr><td>Total</td><td>22</td><td>23</td><td>45</td></tr>
</table>
Diagnostic accuracy results (IgM)
<table>
<tr><td></td><td>Reactive arthritis</td><td>No reactive arthritis</td><td>Total</td></tr>
<tr><td>Antibody positive</td><td>18</td><td>12</td><td>30</td></tr>
<tr><td>Antibody negative</td><td>4</td><td>11</td><td>15</td></tr>
<tr><td>Total</td><td>22</td><td>23</td><td>45</td></tr>
</table>
Diagnostic accuracy results (IgG)
<table>
<tr><td></td><td>Reactive arthritis</td><td>No reactive arthritis</td><td>Total</td></tr>
</table></td></tr>
</table>

Full citation	**Mattila L, Leirisalo-Repo M, Pelkonen P, et al. Reactive arthritis following an outbreak of Salmonella Bovismorbificans infection. Journal of Infection 1998 36:289-95**
	Antibody positive: 17 / 12 / 30 Antibody negative: 5 / 11 / 15 Total: 22 / 23 / 45
Comments	Risk of bias: No rigorous method used for diagnosing reactive arthritis Only 191 of 210 people returned questionnaires Only 45 people out of 52 with joint symptoms underwent clinical examination

Full citation	**Toivanen A, Lahesmaa-Rantala R, Vuento R, et al. Association of persisting IgA response with Yersinia triggered reactive arthritis: a study on 104 patients. Annals of the Rheumatic Diseases 1987 46:898-901**
Study details	Country/ies where the study was carried out: Finland Study type: Prospective cohort study Aim of the study: To investigate the persistence of IgM, IgG and IgA antibodies after Yerisnia infection in people who do/do not develop reactive arthritis Study dates: Not reported Sources of funding: Sigrid Jusélius Foundation, Finnish Medical Foundation, Turku University Foundation, US Public Health Service
Participants	Sample size: 104 people Inclusion criteria Acute infection with Y. enterocolitica serotype O:3, diagnosed by serological/bacteriological findings and clinical picture
Methods	Diagnostic definition of reactive arthritis Joint symptoms and subjective pain Infection tests Blood culture (ELISA for IgM, IgG and IgA antibodies to Yersinia)
Results	Diagnostic accuracy results

ReA diagnosis	1-2 months			6-8 months			12-16 months		
	IgM	IgG	IgA	IgM	IgG	IgA	IgM	IgG	IgA
Negative	35/41	39/41	37/41	15/36	25/36	14/36	5/22	11/22	7/22
Positive	49/60	55/60	60/60	22/56	47/56	45/56	10/39	28/39	33/39

Full citation	**Toivanen A, Lahesmaa-Rantala R, Vuento R, et al. Association of persisting IgA response with Yersinia triggered reactive arthritis: a study on 104 patients. Annals of the Rheumatic Diseases 1987 46:898-901**
Comments	Risk of bias: No rigorous method used for diagnosing reactive arthritis Potentially informative dropout during study

Full citation	**Uotila T, Antonen J, Laine J, et al. Reactive arthritis in a population exposed to an extensive waterborne gastroenteritis outbreak after sewage contamination in Pirkanmaa, Finland. Scandinavian Journal of Rheumatology 2011 40:358-62**
Study details	**Country/ies where the study was carried out:** Finland **Study type:** Cross-sectional study **Aim of the study:** To assess the occurrence, clinical picture and triggering infections of reactive arthritis (ReA) associated with a large waterborne gastroenteritis outbreak **Study dates:** 2007-2008 **Sources of funding:** Medical Research Fund of Tampere University Hospital
Participants	**Sample size:** 45 people (new referrals) **Inclusion criteria** • Swollen joints or sacroiliitis-like symptoms
Methods	**Diagnostic definition of reactive arthritis** • Synovitis, tendinitis, enthesopathy, bursitis or probable sacroiliitis, with symptoms starting within 2 months of the outbreak **Infection tests** • Faecal culture • Blood culture (Antibodies against Campylobacter, Salmonella and Yersinia (EIA))
Results	**Diagnostic accuracy results (antibodies)**

	Reactive arthritis	No reactive arthritis
Antibody positive	6	4
Antibody negative	15	20
Total	21	24

Diagnostic accuracy results (faecal culture)

	Reactive arthritis	No reactive arthritis	Total
Culture positive	2	3	5
Culture negative	19	21	40
Total	21	24	45

Comments	**Risk of bias:**

Full citation	Uotila T, Antonen J, Laine J, et al. Reactive arthritis in a population exposed to an extensive waterborne gastroenteritis outbreak after sewage contamination in Pirkanmaa, Finland. Scandinavian Journal of Rheumatology 2011 40:358-62
	• No rigorous method used for diagnosing reactive arthritis

E.2 Pharmacological management

E.2.1 Pharmacological interventions for axial symptoms of spondyloarthritis

Review question 20

- What is the comparative effectiveness of non-steroidal anti-inflammatory drugs (NSAIDs) for management of axial symptoms of spondyloarthritis?

Table 1: Astorga, 1987

Bibliographic reference	Astorga,G., Double-blind, parallel clinical trial of tenoxicam (Ro 12-0068) versus piroxicam in patients with ankylosing spondylitis, European journal of rheumatology and inflammation, 9, 70-73, 1987
Country/ies where the study was carried out	Chile
Study type	Parallel, double blind
Aim of the study	To determine the efficacy and tolerance of tenoxicam versus piroxicam in patients with ankylosing spondylitis.
Study dates	Not reported
Source of funding	Not reported
Sample size	n=20
Inclusion criteria	Lumbar and stomach pain during the day and night but more marked in the morning Marked morning lumbar stiffness Objective limitation of spinal movement Radiological signs characteristic of affected sacroiliac joints
Exclusion criteria	None reported
Details	Patients were randomly assigned to treatment with tenoxicam or piroxicam
Interventions	Tenoxicam 20mg/ day (TEN) Piroxicam 20mg/ day (PIR) Each patient received one capsule daily, before breakfast of either tenoxicam or piroxicam for a period of 6 months. Controls were carried out every 30 days.
Characteristics	Sex Reported as number female / total (%) TEN: 1/10 (10%) PIR: 2/10 (")%) Age (years) Reported as mean (SD)

Table 1: Astorga, 1987

Bibliographic reference	Astorga,G., Double-blind, parallel clinical trial of tenoxicam (Ro 12-0068) versus piroxicam in patients with ankylosing spondylitis, European journal of rheumatology and inflammation, 9, 70-73, 1987
	TEN:47.8 (8.8) PIR: 46.4 (7.9) Duration of disease (years) Reported as mean (SD) TEN: 72.8 (8.0) PIR: 72.6 (13.9)
Results	Pain: reported as Diurnal lumbosacral pain absent at 6 months: TEN: 3/10 (30%) PIR: 3/10 (30%) Comparison (Mann Whitney U) 6 months did not show a significant difference (p>0.05) Discontinuations due to adverse effects Not reported Discontinuation due to lack of efficacy: Not reported
Overall Risk of Bias	Allocation concealment: not reported Method of randomisation: not reported Dropouts: not reported Very small study
Other information	Pain on movement also reported, though presented in a graph with no figures, only states that significant improvement in the tenoxicam group (p<0.05) but not in the piroxicam group or between groups.
Was the allocation sequence adequately generated?	UNCLEAR
Was allocation adequately concealed?	UNCLEAR
Was knowledge of the allocated intervention	UNCLEAR

Table 1: Astorga, 1987

Bibliographic reference	Astorga,G., Double-blind, parallel clinical trial of tenoxicam (Ro 12-0068) versus piroxicam in patients with ankylosing spondylitis, European journal of rheumatology and inflammation, 9, 70-73, 1987
adequately prevented during the study?	
Were incomplete outcome data adequately addressed?	UNCLEAR
Are reports of the study free of suggestion of selective outcome reporting?	UNCLEAR
Was the study apparently free of other problems that could put it at a high risk of bias?	UNCLEAR

Table 70: Barkhuizen et al., 2006

Bibliographic reference	Barkhuizen,Andre, Steinfeld,Serge, Robbins,Jeffery, West,Christine, Coombs,John, Zwillich,Samuel, Celecoxib is efficacious and well tolerated in treating signs and symptoms of ankylosing spondylitis, The Journal of rheumatology, 33, 1805-1812, 2006
Country/ies where the study was carried out	USA
Study type	Randomised, double blind, placebo-controlled, parallel group study.
Aim of the study	To evaluate the efficacy and safety of celecoxib in patients with AS
Study dates	Not reported.
Source of funding	Supported by Pfizer
Sample size	n=611

<table>
<tr><th>Bibliographic reference</th><th>Barkhuizen,Andre, Steinfeld,Serge, Robbins,Jeffery, West,Christine, Coombs,John, Zwillich,Samuel, Celecoxib is efficacious and well tolerated in treating signs and symptoms of ankylosing spondylitis, The Journal of rheumatology, 33, 1805-1812, 2006</th></tr>
<tr><td>Inclusion criteria</td><td>Patients aged 18-75 years with AS as defined by modified New York criteria (clinical and radiologic) with axial involvement and requiring daily treatment with NSAID during the previous 30 days. Patients with or without peripheral enthesopathy and large peripheral synovitis (hip, knees and or shoulders). Patients with psoriasis were included in the study.
High pain intensity (>50mm on a 100mm VAS scale), worsening by 30% compared with that at the pre-inclusion visit following discontinuation of existing therapy.
Women of childbearing age had to be using and continue to use effective contraception throughout the trial, and had to have a negative pregnancy test at the time of inclusion.
Sulfasalazine was allowed if patient was taking a stable dose for 60 days prior to screening.</td></tr>
<tr><td>Exclusion criteria</td><td>Patients with distal small-joint synovitis were excluded, as were patients with known inflammatory enteropathy (ulcerative colitis, Crohn's disease) any extra-articular signs (e.g. uveitis) or any vertebral compression.
Patients were also excluded if they needed to wear a corset during the course of the trial and if they required commencement of physiotherapy, re-education or manipulation, or if they required constant use of muscle relaxants, hypnotics, anxiolytics, sedatives, tranquilisers or antidepressants (unless taking stable doses for 2 weeks prior to inclusion). Patients receiving corticosteroids for 6 weeks prior to study start were excluded, as were those using anticoagulants, ticlopidine, or lithium. Patients receiving methotrexate >25mg/ week or anti-TNF agents.
Patients with a history of gastroduodenal ulcer confirmed by endoscopy in the 30 days prior to inclusion, or with current GI bleeding, Patients with known hypersensitivity to study drugs, asthma, chronic disease, or current or previous malignancy.</td></tr>
<tr><td>Details</td><td>There was a 14 day pre-treatment period that included a pre-inclusion/ screening visit and a 12 week treatment period. The treatment period included a visit at baseline and assessments at weeks 1,3,6 and 12 (or early termination).
Patients were randomised to receive one of four study drugs. The first dose was taken at baseline visit. Rescue acetaminophen was provided to patients to be taken as needed, but only up to a dose of 2000 mg/day.</td></tr>
<tr><td>Interventions</td><td>Placebo
Celecoxib 200mg qd
Celecoxib 400mg qd
Naproxen 500mg bid</td></tr>
<tr><td>Characteristics</td><td>
<table>
<tr><td>Parameter</td><td>Placebo (n=156)</td><td>Celecoxib 200mg (n=137)</td><td>Celecoxib 400mg (n=161)</td><td>Naproxen 500mg bid (n=157)</td></tr>
<tr><td>Age, years, mean (SD)</td><td>43.8 (11.5)</td><td>43.9 (11.9)</td><td>45.1 (11.6)</td><td>45.4 (12.6)</td></tr>
<tr><td>Male/female, n (%)</td><td>114 (73)/42 (27)</td><td>108 (79)/29 (27)</td><td>112 (70)/49 (30)</td><td>117 (75)/ 40 (25)</td></tr>
</table>
</td></tr>
</table>

<table>
<tr><th>Bibliographic reference</th><th>Barkhuizen,Andre, Steinfeld,Serge, Robbins,Jeffery, West,Christine, Coombs,John, Zwillich,Samuel, Celecoxib is efficacious and well tolerated in treating signs and symptoms of ankylosing spondylitis, The Journal of rheumatology, 33, 1805-1812, 2006</th></tr>
<tr><td></td><td>
<table>
<tr><td>Patients global assessment of pain intensity, mean (SD)</td><td>73.5 (16.6)</td><td>70.8 (15.6)</td><td>71.4 (15.4)</td><td>71.7 (15.6)</td></tr>
<tr><td>Patient's global assessment of disease activity, mean (SD)</td><td>69.1 (21.4)</td><td>65.9 (20.5)</td><td>65.3 (22.5)</td><td>66.1 (20.1)</td></tr>
<tr><td>Functional index (BASFI), mean (SD)</td><td>54.4 (22.2)</td><td>50.0 (25.2)</td><td>51.7 (24.2)</td><td>52.0 (21.8)</td></tr>
</table>
</td></tr>
<tr><td>Results</td><td>Results for VAS global pain intensity only presented graphically, study reports that there was significant reduction in pain were significantly greater (p<0.05) in the naproxen, celecoxib 200mg and celecoxib 400mg groups compared to placebo.
Withdrawals due to adverse events:
<table>
<tr><td>Outcome</td><td>Placebo</td><td>Celecoxib 200mg</td><td>Celecoxib 400mg</td><td>Naproxen 500mg bid</td></tr>
<tr><td>Withdrawals due to adverse events, n (%)</td><td>11 (7)</td><td>3 (2)</td><td>9 (6)</td><td>9 (6)</td></tr>
</table>
Withdrawals due to lack of efficacy (calculated from % of initial participants in each group, actual numbers not reported):
<table>
<tr><td></td><td>Placebo (n=156)</td><td>Celecoxib 200mg (n= 137)</td><td>Celecoxib 400mg (n=161)</td><td>Naproxen 500mg bid (n=157)</td></tr>
<tr><td>Withdrawals due to lack of efficacy, n (%)</td><td>59 (38)</td><td>25 (18)</td><td>23 (14)</td><td>17 (11)</td></tr>
</table>
</td></tr>
<tr><td>Overall Risk of Bias</td><td>Allocation concealment not reported.
High rate of dropouts:
Placebo: n=100 (73%)
Celecoxib 200mg: 100 (73%)
Celecoxib 400mg: 118 (75%)</td></tr>
</table>

Bibliographic reference	Barkhuizen,Andre, Steinfeld,Serge, Robbins,Jeffery, West,Christine, Coombs,John, Zwillich,Samuel, Celecoxib is efficacious and well tolerated in treating signs and symptoms of ankylosing spondylitis, The Journal of rheumatology, 33, 1805-1812, 2006
	Naproxen: 118 (75%) Raw data for VAS pain not presented in study, therefore unable to analyse further.
Other information	Primary efficacy measures were least squares mean changes from baseline to week 12 for patient's assessment of global pain intensity, patient global assessment of disease activity and functional ability (BASFI). Calculated that a sample size of 150 patients per treatment group would allow a least squares mean change from baseline between treatment groups of 10mm in the patients' assessment of pain intensity.. All efficacy analyses were undertaken using ITT, defined as patients who were randomised to treatment and took at least one dose of study medication. Primary outcomes analysed using 2 way ANCOVA, with centre and treatment as effects and baseline as covariate. The primary comparisons were pre-specified to be between celecoxib and placebo.
Was the allocation sequence adequately generated?	YES
Was allocation adequately concealed?	YES
Was knowledge of the allocated intervention adequately prevented during the study?	UNCLEAR
Were incomplete outcome data adequately addressed?	UNCLEAR
Are reports of the study free of suggestion of selective outcome reporting?	UNCLEAR
Was the study apparently free of other problems that could put it at a high risk of bias?	NO

Table 71: Batlle-Gualda et al., 1996

Bibliographic reference	Batlle-Gualda,E., Figueroa,M., Ivorra,J., Raber,A., The efficacy and tolerability of aceclofenac in the treatment of patients with ankylosing spondylitis: a multicenter controlled clinical trial. Aceclofenac Indomethacin Study Group, The Journal of rheumatology, 23, 1200-1206, 1996
Country/ies where the study was carried out	Spain, 18 rheumatology departments
Study type	Multicentre, parallel, double blind trial
Aim of the study	To evaluate the efficacy and tolerability of aceclofenac in patients with AS
Study dates	Not reported
Source of funding	Not reported
Sample size	n=310
Inclusion criteria	Patients with definite AS according to New York criteria, outpatients aged 20-50 years with active disease defined by at least 2 of the following criteria: morning stiffness >30min, pain requiring daily treatment with NSAID, pain >40mm on a 100mm VAS scale. Patients with peripheral joint disease were not excluded.
Exclusion criteria	Reiter's syndrome or any other type of arthritis, pregnancy or lactation, psoriasis, inflammatory bowel disease, Paget's disease, haemachromatosis, uncontrolled hypertension, renal or hepatic disease, concomitant serious medical condition or expected survival time <2 years, MI or stoke in the last 4 months, history of peptic ulceration, or upper GI bleeding, history of angina or asthma associated with an NSAID, hypersensitivity to aspirin or other NSAID, use of sulfasalazine, corticosteroid or immunosuppressive drugs in the previous 3 months, concomitant use of oral anticoagulants, benzodiazepines, lithium, antidepressants, phenytoin, neuroleptics, diuretics, thyroxine or probenecid. Female patients of child bearing age not using contraceptive measures, patients enrolled in any other clinical trial within the previous 3 months.
Details	Initial screening visit followed by 1 week washout period for patients already taking NSAIDs, during which paracetamol alone was used for control of symptoms. Patients were allocated randomly, in balanced groups of 4 within each centre to one of the 2 blinded treatment groups.
Interventions	Aceclofenac group: 1 x 100mg tablet in the morning, one tablet of placebo at noon and 1 x 100mg tablet at night. Indomethacin group: 1 x 25mg tablet in the morning, 1 x 25mg tablet at noon and 1 x 50mg tablet at night. All patients remained on the same dose during the 3 months of the trial. All study tablets were identical. All medication was taken after meals. During the trial, paracetamol (500mg) and antacid (Almax) were allowed. Pill counts were performed. Concurrent corticosteroid injection was not permitted. Patients were instructed to keep the same level of physical activity and physical therapy.
Characteristics	Baseline characteristics (data are mean, SD unless otherwise stated):

Bibliographic reference	**Batlle-Gualda,E., Figueroa,M., Ivorra,J., Raber,A., The efficacy and tolerability of aceclofenac in the treatment of patients with ankylosing spondylitis: a multicenter controlled clinical trial. Aceclofenac Indomethacin Study Group, The Journal of rheumatology, 23, 1200-1206, 1996**

No significant differences between groups at baseline, except that significantly more men in the aceclofenac group (p 0.03). No differences in Right and Left severity of sacroiliitis (graded 0-4 on radiographs).

Parameter	Aceclofenac (n=155)	Indomethacin (n=153)	p
Sex (% men)	90	82	0.03
Age (yrs)	37.8 (7.9)	39.1 (7.6)	0.13
Weight (kg)	71.5 (10.7)	71.7 (11.8)	0.82
Peripheral arthritis (%)	19	26	0.16
Duration of disease (yrs)	7.6 (7.2)	7.4 (7.6)	0.78
Physical therapy (%)	27	30	0.56

Results

Pain (VAS, 10 mm)

	Baseline		Change at 3 months (within group comparisons)		Treatment effect (between group comparisons)	P
	Aceclofenac (n=155)	Indomethacin (n=153)	Aceclofenac (n=155)	Indomethacin (n=153)		
Pain (VAS)	60.2 (1.3)	61.2 (1.3)	-22.4 (2.0)	-25.0 (2.2)	2.6 (-3.3, 8.5)	0.39

Patient global assessment (mean, SEM)

Compared to baseline (data not reported), measured on a Likert scale; 0=nil to 4= very good)

	Change at 3 months (within group comparisons)		Treatment effect (between group comparisons)	P
	Aceclofenac (n=155)	Indomethacin (n=153)		
Patient global assessment	2.5 (0.1)	2.5 (0.1)	0.0 (-0.2, 0.3)	0.79

Withdrawals due to adverse events (n,%)

	Aceclofenac (n=155)	Indomethacin (n=153)

Bibliographic reference	**Batlle-Gualda,E., Figueroa,M., Ivorra,J., Raber,A., The efficacy and tolerability of aceclofenac in the treatment of patients with ankylosing spondylitis: a multicenter controlled clinical trial. Aceclofenac Indomethacin Study Group, The Journal of rheumatology, 23, 1200-1206, 1996**
	Withdrawals due to adverse events (n, %) | 4 (2.6) | 6 (3.9) Withdrawals due to lack of efficacy (n,%) | | Aceclofenac (n=155) | Indomethacin (n=153) | | Withdrawals due to lack of efficacy (n, %) | 10 (6.5) | 7 (4.6) |
Overall Risk of Bias	Allocation concealment not reported. Not reported whether last observation carried forward on ITT analysis. More than 15% dropouts, study powered for this number of dropouts.
Other information	Estimated sample size was 320 (160 per arm) based on alpha level of 0.05, power of 0.90, delta on pain VAS of7mm, SD of 18, assuming a dropout rate of 15%. Comparison of 2 treatment groups by unpaired t test, one way ANOVA or chi- squared testing. ITT and completers only analysis; results were similar, so ITT reported.
Was the allocation sequence adequately generated?	UNCLEAR
Was allocation adequately concealed?	UNCLEAR
Was knowledge of the allocated intervention adequately prevented during the study?	YES
Were incomplete outcome data adequately addressed?	UNCLEAR
Are reports of the study free of suggestion of selective outcome reporting?	YES
Was the study apparently free of other problems that could put it at a high risk of bias?	YES

Table 72: Bird et al., 1986

Bibliographic reference	Bird,H.A., Le Gallez,P., Astbury,C., Looi,D., Wright,V., A parallel group comparison of tenoxicam and piroxicam in patients with ankylosing spondylitis, Pharmatherapeutica, 4, 457-462, 1986
Country/ies where the study was carried out	UK
Study type	Double blind, parallel group
Aim of the study	Not stated
Study dates	Not stated
Source of funding	Roche products for support (no further details provided.
Sample size	n=30 (25 male, 5 female)
Inclusion criteria	Moderately active AS, as defined by the following criteria: (a) Grade 3 to 4 bilateral sacroiliitis associated with at least one of four of the following criteria: 1. limitation of motion of the lumbar spine in all 3 planes 2. history of pain or the presence of pain at the dorso- lumbar junction or in the lumbar spine 3. limitation of chest expansion of 1 inch or less measured at the level of the 9th intercostal space 4. genotype HLA-B27 or grade 3 to 4. or, (b)Unilateral sacroiliitis associated with: 1.l imitation of motion of the lumbar spine in all 3 planes 2. history of pain or the presence of pain at the dorso- lumbar junction or in the lumbar spine together with limitation of chest expansion of 1 inch or less measured at the level of the 9th intercostal space 3. genotype HLA-B27 or, (c) Grade 2 bilateral sacroiliitis associated with one of three criteria: 1.limitation of motion of the lumbar spine in all 3 planes 2. history of pain or the presence of pain at the dorso- lumbar junction or in the lumbar spine together with limitation of chest expansion of 1 inch or less measured at the level of the 9th intercostal space 3. genotype HLA-B27 Patients of either sex, aged 30-75 years, AS of sufficient severity to require the regular use of NSAIDs, normal biochemical indices upon starting the study. Women entering the study gave an undertaking not to become pregnant.
Exclusion criteria	Pregnant women, patients with concomitant or complicating disease that might have interfered with clinical assessment or recording of side effects.

<table>
<tr><th>Bibliographic reference</th><th>Bird,H.A., Le Gallez,P., Astbury,C., Looi,D., Wright,V., A parallel group comparison of tenoxicam and piroxicam in patients with ankylosing spondylitis, Pharmatherapeutica, 4, 457-462, 1986</th></tr>
<tr><td>Details</td><td>For a period of 1 week prior to the start of the trial medication, patients took paracetamol as a back- up analgesic. This was taken on an "as required" basis, to a maximum dose of 4g/day. During this period, patients ceased to take their existing NSAIDs and analgesics and no further anti-arthritic drugs were allowed during the study.
on completing the 1 week run- in, patients were allocated according to a randomised code to the 2 intervention groups.</td></tr>
<tr><td>Interventions</td><td>Tenoxicam 20mg: 1 capsule daily
Piroxicam 20mg: 1 capsule daily
It was not possible to obtain identical capsules, therefore double dummy packaging was used.
Patients attended clinics at 0, 2, 4 weeks. Patients who elected to stay on therapy were assessed once more at 8 weeks.</td></tr>
<tr><td>Characteristics</td><td>
<table>
<tr><td></td><td>Piroxicam 20mg</td><td>Tenoxicam 20mg</td></tr>
<tr><td>Male/female , n</td><td>13/2</td><td>12/3</td></tr>
<tr><td>Mean (SD) age (years)</td><td>45.7 (11.7)</td><td>37.7 (10.5)</td></tr>
<tr><td>Mean (SD) weight (kg)</td><td>74 (12.7)</td><td>66 (7.3)</td></tr>
</table>
</td></tr>
<tr><td>Results</td><td>Spinal pain upon rising in the morning (n)
<table>
<tr><td>Assessment</td><td>Tenoxicam - baseline (n=15)</td><td>Tenoxicam-4 weeks (n=13)</td><td>Piroxicam - baseline (n=15)</td><td>Piroxicam-4 weeks (n=14)</td></tr>
<tr><td>Spinal pain upon rising in the morning</td><td></td><td></td><td></td><td></td></tr>
<tr><td>None</td><td>2</td><td></td><td>3</td><td>5</td></tr>
<tr><td>Very mild</td><td>2</td><td>5</td><td></td><td>2</td></tr>
<tr><td>Mild</td><td>3</td><td>5</td><td>5</td><td>6</td></tr>
<tr><td>Moderate</td><td>4</td><td>3</td><td>3</td><td></td></tr>
<tr><td>Severe</td><td>2</td><td></td><td>2</td><td>1</td></tr>
<tr><td>Very severe</td><td>2</td><td></td><td>2</td><td></td></tr>
</table>
Patient's global assessment of response to treatment at end of study: n of patients
<table>
<tr><td>Assessment</td><td>Tenoxicam</td><td>Piroxicam</td></tr>
</table>
</td></tr>
</table>

Bibliographic reference	Bird,H.A., Le Gallez,P., Astbury,C., Looi,D., Wright,V., A parallel group comparison of tenoxicam and piroxicam in patients with ankylosing spondylitis, Pharmatherapeutica, 4, 457-462, 1986
	<table><tr><td>Excellent</td><td>1</td><td>1</td></tr><tr><td>Good</td><td>10</td><td>9</td></tr><tr><td>Moderate</td><td>4</td><td>3</td></tr><tr><td>Poor</td><td></td><td>2</td></tr></table> Withdrawals due to adverse events n=2 withdrew from Tenoxicam, no withdrawals from Piroxicam in the 4 weeks trial In the 8 week extension, 1 patient withdrew from Tenoxicam and 2 patients stopped piroxicam.
Overall Risk of Bias	Allocation concealment not reported, Randomisation not described.
Other information	Patients were assessed for regular compliance. Continuous data analysed using repeated measures ANOVA after testing for normality and transforming the data as necessary
Was the allocation sequence adequately generated?	UNCLEAR
Was allocation adequately concealed?	UNCLEAR
Was knowledge of the allocated intervention adequately prevented during the study?	YES
Were incomplete outcome data adequately addressed?	UNCLEAR
Are reports of the study free of suggestion of selective outcome reporting?	UNCLEAR
Was the study apparently free of other problems that could put it at a high risk of bias?	UNCLEAR

Table 73: Burry & Siebers, 1980

Bibliographic reference	Burry,H.C., Siebers,R., A comparison of flurbiprofen with naproxen in ankylosing spondylitis, The New Zealand medical journal, 92, 309-311, 1980
Country/ies where the study was carried out	New Zealand
Study type	Double blind, crossover
Aim of the study	Not reported
Study dates	Not reported
Source of funding	Boots company who provided the supplies of active drugs and placebo.
Sample size	n=29
Inclusion criteria	Patients who satisfied the New York criteria for AS, all of whom were HLA B27 positive
Exclusion criteria	Previous history of peptic ulceration, GI haemorrhage, concomitant oral hypoglycaemia or anticoagulant therapy and known intolerance to naproxen.
Details	Patients were allocated to one of two treatment schedules. Group A received Flurbiprofen first for a 2 week period. During a second two week period, naproxen given in identical capsules. Patients in group B received the drugs in reverse order. In both cases, the first treatment period was preceded by a 48 hour washout period, during which no anti-inflammatory or analgesic drugs, other than paracetamol, were allowed. Double blind conditions were observed throughout the study. 100 paracetamol tablets were supplied as a supplementary analgesic. No other analgesic drugs were allowed during the period of the trial.
Interventions	Flurbiprofen 200mg daily Received in an unmarked capsule containing 50mg, one after breakfast, one at midday and two in the evening for two weeks. Naproxen 750mg daily Given in identical capsules containing 250mg, one in the morning, one placebo capsule at midday, two 250mg capsules in the evening.
Characteristics	Baseline characteristics: Male= 26, female= 3. No other baseline characteristics reported.
Results	Pain (recorded daily by the patients according to a 5 point scale (1=no pain, 2=mild, 3=moderate, 4=severe, 5= very severe), mean values. | | Pain (total) | | Baseline value | 76 |

Bibliographic reference	Burry,H.C., Siebers,R., A comparison of flurbiprofen with naproxen in ankylosing spondylitis, The New Zealand medical journal, 92, 309-311, 1980
	<table><tr><td>Flurbiprofen</td><td>58.14</td></tr><tr><td>Naproxen</td><td>58.68</td></tr><tr><td>Flurbiprofen vs baseline</td><td><0.001</td></tr><tr><td>Naproxen vs baseline</td><td><0.001</td></tr><tr><td>Flurbiprofen vs Naproxen</td><td>NS</td></tr></table> Withdrawals due to adverse events: 1 person withdrew whilst taking Flurbiprofen due to abdominal pain
Overall Risk of Bias	Lack of information on baseline characteristics Unclear how allocated to treatment.
Was the allocation sequence adequately generated?	UNCLEAR
Was allocation adequately concealed?	UNCLEAR
Was knowledge of the allocated intervention adequately prevented during the study?	YES
Were incomplete outcome data adequately addressed?	UNCLEAR
Are reports of the study free of suggestion of selective outcome reporting?	UNCLEAR
Was the study apparently free of other problems that could put it at a high risk of bias?	UNCLEAR

Table 74: Dougados et al., 1999

<table>
<tr><th>Bibliographic reference</th><th>Dougados,M., Gueguen,A., Nakache,J.P., Velicitat,P., Veys,E.M., Zeidler,H., Calin,A., Ankylosing spondylitis: what is the optimum duration of a clinical study? A one year versus a 6 weeks non-steroidal anti-inflammatory drug trial, Rheumatology (Oxford, England), 38, 235-244, 1999</th></tr>
<tr><td>Country/ies where the study was carried out</td><td>France</td></tr>
<tr><td>Study type</td><td>Double blind, placebo controlled</td></tr>
<tr><td>Aim of the study</td><td>To consider the relevance of the duration of a clinical trial in ankylosing spondylitis; long term vs short term assessment of a NSAID- placebo controlled study</td></tr>
<tr><td>Study dates</td><td>Not reported</td></tr>
<tr><td>Source of funding</td><td>Supported in part by a grant from Boehringer Ingleheim.</td></tr>
<tr><td>Sample size</td><td>n=473</td></tr>
<tr><td>Inclusion criteria</td><td>Outpatients fulfilling the modified New York criteria for ankylosing spondylitis were recruited, daily NSAID intake during the month preceding the selection visit, a wash-out period for NSAIDs of 2-15 days before the baseline visit, a flare of the disease at baseline defined by both pain evaluated on a 100mm VAS over 40mm and an increase in pain of at least 30% between the screening and the baseline visits.</td></tr>
<tr><td>Exclusion criteria</td><td>Patients with peripheral articular disease, defined by presence at the screening visit of an active (painful or swollen) peripheral arthritis (excluding hip and shoulder) an those with active inflammatory bowel disease, severe concomitant medical illness. Patients who had receive corticosteroids during the previous month an or slow acing drug initiated or with and altered dose during the previous 6 months.</td></tr>
<tr><td>Details</td><td>Patients were randomly assigned to one of 4 groups. Patients received 2 indistinguishable capsules each evening with a glass of water after food. Patients were asked to take the study drugs every day during the 1 year whatever the level of symptoms. Compliance was evaluated by pill count at each visit.</td></tr>
<tr><td>Interventions</td><td>Placebo
Piroxicam 20mg daily
Meloxicam 15mg daily
Meloxicam 22.5mg daily</td></tr>
<tr><td>Characteristics</td><td>
<table>
<tr><th>Characteristic</th><th>Placebo (n=121)</th><th>Piroxicam 20mg (n=108)</th><th>Meloxicam 15mg (n=120)</th><th>Meloxicam 22.5mg (n=124)</th><th>P value</th></tr>
<tr><td>Age (yr) mean (SD)</td><td>40 (12)</td><td>44 (13)</td><td>44 (12)</td><td>42 (12)</td><td>0.04</td></tr>
</table>
</td></tr>
</table>

Bibliographic reference	**Dougados,M., Gueguen,A., Nakache,J.P., Velicitat,P., Veys,E.M., Zeidler,H., Calin,A., Ankylosing spondylitis: what is the optimum duration of a clinical study? A one year versus a 6 weeks non-steroidal anti-inflammatory drug trial, Rheumatology (Oxford, England), 38, 235-244, 1999**

Male (%)	72	77	79	85	NS
Disease duration (yr)	12 (9)	12 (11)	13 (9)	12 (10)	NS
History of peripheral articular disease (%)	29	30	25	27	NS
Pain (VAS), mean (SD)	72 (17)	72 (15)	69 (18)	72 (14)	NS

Results

Pain (VAS) at 1 year follow up, mean change (assessed by ANOVA). *statistically significant (p=<0.05) when compared with placebo

Variable	Placebo	Piroxicam 20mg	Meloxicam 15mg	Meloxicam 22.5mg
Pain (VAS mm)	-11 (28)	-29 (28)*	-31 (30)*	-33 (27)*

Withdrawals due to adverse events

	Placebo	Piroxicam 20mg	Meloxicam 15mg	Meloxicam 22.5mg
n people withdrawn at 1 year follow up	10	21	21	11

Withdrawals due ineffective intervention

	Placebo	Piroxicam 20mg	Meloxicam 15mg	Meloxicam 22.5mg
n people withdrawn at 1 year follow up	53	17	22	17

Other information

Results are reported for Meloxicam 22.5mg, but these are not included in the analysis as this is not a licensed dose of Meloxicam.

Analysed on an ITT basis with last observation carried forward.

Was the allocation sequence adequately generated?	UNCLEAR
Was allocation adequately concealed?	UNCLEAR

Bibliographic reference	Dougados,M., Gueguen,A., Nakache,J.P., Velicitat,P., Veys,E.M., Zeidler,H., Calin,A., Ankylosing spondylitis: what is the optimum duration of a clinical study? A one year versus a 6 weeks non-steroidal anti-inflammatory drug trial, Rheumatology (Oxford, England), 38, 235-244, 1999
Was knowledge of the allocated intervention adequately prevented during the study?	UNCLEAR
Were incomplete outcome data adequately addressed?	YES
Are reports of the study free of suggestion of selective outcome reporting?	YES
Was the study apparently free of other problems that could put it at a high risk of bias?	YES

Table 75: Dougados et al., 2001

Bibliographic reference	Dougados,M., Behier,J.M., Jolchine,I., Calin,A., van der Heijde,D., Olivieri,I., Zeidler,H., Herman,H., Efficacy of celecoxib, a cyclooxygenase 2-specific inhibitor, in the treatment of ankylosing spondylitis: a six-week controlled study with comparison against placebo and against a conventional nonsteroidal anti-inflammatory drug, Arthritis and rheumatism, 44, 180-185, 2001
Country/ies where the study was carried out	76 rheumatology centres in France
Study type	Randomised, double- blind, placebo controlled trial
Aim of the study	To evaluate the short term efficacy of celecoxib in the treatment of AS.
Study dates	Not reported
Source of funding	Supported in part by a grant from Searle Ltd.
Sample size	n=246
Inclusion criteria	Outpatients fulfilling the modified New York criteria, daily NSAID intake during the month preceding the screening visit, NSAID washout period of 2-14 days before the baseline visit, flare of the disease at baseline (defined by pain >40mm on a 100mm VAS scale) and by an increase in pain of at least 30% between the screening and the baseline visits)
Exclusion criteria	Patients with peripheral articular disease defined by the presence of active peripheral arthritis (including hip and shoulder) at the screening visit and those with concomitant severe medical illness. Patients who had received corticosteroids during

<table>
<tr><th>Bibliographic reference</th><th>Dougados,M., Behier,J.M., Jolchine,I., Calin,A., van der Heijde,D., Olivieri,I., Zeidler,H., Herman,H., Efficacy of celecoxib, a cyclooxygenase 2-specific inhibitor, in the treatment of ankylosing spondylitis: a six-week controlled study with comparison against placebo and against a conventional nonsteroidal anti-inflammatory drug, Arthritis and rheumatism, 44, 180-185, 2001</th></tr>
<tr><td></td><td>the previous 6 weeks and or any DMARDS with a change in dosage during the previous 6 months were excluded. Patients with peptic ulcer confirmed by endoscopy within the year preceding the screening visit.</td></tr>
<tr><td>Details</td><td>Concomitant therapies with GI protective agents (such as misoprostol) were stopped when there was no history of gastroduodenal ulcers and were initiated and/or continued when there was a positive history of gastroduodenal ulcers.
Patients were randomly assigned to receive placebo, celecoxib or ketoprofen. All patients took the same dose regardless of the level of symptoms. Compliance was evaluated by pill count at each visit (baseline, 1,3,6 weeks)
Acetaminophen used as analgesic medication (500mg tablets, maximum of 6 tablets/ day), when needed.</td></tr>
<tr><td>Interventions</td><td>Placebo
100mg celecoxib twice daily
100mg ketoprofen, twice daily
Patients took 4 capsules per day (2 at breakfast and 2 at dinner) every day during the 6 weeks of the trial.</td></tr>
<tr><td>Characteristics</td><td>Key baseline characteristics
There were no statistically significant differences between groups for any of the baseline variables reported.
<table>
<tr><th></th><th>Placebo (n=76)</th><th>Ketoprofen 100mg twice daily (n=90)</th><th>Celecoxib 100mg twice daily (n=80)</th></tr>
<tr><td>Age, mean (SD), years</td><td>40 (111)</td><td>38 (11)</td><td>38 (11)</td></tr>
<tr><td>Disease duration</td><td>24.6 (4.0)</td><td>23.4 (3.3)</td><td>24.1 (4.0)</td></tr>
<tr><td>history of peripheral articular disease (%)</td><td>26.3</td><td>30.0</td><td>37.5</td></tr>
</table></td></tr>
<tr><td>Results</td><td>Global pain (VAS). Values are mean (SD). p = 0.0061 (determined by 2 way ANCOVA)
<table>
<tr><th></th><th>Placebo (n=76)</th><th>Ketoprofen 100mg twice daily (n=90)</th><th>Celecoxib 100mg twice daily (n=80)</th></tr>
<tr><td>Baseline</td><td>70 (15)</td><td>66 (15)</td><td>70 (16)</td></tr>
<tr><td>Change from baseline</td><td>-13 (29)</td><td>-21 (26)</td><td>-27 (30)</td></tr>
<tr><td>p value</td><td></td><td></td><td></td></tr>
</table></td></tr>
</table>

<table>
<tr><th>Bibliographic reference</th><td>Dougados,M., Behier,J.M., Jolchine,I., Calin,A., van der Heijde,D., Olivieri,I., Zeidler,H., Herman,H., Efficacy of celecoxib, a cyclooxygenase 2-specific inhibitor, in the treatment of ankylosing spondylitis: a six-week controlled study with comparison against placebo and against a conventional nonsteroidal anti-inflammatory drug, Arthritis and rheumatism, 44, 180-185, 2001</td></tr>
<tr><td></td><td>Patient overall assessment (VAS). Values are mean (SD). p = 0.0028 (determined by 2 way ANCOVA)
<table>
<tr><td></td><td>Placebo (n=76)</td><td>Ketoprofen 100mg twice daily (n=90)</td><td>Celecoxib 100mg twice daily (n=80)</td></tr>
<tr><td>Baseline</td><td>66 (20)</td><td>60 (24)</td><td>67 (20)</td></tr>
<tr><td>Change from baseline</td><td>-8.8 (26)</td><td>-16.7 (31)</td><td>-24.5 (31.3)</td></tr>
<tr><td>p value</td><td></td><td></td><td></td></tr>
</table>
Physician overall assessment (VAS). Values are mean (SD). p = 0.0025 (determined by 2 way ANCOVA)
<table>
<tr><td></td><td>Placebo (n=76)</td><td>Ketoprofen 100mg twice daily (n=90)</td><td>Celecoxib 100mg twice daily (n=80)</td></tr>
<tr><td>Baseline</td><td>59 (17)</td><td>57 (18)</td><td>59 (17)</td></tr>
<tr><td>Change from baseline</td><td>-5.6 (25.8)</td><td>-16.6 (28.2)</td><td>-18.6 (26.7)</td></tr>
<tr><td>p value</td><td></td><td></td><td></td></tr>
</table>
Withdrawal due to ineffective intervention
<table>
<tr><td></td><td>Placebo (n=76)</td><td>Ketoprofen 100mg twice daily (n=90)</td><td>Celecoxib 100mg twice daily (n=80)</td></tr>
<tr><td>6 weeks</td><td>31</td><td>21</td><td>18</td></tr>
</table>
Withdrawal due to adverse event
<table>
<tr><td></td><td>Placebo (n=76)</td><td>Ketoprofen 100mg twice daily (n=90)</td><td>Celecoxib 100mg twice daily (n=80)</td></tr>
<tr><td>6 weeks</td><td>0</td><td>1</td><td>5</td></tr>
</table>
</td></tr>
<tr><td>Overall Risk of Bias</td><td>Allocation concealment not reported</td></tr>
<tr><td>Other information</td><td>Clinical assessments performed by same investigator</td></tr>
</table>

Bibliographic reference	Dougados,M., Behier,J.M., Jolchine,I., Calin,A., van der Heijde,D., Olivieri,I., Zeidler,H., Herman,H., Efficacy of celecoxib, a cyclooxygenase 2-specific inhibitor, in the treatment of ankylosing spondylitis: a six-week controlled study with comparison against placebo and against a conventional nonsteroidal anti-inflammatory drug, Arthritis and rheumatism, 44, 180-185, 2001
	ITT analysis undertaken, all patients randomised and receiving at least one dose of study drug, with last observation carried forward. Primary efficacy criteria evaluated using two-way ANCOVA with treatment and centre as factors and baseline value as covariate For withdrawals due to adverse events, the one person in ketoprofen withdrew because of abdominal symptoms; the 5 in the celecoxib group withdrew for renal colic, atrial fibrillation, pruritus, abdominal pain and heartburn, these were not considered to be related to the study drug. 1 serious adverse event in each group; celecoxib 1 patient died following discontinuation of treatment due to lack of efficacy (considered not to be related to treatment); in ketoprofen group a gastric ulcer was diagnosed with endoscopy performed due to severe epigastric pain after 11 days of treatment
Was the allocation sequence adequately generated?	UNCLEAR
Was allocation adequately concealed?	UNCLEAR
Was knowledge of the allocated intervention adequately prevented during the study?	UNCLEAR
Were incomplete outcome data adequately addressed?	YES
Are reports of the study free of suggestion of selective outcome reporting?	YES
Was the study apparently free of other problems that could put it at a high risk of bias?	YES

Table 76: Gibson & Laurent, 1980

Bibliographic reference	Gibson,T., Laurent,R., Sulindac and indomethacin in the treatment of ankylosing spondylitis: a double-blind cross study, Rheumatology and rehabilitation, 19, 189-192, 1980

Bibliographic reference	**Dougados,M., Behier,J.M., Jolchine,I., Calin,A., van der Heijde,D., Olivieri,I., Zeidler,H., Herman,H., Efficacy of celecoxib, a cyclooxygenase 2-specific inhibitor, in the treatment of ankylosing spondylitis: a six-week controlled study with comparison against placebo and against a conventional nonsteroidal anti-inflammatory drug, Arthritis and rheumatism, 44, 180-185, 2001**
Country/ies where the study was carried out	UK
Study type	Randomised controlled trial
Aim of the study	To determine to what extent the effectiveness of sulindac is comparable to that of indomethacin in ankylosing spondylitis
Study dates	Not reported
Source of funding	None
Sample size	23 people
Inclusion criteria	Signs and symptoms of ankylosing spondylitis Radiological evidence of bilateral sacroiliitis
Exclusion criteria	History of peptic ulceration Intolerance to indomethacin or sulindac
Interventions	Sulindac: 200mg twice daily Indomethacin: 25mg 4 times daily
Characteristics	22 male and 1 female Mean age of 38 years Mean duration of symptoms of 11.5 years
Results	Pain (0-4 scale), mean (SD)

Bibliographic reference	**Dougados,M., Behier,J.M., Jolchine,I., Calin,A., van der Heijde,D., Olivieri,I., Zeidler,H., Herman,H., Efficacy of celecoxib, a cyclooxygenase 2-specific inhibitor, in the treatment of ankylosing spondylitis: a six-week controlled study with comparison against placebo and against a conventional nonsteroidal anti-inflammatory drug, Arthritis and rheumatism, 44, 180-185, 2001**
	<table><tr><td></td><td>Pre treatment</td><td colspan="2">After 4 weeks treatment</td></tr><tr><td></td><td>All</td><td>Sulindac</td><td>Indomethacin</td></tr><tr><td>Pain</td><td>2.2 (0.9)</td><td>1.6 (1.0)</td><td>1.5 (0.6)</td></tr></table><u>Withdrawals due to adverse events:</u> Sulindac: n= 7 Indomethacin: n= 1 <u>Withdrawals due to lack of efficacy:</u> Sulindac: n=1 Indomethacin: n= 2
Was the allocation sequence adequately generated?	UNCLEAR
Was allocation adequately concealed?	UNCLEAR
Was knowledge of the allocated intervention adequately prevented during the study?	UNCLEAR
Were incomplete outcome data adequately addressed?	NO
Are reports of the study free of suggestion of selective outcome reporting?	UNCLEAR

Bibliographic reference	Dougados,M., Behier,J.M., Jolchine,I., Calin,A., van der Heijde,D., Olivieri,I., Zeidler,H., Herman,H., Efficacy of celecoxib, a cyclooxygenase 2-specific inhibitor, in the treatment of ankylosing spondylitis: a six-week controlled study with comparison against placebo and against a conventional nonsteroidal anti-inflammatory drug, Arthritis and rheumatism, 44, 180-185, 2001
Was the study apparently free of other problems that could put it at a high risk of bias?	UNCLEAR

Table 77: Good & Mena, 1977

Bibliographic reference	Good,A., Mena,H., Treatment of ankylosing spondylitis with flurbiprofen and indomethacin, Current medical research and opinion, 5, 117-121, 1977
Country/ies where the study was carried out	USA
Study type	Parallel, double blind, randomised trial.
Aim of the study	Purpose was to compare the effects of Flurbiprofen with indomethacin in the symptomatic management of an exacerbation of ankylosing spondylitis.
Study dates	Not reported
Source of funding	Not reported.
Sample size	n=26 (13 assigned to each group)
Inclusion criteria	All patients had abnormal or ankylosed sacroiliac joints by radiographic criteria (except 1 patient where radiographic changes of sacroiliac joints were read as suspicious, but the patient fulfilled the Rome clinical criteria of AS). All patients had at least 2 of the 2 Rome clinical criteria of the disease. At the time of entering the study, the patients were suffering an exacerbation of their disease. Exacerbation was defined as a clear increase in spinal or sacroiliac pain and one or more of the following- muscle spasm in the back; decreased range of motion in some part of the spine; elevation of ESR.
Exclusion criteria	Aged below 19 years, involvement of two or more peripheral joints not including the shoulder or hips; probability of pregnancy during the trial; hypersensitivity to the experimental drug; other rheumatoid variants; positive rheumatoid factor or serious concomitant disease.

<table>
<tr><th>Bibliographic reference</th><th>Good,A., Mena,H., Treatment of ankylosing spondylitis with flurbiprofen and indomethacin, Current medical research and opinion, 5, 117-121, 1977</th></tr>
<tr><td>Details</td><td>Patients were randomly assigned to each treatment group.
The rugs were available as identical looking capsules of 25mg indomethacin or 50mg Flurbiprofen. The contents of the capsules were not known to the patient or the investigator. The patients were instructed to take 3 or 4 capsules per day for 6 weeks. The use of any other analgesic or anti-inflammatory drug was discouraged.
Patients were evaluated at the start of the study and every 2 weeks thereafter.</td></tr>
<tr><td>Interventions</td><td>Flurbiprofen 100mg- 200mg daily
Indomethacin 75mg - 100mg daily</td></tr>
<tr><td>Characteristics</td><td>HLA B27 antigen was tested in 8 patients and only 1 was negative. All patients were of white ethnicity. There were 2 females in each group. The mean age and duration of the disease was similar in both treatment groups.</td></tr>
<tr><td>Results</td><td><u>Pain:</u> (assessed using Keele scale from 0 -4; no pain, slight, moderate to severe, severe)
<table>
<tr><td>Pain</td><td colspan="3">Indomethacin</td><td colspan="3">Flurbiprofen</td></tr>
<tr><td></td><td>Week 0</td><td>Change at 6 weeks</td><td>p</td><td>Week 0</td><td>Change at 6 weeks</td><td>p</td></tr>
<tr><td>Day</td><td>2.6</td><td>-0.9</td><td>0.02</td><td>2.5</td><td>-0.7</td><td>NS</td></tr>
<tr><td>Night</td><td>1.9</td><td>-0.8</td><td>0.05</td><td>1.8</td><td>-0.8</td><td>0.01</td></tr>
</table>
<u>Withdrawals due to adverse events (n):</u>
Indomethacin: 1
Flurbiprofen: 2</td></tr>
<tr><td>Overall Risk of Bias</td><td>Not reported whether ITT analysis.
Allocation concealment not reported.
Lack of baseline information.</td></tr>
<tr><td>Was the allocation sequence adequately generated?</td><td>UNCLEAR</td></tr>
<tr><td>Was allocation adequately concealed?</td><td>UNCLEAR</td></tr>
</table>

Bibliographic reference	Good,A., Mena,H., Treatment of ankylosing spondylitis with flurbiprofen and indomethacin, Current medical research and opinion, 5, 117-121, 1977
Was knowledge of the allocated intervention adequately prevented during the study?	UNCLEAR
Were incomplete outcome data adequately addressed?	UNCLEAR
Are reports of the study free of suggestion of selective outcome reporting?	YES
Was the study apparently free of other problems that could put it at a high risk of bias?	UNCLEAR

Table 78: Guellec et al., 2014

Bibliographic reference	Guellec,D., Nocturne,G., Tatar,Z., Pham,T., Sellam,J., Cantagerl,A., Saraux,A., Should no-steroidal anti-inflammatory drugs be used continuously in ankylosing spondylitis, Joint, Bone and Spine, 81, 308-12, 2014
Study type	Systematic review
Aim of the study	To compare enteric coated and plain naproxen tablets.
Study dates	Up to June 2012
Source of funding	Abbott
Sample size	3 RCTs

Bibliographic reference	**Guellec,D., Nocturne,G., Tatar,Z., Pham,T., Sellam,J., Cantagerl,A., Saraux,A., Should no-steroidal anti-inflammatory drugs be used continuously in ankylosing spondylitis, Joint, Bone and Spine, 81, 308-12, 2014**
Inclusion criteria	Studies comparing continuous versus on-demand NSAID therapy in terms of disease control, radiographic progression and safety
Interventions	Continuous NSAID therapy On-demand NSAID therapy
Characteristics	3 RCTs identified, only one of which (Wanders 2005) reported data on pain and radiographic progression
Results	

	Continuous (SD)	On-demand (SD)	p value
Global pain (VAS)	37(22)	40 (23)	0.44
Radiographic progression (m-SASSS)	0.4 (1.7)	1.5 (2.5)	0.002
Depression (No of cases)	15	4	0.03

Overall Risk of Bias	High quality systematic review, containing an RCT judged to be at low risk of bias

Table 79: Johnsen et al., 1992

Bibliographic reference	**Johnsen,V., Brun,J.G., Fjeld,E., Hansen,K., Sydnes,O.A., Ugstad,M.B., Morning stiffness and nightime pain in ankylosing spondylitis. A comparison between enteric-coated and plain naproxen tablets, European journal of rheumatology and inflammation, 12, 37-42, 1992**
Country/ies where the study was carried out	Norway, 5 different rheumatology departments.
Study type	Randomised, double blind, double dummy, multi crossover study
Aim of the study	To compare enteric coated and plain naproxen tablets.

Bibliographic reference	**Johnsen,V., Brun,J.G., Fjeld,E., Hansen,K., Sydnes,O.A., Ugstad,M.B., Morning stiffness and nightime pain in ankylosing spondylitis. A comparison between enteric-coated and plain naproxen tablets, European journal of rheumatology and inflammation, 12, 37-42, 1992**
Study dates	Not reported
Source of funding	Not reported
Sample size	n=45
Inclusion criteria	Outpatients satisfying the New York criteria for AS, aged 18-70 years. Patients had at least 15 minutes duration of morning stiffness when being on constant medication of at least 500mg/day. Concomitant treatment with non-aspirin containing analgesic was permitted.
Exclusion criteria	Patients with previous or present GI disease, asthma, hepatic, renal or bleeding disorders or relevant drug hypersensitivity, pregnant or breastfeeding patients and patients using other NSAIDs, aspirin, AL- containing antacids, hypnotics or corticosteroids.
Details	Patients randomly allocated to 2 treatment sequences, enteric coated (ECT) and plain coated (PT) naproxen tablets. The daily dosage of naproxen was consistent throughout the whole study: patients either took 500mg in the evening or 250mg in the morning and 500mg in the evening. The morning tablets were taken with breakfast and the evening tablets between 8=9pm. The tablets were packed into daily dose units. A multi cross over model was used: the duration of treatment was 24 days, divided into 6 periods of 4 days, where patients alternated between the two treatments. As both regimens contained the same daily dosage of naproxen, a period length of 4 days was supposed to be long enough to detect possible differences in clinical effects.
Interventions	Enteric coated naproxen Plain coated naproxen
Characteristics	There was no difference between the 2 treatment sequences regarding age, sex, weight, height, dose of naproxen, degree and duration of morning stiffness and degree of pain during the night.

Parameter	
Age (yrs), mean (SD)	40.1 (10.7)
Weight (kg), mean (SD)	71.8 (10.9)

Bibliographic reference	**Johnsen,V., Brun,J.G., Fjeld,E., Hansen,K., Sydnes,O.A., Ugstad,M.B., Morning stiffness and nightime pain in ankylosing spondylitis. A comparison between enteric-coated and plain naproxen tablets, European journal of rheumatology and inflammation, 12, 37-42, 1992**

Height (cm), mean (SD)	174.6 (8.7)
Degree of night time pain (n):	
No pain	5
Little pain	12
Moderate pain	19
Strong pain	3
Very strong pain	0

Total daily dose of naproxen

Dose	N of patients on entry into the study	N of patients during the study
500mg	5	2
750mg	30	37
1000mg	4	0

Results

37 of the 39 patients who completed the study were taking a daily dose of 750mg naproxen, 2 patients were taking 500mg.
Pain (1= no pain, 2= weak pain, 3= moderate pain, 4= strong pain, 5= very strong pain)

	ECT	PT	Difference

Bibliographic reference	**Johnsen,V., Brun,J.G., Fjeld,E., Hansen,K., Sydnes,O.A., Ugstad,M.B., Morning stiffness and nightime pain in ankylosing spondylitis. A comparison between enteric-coated and plain naproxen tablets, European journal of rheumatology and inflammation, 12, 37-42, 1992**
	<table><tr><td>N</td><td>39</td><td>39</td><td></td></tr><tr><td>Mean</td><td>1.5</td><td>1.5</td><td>0</td></tr><tr><td>95% CIM</td><td>1.3-1.7</td><td>1.3- 1.6</td><td>-0.4, 0.1</td></tr><tr><td>Range</td><td>0-2.6</td><td>0.3-2.4</td><td>-0.6, 1.1</td></tr></table> Withdrawals due to adverse events: n=3 (numbers not given for two treatment groups)
Overall Risk of Bias	Patients only took each tablet type for four days before switching to the other intervention. No allocation concealment reported. Unclear as to whether analysed ITT and what happened to missing data/ dropouts. Adverse events reported for full cohort only.
Other information	Initial sample size was calculated assessing 90% power at the 5% significance level.. A sample size of 38 patients was required to detect a difference in mean duration of morning stiffness of 14 minutes. For comparison between the 2 regimens, two-sided Wilcoxon signed midrank test with a significance level of 5% was used.
Was the allocation sequence adequately generated?	UNCLEAR
Was allocation adequately concealed?	UNCLEAR
Was knowledge of the allocated intervention adequately prevented during the study?	YES
Were incomplete outcome data adequately addressed?	UNCLEAR

Bibliographic reference	Johnsen,V., Brun,J.G., Fjeld,E., Hansen,K., Sydnes,O.A., Ugstad,M.B., Morning stiffness and nightime pain in ankylosing spondylitis. A comparison between enteric-coated and plain naproxen tablets, European journal of rheumatology and inflammation, 12, 37-42, 1992
Are reports of the study free of suggestion of selective outcome reporting?	UNCLEAR
Was the study apparently free of other problems that could put it at a high risk of bias?	UNCLEAR

Table 80: Juvakoski & Lassus, 1982

Bibliographic reference	Juvakoski,T., Lassus,A., A double-blind cross-over evaluation of ketoprofen and indomethacin in Reiter's disease, Scandinavian journal of rheumatology, 11, 106-108, 1982
Country/ies where the study was carried out	Finland
Study type	Double blind crossover
Aim of the study	To compare the effect of 200mg ketoprofen/day to 100mg indomethacin
Study dates	1978-79
Source of funding	Not reported
Sample size	n=50 (n=44 completed)
Inclusion criteria	Patients with Reiter's disease attending the outpatients departments for Venereology or Dermatology, University central hospital, Helsinki. Patients had either the complete Reiter triad, or one or more other signs (HLA-B27 positive), radiological evidence of arthritis with negative Rose-Waaler and latex-fixation tests
Exclusion criteria	Not reported
Details	Total trial duration was 17 weeks. Trial was a double blind crossover with each patient serving as his or her own control. All analgesic and anti-inflammatory medication withdrawn 1 week before initiation of 1st treatment period in the study, no additional analgesics or anti-inflammatories were permitted during the study period. The patients received treatment with each of the two preparations in a randomised sequence. The treatment periods were separated by 1 week washout. Identical capsules were dispensed containing either 50mg ketoprofen or 25mg indomethacin.

<table>
<tr><th>Bibliographic reference</th><th>Juvakoski,T., Lassus,A., A double-blind cross-over evaluation of ketoprofen and indomethacin in Reiter's disease, Scandinavian journal of rheumatology, 11, 106-108, 1982</th></tr>
<tr><td>Interventions</td><td>Indomethacin, 100mg/ day
- in 25mg capsules, standard regimen for both groups was 4 capsules/ day
Ketoprofen 200mg/ day
-in 50mg capsules, standard regimen for both groups was 4 capsules/ day</td></tr>
<tr><td>Characteristics</td><td>Baseline characteristics:
<table>
<tr><td>Parameter</td><td>n</td></tr>
<tr><td>Males</td><td>46/50</td></tr>
<tr><td>Mean age (yrs)</td><td>36 (range 23-68)</td></tr>
<tr><td>Mean duration of arthritis (yrs)</td><td>6 (1-19)</td></tr>
<tr><td>Complete Reiter's syndrome</td><td>29</td></tr>
<tr><td>Urethritis - arthritis - circinate balanitis</td><td>14</td></tr>
<tr><td>Urethritis - arthritis - keratoma blennorrhagica</td><td>4</td></tr>
<tr><td>Urethritis - arthritis - circinate balanitis- keratoma blennorrhagica</td><td>3</td></tr>
<tr><td>HLA-B27 positive</td><td>44</td></tr>
</table></td></tr>
<tr><td>Results</td><td>Joint pain (unclear what scale measured on; paper seems to state 0-4).
<table>
<tr><td></td><td colspan="2">Scores</td></tr>
<tr><td></td><td>0</td><td>17</td></tr>
<tr><td>Ketoprofen</td><td>71</td><td>29</td></tr>
<tr><td>Indomethacin</td><td>63</td><td></td></tr>
</table>
Withdrawals due to adverse events:
Ketoprofen: n=1
Indomethacin: n=2
Withdrawal due to lack of efficacy:
Ketoprofen: n=2
Indomethacin: n=1</td></tr>
</table>

Bibliographic reference	Juvakoski,T., Lassus,A., A double-blind cross-over evaluation of ketoprofen and indomethacin in Reiter's disease, Scandinavian journal of rheumatology, 11, 106-108, 1982
Overall Risk of Bias	Study did not explicitly report inclusion criteria, no exclusion criteria reported. Unclear what scale joint pain measured on: study appears to state measured on scale of 0-4, but this is not clear.
Other information	Paired t tests were performed: paired t test between improvement scores, unpaired t tests between improvement scores, one way ANOVA. Chi squared tests.
Was the allocation sequence adequately generated?	UNCLEAR
Was allocation adequately concealed?	UNCLEAR
Was knowledge of the allocated intervention adequately prevented during the study?	YES
Were incomplete outcome data adequately addressed?	UNCLEAR
Are reports of the study free of suggestion of selective outcome reporting?	UNCLEAR
Was the study apparently free of other problems that could put it at a high risk of bias?	UNCLEAR

Table 81: Khan, 1987

Bibliographic reference	Khan,M.A., A double blind comparison of diclofenac and indomethacin in the treatment of ankylosing spondylitis, The Journal of rheumatology, 14, 118-123, 1987
Country/ies where the study was carried out	USA
Study type	Multicentre, randomised, parallel group trial.
Aim of the study	Not reported
Study dates	Not reported
Source of funding	Not reported
Sample size	n=284

<table>
<tr><th>Bibliographic reference</th><th>Khan,M.A., A double blind comparison of diclofenac and indomethacin in the treatment of ankylosing spondylitis, The Journal of rheumatology, 14, 118-123, 1987</th></tr>
<tr><td>Inclusion criteria</td><td>All patients had a confirmed diagnosis of AS, for which they had been treated with aspirin or an NSAID for at least 3 months. Criteria for diagnosis of AS were definite or advanced bilateral sacroiliitis by radiology and a definite history of at least 2 of the following clinical criteria 1. lumbar or thoracolumbar junction pain and stiffness, 2. major limitation of motion of lumbar spine, 3. pain and stiffness in thoracic region, 4. limited chest expansion, and 5. nocturnal pain with morning predominance and stiffness, or both, and pain in either buttock. All patient met the criteria of ARA functional class 1,2 or 3.
Patients with evidence of active disease (flare) during the single blind washout phase were enrolled in the double blind period.
Flare was defined as the presence during the washout period compared to visit 1, of the following criteria, 1. a 1 point increase in cervical, thoracic or lumbar/ sacroiliac pain on a 0-4 scale as assessed by the patient (minimum grade 2), and 2. 2 or more of the following, 1. increased duration of morning stiffness (>30 minutes increase), decreased anterior flexion as measured by the Schober test (by 1cm or more), decreased chest expansion (by 1cm or more), increased distance from fingertips to floor (by 5cm or more), one or more peripheral joints affected by swelling and tenderness, ESR>28mm/hr.</td></tr>
<tr><td>Exclusion criteria</td><td>Patients with evidence of coexisting rheumatic disease or important concomitant medical illness were excluded from the study.</td></tr>
<tr><td>Details</td><td>The duration of the study was up to 15 weeks.
Patients were randomised at each study centre using a blocking factor of 1. The study was divided into 2 phases, a single blind placebo washout phase of 2 days to 2 weeks, and a 13 week double blind treatment phase.
In the double blind period, patients received therapy with either diclofenac or indomethacin. The period started with a dose titration phase (visit 3-6, approximately weeks 2-5), followed by a fixed dose period (visit 7-9, approximately weeks 7-15).</td></tr>
<tr><td>Interventions</td><td>At visit 3 (approx. 2 weeks), treatment initiated with 25mg TID of wither diclofenac or indomethacin (75mg daily dose of either study drug).
One group instructed to take one 25mg enteric coated diclofenac tablet and one placebo capsule TID, and the other was instructed to take one 25mg indomethacin capsule and one placebo tablet TID.
At visit 4 (3 weeks) dosage increased by 25mg/ day to a total daily dose of 100mg and at visit 5 (4 weeks) by another 25mg/ day to a maximum daily dose of 125mg.
Dosage adjustments were permitted within the range of 75-125mg/day if patients experience any adverse effects.
After 5 weeks (visit 6), optimal dosage established and fixed for the remainder of the trial.</td></tr>
<tr><td>Characteristics</td><td>Baseline characteristics:
<table>
<tr><td></td><td>Diclofenac</td><td>Indomethacin</td></tr>
<tr><td>n (efficacy)</td><td>118</td><td>106</td></tr>
<tr><td>men/ women, n (%), range</td><td>102 (86.4)/ 16 (13.6),</td><td>85 (80.2)/ 21 (19.8)</td></tr>
<tr><td>Age (yrs), mean, range</td><td>38.6, 19-64</td><td>37.8, 19-64</td></tr>
</table>
</td></tr>
</table>

Bibliographic reference	**Khan,M.A., A double blind comparison of diclofenac and indomethacin in the treatment of ankylosing spondylitis, The Journal of rheumatology, 14, 118-123, 1987**
Results	Patient assessment of spinal pain (cervical, thoracic, lumbosacral) - measured on a 5 point scale (0= no pain to 4 (extreme pain), values are unadjusted means:

Spinal pain (0-4)	Diclofenac			Indomethacin		
	Baseline (n=118)	T1 (5 weeks)(n=118)	T2 (9-13 weeks)(n=93)	Baseline (n=106)	T1 (5 weeks)((n=106)	T2 (9-13 weeks)(n=81)
Lumbar sacroiliac	2.38	1.03	0.93	2.45	1.03	0.93
Thoracic	1.92	0.76	0.66	1.96	0.63	0.60
Cervical	1.93	0.82	0.66	1.99	0.91	0.77
Nocturnal pain	1.99	0.83 (n=117)	0.77 (n=92)	2.0	0.75	0.43 (n=79)

Withdrawals due to adverse events:

Diclofenac: n=1 (severe epigastric pain)

Indomethacin: n=7 (due to headache)

Unclear whether study selectively reported those in the indomethacin group who withdrew due to headache only, or whether these were all the withdrawals due to adverse events.

Paper states that 17/130 (13.1%) of patients receiving indomethacin withdrew and 13/132 (9.8%) of people taking diclofenac withdrew

Withdrawals due to lack of efficacy:

Diclofenac: 13.6%, n=16 (n calculated by analyst)

Indomethacin: 11.3%, n= 12 (n calculated by analyst)

p=0.68

Overall Risk of Bias	Duration of study "up to" 15 weeks. Variable washout period, from 2 days to 2 weeks.

Bibliographic reference	Khan,M.A., A double blind comparison of diclofenac and indomethacin in the treatment of ankylosing spondylitis, The Journal of rheumatology, 14, 118-123, 1987
	Unclear whether all dropouts due to adverse events were reported.
Other information	Visit 8 (week 11) or 9 (week 15), 98% of acceptable diclofenac treated patients and 91.4% of acceptable indomethacin treated patients were at a dose of 125mg/day. 284 patients entered the study, 22 patients left during the trial, 262 patients entered the double- blind treatment phase. All 262 were evaluated for safety and 224 for efficacy (38 were excluded from the efficacy analysis - reasons detailed in study).
Was the allocation sequence adequately generated?	UNCLEAR
Was allocation adequately concealed?	UNCLEAR
Was knowledge of the allocated intervention adequately prevented during the study?	YES
Were incomplete outcome data adequately addressed?	UNCLEAR
Are reports of the study free of suggestion of selective outcome reporting?	UNCLEAR
Was the study apparently free of other problems that could put it at a high risk of bias?	UNCLEAR

Table 82: Lomen et al., 1986

Bibliographic reference	Lomen,P.L., Turner,L.F., Lamborn,K.R., Brinn,E.L., Flurbiprofen in the treatment of ankylosing spondylitis. A comparison with indomethacin, The American journal of medicine, 80, 127-132, 1986
Country/ies where the study was carried out	USA
Study type	Randomised, double blind study
Aim of the study	Not reported
Study dates	Not reported
Source of funding	Not reported

Bibliographic reference	Lomen,P.L., Turner,L.F., Lamborn,K.R., Brinn,E.L., Flurbiprofen in the treatment of ankylosing spondylitis. A comparison with indomethacin, The American journal of medicine, 80, 127-132, 1986
Sample size	n=60
Inclusion criteria	Patients between 18-60 years with definitive diagnosis of AS. Clinical and radiographic feature included pain and stiffness in the lumbar region for more than 3 months, major limitation of motion in the lumbar spine in all 3 planes, pain and stiffness in the thoracic region for more than 3 months, limitation of chest expansion, night pain, history or evidence of iritis or its sequelae, bilateral sacroiliac disease on radiographic examination.
Exclusion criteria	Not reported.
Details	Study duration = 26 weeks. All previous anti-inflammatory medications were discontinued upon entry into the study for a washout period of at least 48 hours to allow for exacerbation of symptoms. Assignment to the two treatment groups was in accordance with a standardised randomisation schedule. Treatment was double blind, bottles for the two groups were identical with attached decoding labels. Efficacy assessed at one week, patient was withdrawn from the study before the end of the 1st week if a serious AE occurred. Dose could be escalated at 1 week. De-escalation of dose was always encouraged to determine the minimum effective dose for each patient, and there was a de-escalation schedule.
Interventions	Flurbiprofen 50mg capsules, three times daily (total initial daily dose 150mg). Assessment of efficacy after 1 week. If poor control of symptoms and no AEs, dose escalated to maximum maintenance dose of 200mg Flurbiprofen (50mg, four times daily). This regimen was continued throughout the study in patients whose symptoms remained adequately controlled and who were not experiencing side effects. In patients whose symptoms were not adequately controlled on the maintenance dose, and experienced no serious AEs, after treatment for 1 week at the maintenance dose, the total daily dose was increased to 250mg Flurbiprofen (100mg, 50mg, 50mg, 50mg divided doses) These doses - the low escalation regimen- could be taken for a total of 14 days during the study, either consecutively or following an exacerbation whilst on the maintenance dose. If the low dose escalation regimen was required for more than a total of 14 days, the patient was withdrawn from the study. In patients who did not gain adequate symptom control on 250mg after 1 week, the dose was increased to 300mg (100mg, 50mg, 50mg, 100mg divided doses). This dose could not be taken for more than 4 days. If symptoms did not subside after this time the patient was withdrawn from the study. Indomethacin 25mg capsules, three times daily (total initial daily dose 75mg). Assessment of efficacy after 1 week. If poor control of symptoms and no AEs, dose escalated to maximum maintenance dose of 100mg Indomethacin (25mg, four times daily). This regimen was continued throughout the study in patients whose symptoms remained adequately controlled and who were not experiencing side effects. In patients whose symptoms were not adequately controlled on the maintenance dose, and experienced no serious AEs, after treatment for 1 week at the maintenance dose, the total daily dose was increased to 125mg Indomethacin (50mg, 25mg, 25mg, 25mg divided doses). These doses - the low escalation regimen- could be taken for a total of 14 days during

Bibliographic reference	**Lomen,P.L., Turner,L.F., Lamborn,K.R., Brinn,E.L., Flurbiprofen in the treatment of ankylosing spondylitis. A comparison with indomethacin, The American journal of medicine, 80, 127-132, 1986**
	the study, either consecutively or following an exacerbation whilst on the maintenance dose. If the low dose escalation regimen was required for more than a total of 14 days, the patient was withdrawn from the study. In patients who did not gain adequate symptom control on 125mg after 1 week, the dose was increased to 150mg (50mg, 25mg, 25mg, 50mg divided doses). This dose could not be taken for more than 4 days. If symptoms did not subside after this time the patient was withdrawn from the study.
Characteristics	Baseline characteristics: No statistically significant differences between groups for race, Stein rocker functional class, sex, age and duration of disease or patients and investigators week 0 assessment of disease. No statistically significant differences between the two groups for previous therapy for AS.

Parameter	Flurbiprofen	Indomethacin
n	30	27
ethnicity:		
white	30	26
NR	0	1
Sex: m/f	26/4	24/3
Age (yrs)		
20-29	6	8
30-39	11	10
40-49	8	4
50-59	3	4
>60	2	1
Duration of disease:		
0-4	6	7
5-9	5	8
10-14	7	2
15-19	4	3

Bibliographic reference	**Lomen,P.L., Turner,L.F., Lamborn,K.R., Brinn,E.L., Flurbiprofen in the treatment of ankylosing spondylitis. A comparison with indomethacin, The American journal of medicine, 80, 127-132, 1986**

20-24	4	5
25-29	1	0
>30	3	2

Results

Pain

Efficacy measurement	Flurbiprofen			Indomethacin		
	n at 26 weeks	Mean improvement	Median improvement	n at 26 weeks	Mean improvement	Median improvement
Night pain (0-3)	24	1.3	1.0	29	1.3	1.0
Spinal pain (0-4)	23	1.5	2.0	21	1.5	2.0
Rest pain (0-6)	24	1.9	2.0	21	1.8	2.0
Motion pain (0-6)	25	2.0	2.0	21	2.2	2.0

Withdrawals due to adverse events:

Flurbiprofen: n=1

Indomethacin: n=1

Withdrawals due to lack of efficacy of study drug:

Flurbiprofen: n=2

Indomethacin: n=1

Overall Risk of Bias

Study drugs were titrated, therefore participants on different doses.

Randomisation not described.

Not clear whether those withdrawn in the first week due to AEs are recorded as having AES, therefore potential bias and under-reporting.

Only mean values reported for pain outcome, no SD or SEM.

Paper indicates ITT analysis, but not clear what happens to missing data.

No details on exclusion criteria for study.

Other information

Whenever possible, comparisons were made with baseline measurements (week 0), if these were unavailable the pre-washout or initial values were used.

Bibliographic reference	**Lomen,P.L., Turner,L.F., Lamborn,K.R., Brinn,E.L., Flurbiprofen in the treatment of ankylosing spondylitis. A comparison with indomethacin, The American journal of medicine, 80, 127-132, 1986**

For efficacy analyses only, analyses were performed on baseline to final change scores (final visit defined as last report on study drug for a patient regardless of when it occurred. (ITT).

2-tailed paired t tests were conducted on efficacy measurements; ANOVA were performed on baseline measurements an on key follow up change scores for efficacy. 2 sided Fisher's test was used in a few instances and the 2 sample Wilcoxon test was used extensively.

Dosage summary of study drugs:

	Flurbiprofen	Indomethacin
QID regimen (4 x daily)		
Total n of patients following QID regimen	20	17
Mean % of total days on QID regimen for those following that regimen	76.6	67.8
TID regimen (3 x daily)		
Total n of patients following TID regimen	30	26*
Mean % of total days on TID regimen for those following that regimen	40.3	55.7
BID regimen (2 x daily)		
Total n of patients following BID regimen	10	8
Mean % of total days on BID regimen for those following that regimen	16.7	7.9
Range of % total days on BID regimen for those following that regimen	0.5-94.1	0.5- 23.4

Bibliographic reference	Lomen,P.L., Turner,L.F., Lamborn,K.R., Brinn,E.L., Flurbiprofen in the treatment of ankylosing spondylitis. A comparison with indomethacin, The American journal of medicine, 80, 127-132, 1986
Was the allocation sequence adequately generated?	UNCLEAR
Was allocation adequately concealed?	UNCLEAR
Was knowledge of the allocated intervention adequately prevented during the study?	YES
Were incomplete outcome data adequately addressed?	UNCLEAR
Are reports of the study free of suggestion of selective outcome reporting?	UNCLEAR
Was the study apparently free of other problems that could put it at a high risk of bias?	NO

Table 83: Mayrhofer et al., 1990

Bibliographic reference	Mayrhofer,F., Broll,H., Eberl,R., Ebner,W., Klein,G., Rainer,F., Schorsch,G., Thumb,N., Tenoxicam versus diclofenac in patients with ankylosing spondylitis. A double-blind study, Drug Investigation, 2, 52-53, 1990
Country/ies where the study was carried out	Austria
Study type	Double blind, randomised
Aim of the study	Not reported
Study dates	Not reported
Source of funding	Not reported

Bibliographic reference	Mayrhofer,F., Broll,H., Eberl,R., Ebner,W., Klein,G., Rainer,F., Schorsch,G., Thumb,N., Tenoxicam versus diclofenac in patients with ankylosing spondylitis. A double-blind study, Drug Investigation, 2, 52-53, 1990
Sample size	n=57
Inclusion criteria	Not reported
Exclusion criteria	Not reported
Details	Patients were randomised (10 patients per centre, 5 on tenoxicam, 5 on diclofenac). After a washout period of at least 3 days patients were randomly allocated treatment groups. Treatment was for 21 days and patients also took part in a physical therapy programme as part of the study. Clinical assessment performed prior to treatment and on days 7,14 and 21.
Interventions	Tenoxicam 20mg/day (n=28) Diclofenac 100mg/day (n=29, calculated by analyst)
Characteristics	Baseline characteristics: 49 men, 8 women Age range: 22-67 (mean 42) 82% people HLA B27 positive
Results	Pain intensity (VAS scale): This data was presented in graphical form only for lumbosacral pain on movement, made into discrete data (e.g. >50% improvement), therefore this data could not be reported here. Lumbosacral pain during the day and lumbosacral pain at night was stated to be improved similarly in both groups, but no data was presented within the paper. Withdrawals due to adverse events: Tenoxicam: n=0 Diclofenac: n=3 Withdrawals due to lack of efficacy of study drug: Tenoxicam: n=3 Diclofenac: n=2
Overall Risk of Bias	Inclusion and exclusion criteria not reported. Outcomes not reported fully, data could not be analysed.
Was the allocation sequence adequately generated?	UNCLEAR

Bibliographic reference	Mayrhofer,F., Broll,H., Eberl,R., Ebner,W., Klein,G., Rainer,F., Schorsch,G., Thumb,N., Tenoxicam versus diclofenac in patients with ankylosing spondylitis. A double-blind study, Drug Investigation, 2, 52-53, 1990
Was allocation adequately concealed?	UNCLEAR
Was knowledge of the allocated intervention adequately prevented during the study?	UNCLEAR
Were incomplete outcome data adequately addressed?	UNCLEAR
Are reports of the study free of suggestion of selective outcome reporting?	NO
Was the study apparently free of other problems that could put it at a high risk of bias?	UNCLEAR

Table 84: Nahir & Scharf, 1980

Bibliographic reference	Nahir,A.M., Scharf,Y., A comparative study of diclofenac and sulindac in ankylosing spondylitis, Rheumatology and rehabilitation, 19, 189-198, 1980
Country/ies where the study was carried out	Israel
Study type	Double blind, single centre trial.
Aim of the study	To compare the efficacy and tolerability of diclofenac sodium (Voltaren) 150mg daily and Sulindac 400mg daily in people with AS.
Study dates	Not reported
Source of funding	Not reported
Sample size	n=62

<table>
<tr><th>Bibliographic reference</th><th>Nahir,A.M., Scharf,Y., A comparative study of diclofenac and sulindac in ankylosing spondylitis, Rheumatology and rehabilitation, 19, 189-198, 1980</th></tr>
<tr><td>Inclusion criteria</td><td>Patients were currently receiving treatment at the Rheumatology out-patient department of the Rambam medical centre. All had radiographic evidence of sacroiliitis and clinically active disease. All patients demonstrated spinal pain, decreased range of motion in some part of the spine and an increased ESR.</td></tr>
<tr><td>Exclusion criteria</td><td>Patients with hepatic, renal, gastric disease or previous intolerance to indomethacin were excluded.</td></tr>
<tr><td>Details</td><td>After a 7 day washout period, where no anti-inflammatory/ analgesic medication was permitted, the patients were randomly assigned to the 2 treatment groups.</td></tr>
<tr><td>Interventions</td><td>Diclofenac 150mg daily:
50mg, 3 x daily plus sulindac placebo 2 x daily
Sulindac 400mg daily:
Sulindac 200mg, 3 x daily plus diclofenac placebo 3 x daily</td></tr>
<tr><td>Characteristics</td><td>Baseline characteristics
<table>
<tr><td>Parameter</td><td>Diclofenac</td><td>Sulindac</td><td>Total</td></tr>
<tr><td>Age (yrs) mean (range)</td><td>37 (26-58)</td><td>37 (20-57)</td><td>37 (20-58)</td></tr>
<tr><td>Sex: m/f (%)</td><td>30 (97)/1 (3)</td><td>30 (97)/1 (3)</td><td>60/2</td></tr>
<tr><td>Duration of illness:</td><td></td><td></td><td></td></tr>
<tr><td>1-5 years</td><td>10 (32%)</td><td>13 (42%)</td><td>23 (37%)</td></tr>
<tr><td>>5 years</td><td>21 (68%)</td><td>18 (58%)</td><td>39 (63%)</td></tr>
<tr><td>Criteria for active disease:</td><td></td><td></td><td></td></tr>
<tr><td>Increased muscle spasm in back: n, (%)</td><td>29 (94)</td><td>28 (93)</td><td>57 (93)</td></tr>
<tr><td>Decreased ROM in some part of spine: n, (%)</td><td>31 (100)</td><td>30 (100)</td><td>61 (100)</td></tr>
<tr><td>Increased ESR: n, (%)</td><td>30 (97)</td><td>29 (97)</td><td>59 (97)</td></tr>
<tr><td>Not stated: n</td><td>-</td><td>1</td><td>1</td></tr>
</table></td></tr>
<tr><td>Results</td><td>Pain (100mm VAS), mean (SD)
<table>
<tr><td></td><td>Diclofenac</td><td>Sulindac</td></tr>
<tr><td>Pre washout</td><td>43 (18) n=30</td><td>52 (18) n=29</td></tr>
<tr><td>Baseline</td><td>85 (9) n=31</td><td>88 (8) n=31</td></tr>
</table></td></tr>
</table>

Bibliographic reference	**Nahir,A.M., Scharf,Y., A comparative study of diclofenac and sulindac in ankylosing spondylitis, Rheumatology and rehabilitation, 19, 189-198, 1980**
	<table><tr><td>Day 28</td><td>25* (19) n=30</td><td>36* (21) n=30</td></tr></table> *significant difference between groups on day 28 in favour of diclofenac Withdrawals due to adverse events: Diclofenac: n=0 Sulindac: n=1 Withdrawals due to lack of efficacy: Diclofenac: n=1 Sulindac: n=0
Overall Risk of Bias	Not reported whether ITT analysis, no information provided on statistics used to analyse data.
Was the allocation sequence adequately generated?	UNCLEAR
Was allocation adequately concealed?	UNCLEAR
Was knowledge of the allocated intervention adequately prevented during the study?	YES
Were incomplete outcome data adequately addressed?	UNCLEAR
Are reports of the study free of suggestion of selective outcome reporting?	UNCLEAR
Was the study apparently free of other problems that could put it at a high risk of bias?	UNCLEAR

Table 85: Pasero et al., 1994

Bibliographic reference	**Pasero,G., Ruju,G., Marcolongo,R., Senesi,M., Seni,U., Mannoni,A., Accardo,S., Seriolo,B., Colombo,B., Ligniere,G.C., Consoli,G., De,Santis D., Ferri,S., Amoresano,C., Frizziero,L., Reta,M., Giorgianni,G., Martorana,U., Termine,S., Mattara,L., Franceschini,M., Oriente,P., Scarpa,R., Perpignano,G., Bogliolo,A., Torri,G., Trotta,F., Govoni,F., Aceclofenac versus naproxen in the treatment of ankylosing spondylitis: A double-blind, controlled study, Current Therapeutic Research - Clinical and Experimental, 55, 833-842, 1994**
Country/ies where the study was carried out	Italy
Study type	Double blind, multicentre, controlled study
Aim of the study	To assess the efficacy and tolerability of Aceclofenac and naproxen sodium in the treatment of AS.
Study dates	Not reported
Source of funding	Not reported
Sample size	n=130 (n=126 fully complied with the inclusion criteria).
Inclusion criteria	Both sexes, aged 20-50 years, with active definite AS. AS defined by presence of spinal and/or sacroiliac pain and back muscle spasm and/or decreased spinal motion or increased ESR. with a negative test for faecal occult blood. Definite AS was defined by presence of grade 2, 3, or 4 sacroiliitis confirmed by radiography and at least 2 of the following clinical criteria. lumbar or dorsal/ lumbar junction pain and stiffness of over 3 months duration; major limitation of motion of the lumbar spine in 3 directions - flexion/extension, lateral bending and rotation; pain and stiffness in the thoracic region of over 3 months duration; limited chest expansion; nocturnal pain with morning predominance and/or morning stiffness and/or pain in one or both buttocks.
Exclusion criteria	Patients with other arthropathies, CV, neoplastic, GI or renal diseases, or treated with drugs that could interfere with the study drugs were excluded. Pregnant or nursing women, women receiving hormonal contraception and patients, who in the opinion of the investigators would be unable to comply fully with trial requirements.
Details	Study duration 3 months. Patients were randomised to treatment with aceclofenac or naproxen
Interventions	Aceclofenac 200mg/ day (n=63, 60 fully complied) 100mg, twice daily. Naproxen 1g/ day (n=66, 60 fully complied) 500mg, twice daily.
Characteristics	Baseline characteristics: Groups similar for all characteristics apart from significant difference ($p<0.05$) between hand to floor distance (by split plot ANOVA). All values mean (SD)

Parameter	Aceclofenac (n=60)	Naproxen (n=66)
Age (yrs)	39.10 (7.93)	38.50 (8.94)

<table>
<tr><th>Bibliographic reference</th><td colspan="3">Pasero,G., Ruju,G., Marcolongo,R., Senesi,M., Seni,U., Mannoni,A., Accardo,S., Seriolo,B., Colombo,B., Ligniere,G.C., Consoli,G., De,Santis D., Ferri,S., Amoresano,C., Frizziero,L., Reta,M., Giorgianni,G., Martorana,U., Termine,S., Mattara,L., Franceschini,M., Oriente,P., Scarpa,R., Perpignano,G., Bogliolo,A., Torri,G., Trotta,F., Govoni,F., Aceclofenac versus naproxen in the treatment of ankylosing spondylitis: A double-blind, controlled study, Current Therapeutic Research - Clinical and Experimental, 55, 833-842, 1994</td></tr>
<tr><td></td><td>Sex (m/f)</td><td>50/10</td><td>57/9</td></tr>
<tr><td></td><td>Disease onset (months)</td><td>89.77 (74.22)</td><td>85.82 (85.39)</td></tr>
<tr><td></td><td>Pain (VAS)</td><td>52.80 (20.27)</td><td>53.48 (21.95)</td></tr>
<tr><td></td><td>Pain on movement (score 0-3)</td><td>1.92 (0.74)</td><td>1.79 (0.79)</td></tr>
<tr><td></td><td>Pain at rest (score 0-3)</td><td>1.48 (0.77)</td><td>1.56 (0.81)</td></tr>
<tr><td>Results</td><td colspan="3">Spontaneous pain (measured on 100mm VAS, 0= no pain, 100= unbearable pain). Mean values, data estimated from graph (no raw data provided in study).

<table><tr><td></td><td>Aceclofenac</td><td>Naproxen</td></tr><tr><td>Baseline</td><td>53</td><td>53</td></tr><tr><td>3 months</td><td>25</td><td>29</td></tr></table>
n=13 patients withdrew from the study - no information provided as to whether this was due to AEs or lack of efficacy.</td></tr>
<tr><td>Overall Risk of Bias</td><td colspan="3">Lack of detail on intervention.</td></tr>
<tr><td>Other information</td><td colspan="3">Variation within and between groups was studied by split- plot analysis of variance and Tukey test, Friedman and Mann-Whitney U, and student's t test for parametric variables. The ANOVA, Friedman and Mann Whitney U and Chi squared test were performed for nonparametric variables.</td></tr>
<tr><td>Was the allocation sequence adequately generated?</td><td colspan="3">UNCLEAR</td></tr>
<tr><td>Was allocation adequately concealed?</td><td colspan="3">UNCLEAR</td></tr>
<tr><td>Was knowledge of the allocated intervention adequately prevented during the study?</td><td colspan="3">UNCLEAR</td></tr>
</table>

Bibliographic reference	Pasero,G., Ruju,G., Marcolongo,R., Senesi,M., Seni,U., Mannoni,A., Accardo,S., Seriolo,B., Colombo,B., Ligniere,G.C., Consoli,G., De,Santis D., Ferri,S., Amoresano,C., Frizziero,L., Reta,M., Giorgianni,G., Martorana,U., Termine,S., Mattara,L., Franceschini,M., Oriente,P., Scarpa,R., Perpignano,G., Bogliolo,A., Torri,G., Trotta,F., Govoni,F., Aceclofenac versus naproxen in the treatment of ankylosing spondylitis: A double-blind, controlled study, Current Therapeutic Research - Clinical and Experimental, 55, 833-842, 1994
Were incomplete outcome data adequately addressed?	UNCLEAR
Are reports of the study free of suggestion of selective outcome reporting?	UNCLEAR
Was the study apparently free of other problems that could put it at a high risk of bias?	UNCLEAR

Table 86: Rejholec et al., 1980

Bibliographic reference	Rejholec,V., Vapaatalo,H., Tokola,O., Gothoni,G., Tolfenamic acid in rheumatoid arthritis and ankylosing spondylitis, Scandinavian journal of rheumatology.Supplement, Suppl 33, 50-, 1980
Country/ies where the study was carried out	Finland
Study type	RCT
Aim of the study	Not reported.
Study dates	Not reported.
Source of funding	Not reported.
Sample size	n=50
Inclusion criteria	Diagnosis verified clinically and radiographically. Patients were treated with various anti-inflammatory analgesics in the 3 months preceding the trial.
Exclusion criteria	Not reported.

<table>
<tr><th>Bibliographic reference</th><th>Rejholec,V., Vapaatalo,H., Tokola,O., Gothoni,G., Tolfenamic acid in rheumatoid arthritis and ankylosing spondylitis, Scandinavian journal of rheumatology.Supplement, Suppl 33, 50-, 1980</th></tr>
<tr><td>Details</td><td>Treatment period was 6 months.</td></tr>
<tr><td>Interventions</td><td><u>Tolfenamic acid</u>
Administered in dose of 200mg, 3 x daily.
<u>Indomethacin</u>
25mg doses, 3 x daily
Drugs were administered in gelatine capsules of identical appearance.</td></tr>
<tr><td>Characteristics</td><td><u>Baseline characteristics:</u>
not reported whether variance SD, SE etc.
<table>
<tr><td>Parameter</td><td>Tolfenamic acid</td><td>Indomethacin</td></tr>
<tr><td>n</td><td>25</td><td>25</td></tr>
<tr><td>Men/ women</td><td>21/4</td><td>22/3</td></tr>
<tr><td>Age, yrs (mean)</td><td>38.6 (2.6)</td><td>35.6 (2.7)</td></tr>
<tr><td>Duration of disease, yrs (mean)</td><td>13.9 (2.4)</td><td>10.4 (2.1)</td></tr>
</table></td></tr>
<tr><td>Results</td><td><u>Pain (0-3 scale:0= no pain; 1= slight, occasional; 2= inconsistent, tolerable; 3= continuous, severe).</u>
Mean values presented. Data estimated from graphical data by analyst as raw data was not presented in the paper.
<table>
<tr><td></td><td>Tolfenamic acid</td><td>Indomethacin</td></tr>
<tr><td>Baseline</td><td>1.9</td><td>1.3</td></tr>
<tr><td>6 months</td><td>0.7</td><td>1.2</td></tr>
</table>
<u>Withdrawals due to adverse events:</u>
Tolfenamic acid: n=0</td></tr>
</table>

Bibliographic reference	Rejholec,V., Vapaatalo,H., Tokola,O., Gothoni,G., Tolfenamic acid in rheumatoid arthritis and ankylosing spondylitis, Scandinavian journal of rheumatology.Supplement, Suppl 33, 50-, 1980
	Indomethacin: n=4 <u>Withdrawals due to lack of efficacy:</u> Not reported
Overall Risk of Bias	Data on pain was estimated from graphical data as the paper did not present the raw data.
Was the allocation sequence adequately generated?	UNCLEAR
Was allocation adequately concealed?	UNCLEAR
Was knowledge of the allocated intervention adequately prevented during the study?	YES
Were incomplete outcome data adequately addressed?	UNCLEAR
Are reports of the study free of suggestion of selective outcome reporting?	UNCLEAR
Was the study apparently free of other problems that could put it at a high risk of bias?	UNCLEAR

Table 87: Schwarzer et al., 1990

Bibliographic reference	Schwarzer,A.C., Cohen,M., Arnold,M.H., Kelly,D., McNaught,P., Brooks,P.M., Tenoxicam compared with diclofenac in patients with ankylosing spondylitis, Current medical research and opinion, 11, 648-653, 1990
Country/ies where the study was carried out	Australia
Study type	Randomised comparative trial
Aim of the study	Not reported
Study dates	Not reported
Source of funding	Roche
Sample size	n=24
Inclusion criteria	Age 16-65 years, diagnosis of definite or probably AS according to the New York criteria (1966). Patients suitable for study entry entered a 3 day washout period when usual NSAID drug therapy was ceased. Only patients noticing an increase in back pain and stiffness were allocated to treatment.
Exclusion criteria	Patients with spinal arthritis showing active manifestations (articular or not), spinal arthritis secondary to intestinal lesion or Behcet's syndrome, disc lesions in spinal arthritis, ulcers or severe organic disease (e.g. hepatic, cardiac)known intolerance to other NSAIDs, current treatment with anticoagulants, patients treated in previous 2 months with radiotherapy, gold, thorium, immunosuppressives or steroids.
Details	After 3 day run in, patient's randomly allocated to Tenoxicam or Diclofenac groups. Patients assessed prior to commencement and at 2,4,6,8 and 12 weeks after the start of treatment.
Interventions	20mg Tenoxicam daily 100mg Diclofenac (2 x 50g doses per day) Patients were allocated to study drug for 12 weeks.
Characteristics	Baseline characteristics

	Tenoxicam	Diclofenac
Number studied	12	12
Male/ female, n	12	9/3
Age (years, mean)	42	40
Duration of disease (years, mean)	9	7
Duration of stiffness (minutes, mean)	30	60

<table>
<tr><th>Bibliographic reference</th><th>Schwarzer,A.C., Cohen,M., Arnold,M.H., Kelly,D., McNaught,P., Brooks,P.M., Tenoxicam compared with diclofenac in patients with ankylosing spondylitis, Current medical research and opinion, 11, 648-653, 1990</th></tr>
<tr><td>Results</td><td>Diurnal pain [score 0 (none) - 3 (severe)], mean (SD)
<table>
<tr><td></td><td>Tenoxicam</td><td>Diclofenac</td></tr>
<tr><td>Baseline</td><td>1.8 (0.8)</td><td>1.8 (0.8)</td></tr>
<tr><td>Week 12</td><td>1.3 (0.8)</td><td>0.9 (0.6)</td></tr>
</table>
Global assessment at week 12, mean (SD)
<table>
<tr><td></td><td>Tenoxicam</td><td>Diclofenac</td></tr>
<tr><td>Investigators</td><td>2.5 (2.1)</td><td>2.4 (1.2)</td></tr>
<tr><td>Patients</td><td>2.3 (2.0)</td><td>1.6 (1.2)</td></tr>
</table>
Withdrawals due to adverse events:
Only 1 due to serious adverse event (depression); paper does not state which group the patient withdrew from.

Withdrawals due to lack of efficacy (n)
<table>
<tr><td>Tenoxicam</td><td>Diclofenac</td></tr>
<tr><td>4</td><td>3</td></tr>
</table></td></tr>
<tr><td>Overall Risk of Bias</td><td>Does not reported allocation concealment or randomisation.
Does not state whether ITT analysis
Large number of dropouts.</td></tr>
<tr><td>Other information</td><td>Unpaired t test and Mann Whitney test used for comparison of drug groups for continuous measures
Fishers exact test used for comparing groups for categorical measures. For ordered categorical measures an exact probability test for a difference in trend across the ordered variable between the 2 drugs was performed. Paired t tests and sign tests were used to analyse the differences from the baseline measurements within each drug group.</td></tr>
<tr><td>Was the allocation sequence adequately generated?</td><td>UNCLEAR</td></tr>
<tr><td>Was allocation adequately concealed?</td><td>UNCLEAR</td></tr>
<tr><td>Was knowledge of the allocated intervention</td><td>UNCLEAR</td></tr>
</table>

Bibliographic reference	Schwarzer,A.C., Cohen,M., Arnold,M.H., Kelly,D., McNaught,P., Brooks,P.M., Tenoxicam compared with diclofenac in patients with ankylosing spondylitis, Current medical research and opinion, 11, 648-653, 1990
adequately prevented during the study?	
Were incomplete outcome data adequately addressed?	UNCLEAR
Are reports of the study free of suggestion of selective outcome reporting?	UNCLEAR
Was the study apparently free of other problems that could put it at a high risk of bias?	UNCLEAR

Table 88: Shipley et al., 1980

Bibliographic reference	Shipley,M., Berry,H., Bloom,B., A double-blind cross-over trial of indomethacin, fenoprofen and placebo in ankylosing spondylitis, with comments on patient assessment, Rheumatology and rehabilitation, 19, 122-125, 1980
Country/ies where the study was carried out	UK
Study type	Double blind, double dummy placebo controlled crossover trial.
Aim of the study	To assess efficacy and safety of Indomethacin and Fenoprofen in people with AS.
Study dates	Not reported
Source of funding	Dista products Ltd provided the capsules for the study.
Sample size	n=19
Inclusion criteria	Patients with symptomatic AS, diagnosed by clinical and radiological criteria.

<table>
<tr><th>Bibliographic reference</th><th>Shipley,M., Berry,H., Bloom,B., A double-blind cross-over trial of indomethacin, fenoprofen and placebo in ankylosing spondylitis, with comments on patient assessment, Rheumatology and rehabilitation, 19, 122-125, 1980</th></tr>
<tr><td>Exclusion criteria</td><td>None</td></tr>
<tr><td>Details</td><td>3 x 2 week treatment periods, therefore 6 week study period.

A standard number of paracetamol tablets was provided at the beginning of every treatment period in addition to the trial capsules. Allocation of patients was randomised. No washout periods were included. Patients were seen and assessed in the late afternoon by a single observer at the beginning of the trial and then fortnightly for 6 weeks.</td></tr>
<tr><td>Interventions</td><td><u>Placebo:</u>
No details on dosage provided
<u>Fenoprofen:</u>
600mg, three times daily
<u>Indomethacin:</u>
50mg, three times daily</td></tr>
<tr><td>Characteristics</td><td>n=19
Age (yrs),mean (range): 38 (21-53)
Sex (m/f): 18/1</td></tr>
<tr><td>Results</td><td><u>Pain (VAS):</u> (Pain over the previous fortnight was assessed by the patients).
<table>
<tr><td></td><td>Placebo</td><td>Fenoprofen</td><td>Indomethacin</td></tr>
<tr><td>Mean</td><td>4.48</td><td>2.95</td><td>2.22</td></tr>
<tr><td>Difference from placebo</td><td>-</td><td>-1.53</td><td>-2.26</td></tr>
<tr><td>p</td><td>-</td><td><0.05</td><td><0.01</td></tr>
</table>
<u>Withdrawals due to adverse events:</u>
n= 0
<u>Withdrawals due to lack of efficacy:</u>
n=1 during placebo period.</td></tr>
</table>

Bibliographic reference	Shipley,M., Berry,H., Bloom,B., A double-blind cross-over trial of indomethacin, fenoprofen and placebo in ankylosing spondylitis, with comments on patient assessment, Rheumatology and rehabilitation, 19, 122-125, 1980
Overall Risk of Bias	Patients continued with regular analgesic medication. Lack of baseline characteristics. 3 patients failed to complete the trial; unclear how missing data assessed. No SD/SE/95%CI reported for pain outcomes. No details on how placebo given - not clear whether adequate to maintain blinding.
Other information	Returned tablets were counted to assess adherence. 14 of the 19 patients took regular medication in addition to study medication: 8 took indomethacin, 2 took naproxen, 1 took Phenylbutazone, 1 ibuprofen and 2 distalgesic.
Was the allocation sequence adequately generated?	UNCLEAR
Was allocation adequately concealed?	UNCLEAR
Was knowledge of the allocated intervention adequately prevented during the study?	UNCLEAR
Were incomplete outcome data adequately addressed?	UNCLEAR
Are reports of the study free of suggestion of selective outcome reporting?	UNCLEAR
Was the study apparently free of other problems	UNCLEAR

Bibliographic reference	Shipley,M., Berry,H., Bloom,B., A double-blind cross-over trial of indomethacin, fenoprofen and placebo in ankylosing spondylitis, with comments on patient assessment, Rheumatology and rehabilitation, 19, 122-125, 1980
that could put it at a high risk of bias?	

Table 89: Sieper et al., 2008

Bibliographic reference	Sieper,J., Klopsch,T., Richter,M., Kapelle,A., Rudwaleit,M., Schwank,S., Regourd,E., May,M., Comparison of two different dosages of celecoxib with diclofenac for the treatment of active ankylosing spondylitis: results of a 12-week randomised, double-blind, controlled study, Annals of the rheumatic diseases, 67, 323-329, 2008
Country/ies where the study was carried out	Germany, 47 investigational centres
Study type	Randomised, double blind, controlled study.
Aim of the study	To demonstrate the non- inferiority of celecoxib compared with diclofenac in patients with Ankylosing Spondylitis
Study dates	Not reported.
Source of funding	Sponsored by Pfizer.
Sample size	n=458
Inclusion criteria	Age range of 18-75 years, confirmed diagnosis of AS according to modified New York criteria, presence of axial involvement, no peripheral involvement (apart from hips or shoulders), the need for daily treatment with NSAIDs. Acute episode of moderate to severe pain at baseline (>40mm on 100mm VAS scale) and with an increase in pain VAS of >30% compared to screening visit after cessation of NSAID treatment.
Exclusion criteria	Present or previous episodes of inflammatory bowel disease or a history of upper GI ulcers within the previous year and confirmed by endoscopy were regarded as exclusion criteria.
Details	People with AS recruited by rheumatologists in outpatient units or in private practice. Eligible subjects entered a 2 week washout phase of 2-14 days during which all NSAIDs and other analgesics were withdrawn. Eligible subjects randomised 1:1:1 to double dummy study medication (capsules of celecoxib, diclofenac and matching placebo) for oral administration over a treatment period of 12 weeks. Concomitant treatment with DMARDS (if used at a stable dose for at least 3 months prior to study start and no change planned during the study period) and prednisolone equivalents of >10mg/day at stable doses were permitted. The concomitant administration of proton pump inhibitors was allowed at the discretion of the investigators.
Interventions	Celecoxib 200mg twice a day

<table>
<tr><th>Bibliographic reference</th><td>Sieper,J., Klopsch,T., Richter,M., Kapelle,A., Rudwaleit,M., Schwank,S., Regourd,E., May,M., Comparison of two different dosages of celecoxib with diclofenac for the treatment of active ankylosing spondylitis: results of a 12-week randomised, double-blind, controlled study, Annals of the rheumatic diseases, 67, 323-329, 2008</td></tr>
<tr><td></td><td>Celecoxib 200mg once a day
Diclofenac 75mg slow release (SR), twice a day</td></tr>
<tr><td>Characteristics</td><td>n=458 (69% male, n=317)
Mean age 44.8 years (range 18-77 years)</td></tr>
<tr><td>Results</td><td>VAS pain (100mm VAS scale)
<table>
<tr><td></td><td>Celecoxib 200mg once a day</td><td>Celecoxib 200mg twice a day</td><td>Diclofenac 75mg twice a day</td></tr>
<tr><td>Baseline, mean (SD)</td><td>65.6 (14.9)</td><td>68.1 (16.4)</td><td>64.3 (16.6)</td></tr>
<tr><td>Week 12, mean (SD)</td><td>37.4 (25.6)</td><td>38.7 (24.9)</td><td>33.8 (27.1)</td></tr>
<tr><td>Mean change from baseline, mean (SD)</td><td>-28.2 (27.2)</td><td>-29.8 (25.1)</td><td>-30.8 (25.6)</td></tr>
<tr><td>LS mean treatment contrast, mean (SEM)</td><td>2.9 (2.7)</td><td>2.1 (2.8)</td><td>NA</td></tr>
<tr><td>95%CI for the treatment contrast</td><td>-2.4, 8.2</td><td>-3.3, 7.6</td><td>NA</td></tr>
</table>
Global assessment of disease activity (o (inactive)- 10 (highly active))
<table>
<tr><td></td><td>Celecoxib 200mg once a day</td><td>Celecoxib 200mg twice a day</td><td>Diclofenac 75mg twice a day</td></tr>
<tr><td>Baseline, mean (SD)</td><td>6.1 (1.8)</td><td>6.5 (1.7)</td><td>6.1 (1.8)</td></tr>
<tr><td>Week 12, mean (SD)</td><td>4.1 (2.4)</td><td>4.3 (2.5)</td><td>3.8 (2.6)</td></tr>
<tr><td>Mean change from baseline, mean (SD)</td><td>-2.0 (2.7)</td><td>-2.2 (2.5)</td><td>-2.3 (2.6)</td></tr>
<tr><td>LS mean treatment contrast, mean (SEM)</td><td>0.3 (0.3)</td><td>0.3 (0.3)</td><td>NA</td></tr>
</table></td></tr>
</table>

Bibliographic reference	**Sieper,J., Klopsch,T., Richter,M., Kapelle,A., Rudwaleit,M., Schwank,S., Regourd,E., May,M., Comparison of two different dosages of celecoxib with diclofenac for the treatment of active ankylosing spondylitis: results of a 12-week randomised, double-blind, controlled study, Annals of the rheumatic diseases, 67, 323-329, 2008**
	95%CI for the treatment contrast | -0.2, 0.8 | -0.2, 0.8 | NA Withdrawals due to adverse events | | celecoxib 200mg qd | celecoxib 200 mg bid | Diclofenac 75mg SR bid | | 12 weeks | 8/153 | 12/150 | 15/155 | Withdrawals due to lack of efficacy (the analysis of premature withdrawal was based on the allocation of 1 primary reason for withdrawal in the case of multiple reasons - 14 patients had an additional specification of "lack of efficacy" but were allocated to another (primary) category. The paper states that the number of patients with lack of efficacy was comparable between treatment groups) | | celecoxib 200mg qd | celecoxib 200 mg bid | Diclofenac 75mg SR bid | | 12 weeks | 5 | 5 | 4 |
Overall Risk of Bias	Allocation concealment not reported. >10% dropouts in each group, though these were equally distributed between groups.
Other information	Primary analysis performed hierarchically in the per protocol population. Primary and secondary efficacy variables were analysed using several ANCOVA models. For the primary analysis (Global pain intensity at week 12), baseline, VAS and age were used as covariates, and sex, treatment and pooled centre as factors. The safety analysis was performed descriptively. Study adequately powered.
Was the allocation sequence adequately generated?	UNCLEAR
Was allocation adequately concealed?	UNCLEAR
Was knowledge of the allocated intervention adequately prevented during the study?	UNCLEAR
Were incomplete outcome data adequately addressed?	YES

Bibliographic reference	Sieper,J., Klopsch,T., Richter,M., Kapelle,A., Rudwaleit,M., Schwank,S., Regourd,E., May,M., Comparison of two different dosages of celecoxib with diclofenac for the treatment of active ankylosing spondylitis: results of a 12-week randomised, double-blind, controlled study, Annals of the rheumatic diseases, 67, 323-329, 2008
Are reports of the study free of suggestion of selective outcome reporting?	YES
Was the study apparently free of other problems that could put it at a high risk of bias?	YES

Table 90: Sturrock & Hart, 1974

Bibliographic reference	Sturrock,R.D., Hart,F.D., Double-blind cross-over comparison of indomethacin, flurbiprofen, and placebo in ankylosing spondylitis, Annals of the Rheumatic Diseases, 33, 129-131, 1974
Country/ies where the study was carried out	UK
Study type	Double blind, crossover
Aim of the study	Not reported
Study dates	Not reported
Source of funding	Financial support of the Arthritis and Rheumatism Council for Research.
Sample size	n=24 (20 completed the trial)
Inclusion criteria	Negative sheep cell agglutination test, fulfilled the criteria for the diagnosis of ankylosing spondylosis (Bennett and Wood, 1968)
Exclusion criteria	History of peptic ulcers, intolerance to indomethacin, concurrent steroid therapy.
Details	Patients were randomly allocated to one of 6 treatment sequences. The capsules were of identical size shape and colouring. A return capsule count was made at the end of each treatment period. The use of paracetamol tablets was allowed during the course of the trial and the number taken daily was recorded on a pain diary. The trial period consisted of three, 2 - week treatment intervals. Assessments taken at the end of each 2 week period.
Interventions	Indomethacin 25mg, three times a day Flurbiprofen 50mg, three times a day Placebo
Characteristics	n= 24 (21 male, 3 female) Mean age (years) 43.2

<table>
<tr><th>Bibliographic reference</th><th>Sturrock,R.D., Hart,F.D., Double-blind cross-over comparison of indomethacin, flurbiprofen, and placebo in ankylosing spondylitis, Annals of the Rheumatic Diseases, 33, 129-131, 1974</th></tr>
<tr><td></td><td>Mean duration of disease (yrs) 16.5</td></tr>
<tr><td>Results</td><td>Subjective impression of pain (VAS)
<table>
<tr><th>Comparison</th><th>indomethacin</th><th>Placebo</th><th>Flurbiprofen</th><th>Difference</th><th>S.E</th><th>No. of cases</th><th>t</th><th>Probability</th></tr>
<tr><td>Placebo vs indomethacin</td><td>1.30</td><td>1.77</td><td></td><td>0.47</td><td>0.23</td><td>19</td><td>2.08</td><td>p=0.05</td></tr>
<tr><td>Placebo vs flurbiprofen</td><td></td><td>1.77</td><td>1.16</td><td>0.61</td><td>0.20</td><td>19</td><td>2.98</td><td>p<0.01</td></tr>
<tr><td>Indomethacin vs flurbiprofen</td><td>1.30</td><td></td><td>1.16</td><td>0.14</td><td>0.17</td><td>19</td><td>0.79</td><td>p>0.02</td></tr>
</table>
Mean daily pain scores
<table>
<tr><th>Comparison</th><th>Wilcoxon’s T</th><th>No. of cases</th><th>Critical 5% value of T</th><th>Probability</th><th></th></tr>
<tr><td>Placebo vs indomethacin</td><td>77</td><td>19</td><td>53</td><td>p>0.1</td><td>favours indomethacin</td></tr>
<tr><td>Placebo vs flurbiprofen</td><td>32</td><td>17</td><td>34</td><td>0.05>p>0.02</td><td>favours flurbiprofen</td></tr>
<tr><td>Indomethacin vs flurbiprofen</td><td>51.5</td><td>19</td><td>53</td><td>0.05>p>0.02</td><td>favours flurbiprofen</td></tr>
</table>
Withdrawals:
4 in total;
2 on indomethacin (indigestion and nausea)
1 on Flurbiprofen (vertigo)
1 during placebo (severe exacerbation of pain and stiffness)</td></tr>
<tr><td>Overall Risk of Bias</td><td>Very small trial.
Unclear whether ITT analysis.</td></tr>
</table>

Bibliographic reference	Sturrock,R.D., Hart,F.D., Double-blind cross-over comparison of indomethacin, flurbiprofen, and placebo in ankylosing spondylitis, Annals of the Rheumatic Diseases, 33, 129-131, 1974
	Allocation concealment not reported.
Other information	Unclear whether there was a washout period between the three treatment periods.
Was the allocation sequence adequately generated?	UNCLEAR
Was allocation adequately concealed?	UNCLEAR
Was knowledge of the allocated intervention adequately prevented during the study?	UNCLEAR
Were incomplete outcome data adequately addressed?	UNCLEAR
Are reports of the study free of suggestion of selective outcome reporting?	UNCLEAR
Was the study apparently free of other problems that could put it at a high risk of bias?	UNCLEAR

Table 91: Sydnes, 1981

Bibliographic reference	Sydnes,O.A., Comparison of piroxicam with indomethacin in ankylosing spondylitis: a double-blind crossover trial, The British journal of clinical practice, 35, 40-44, 1981
Country/ies where the study was carried out	Norway, 13 rheumatology departments.
Study type	Double blind, crossover
Aim of the study	To assess the efficacy and tolerability of Piroxicam and Indomethacin.
Study dates	Not reported
Source of funding	Not reported
Sample size	n=93
Inclusion criteria	Patients of either sex, aged 18-70 years suffering from classical or definite AS, as defined by the American Rheumatism Association were included. All patients had active disease requiring treatment with NSAIDs.

Bibliographic reference	Sydnes,O.A., Comparison of piroxicam with indomethacin in ankylosing spondylitis: a double-blind crossover trial, The British journal of clinical practice, 35, 40-44, 1981
Exclusion criteria	History of primary disease of less than 6 months duration, AS associated with psoriasis, systematically or intra-articularly administered corticosteroids in the preceding 3 months, anticipated corticosteroid requirement during the course of the trial, pregnancy or nursing mothers, blood, liver or renal abnormalities unrelated to the primary disease, peptic ulceration or severe dyspepsia in the preceding 12 months, known hypersensitivity to NSAID
Details	A double blind, crossover design was used. The order in which the drugs were given was randomised with a restriction to ensure a balance between treatments and orders. At the first visit, patients underwent clinical examination and any NSAID and analgesics except paracetamol were stopped and patients received placebo for one week. Those patients meeting the selection criteria were entered into the trial. The duration of each drug treatment was 4 weeks; the treatment periods were separated by 1 week of placebo. Patients attended for assessment after 1, 5, 6 and 10 weeks; as far as possible at the same hour of the day and seen by the same observer on each occasion. If during a placebo period, pain or morning stiffness worsened considerably, the investigator was allowed to shorten the period and proceed immediately to the next treatment as scheduled. A fixed dose of all study drugs was given to patients throughout the trial. All capsules were identical in appearance and supplied in dosing boxes, each box containing capsules for one week. At return, a capsule count was undertaken. Paracetamol was permitted as an escape medication. Those patients receiving physiotherapy continued with this, unchanged, throughout the entire trial period.
Interventions	Piroxicam One capsule (20mg) taken in the evening, 2 placebo capsules taken to maintain blinding. Indomethacin One 25mg capsule, taken 3 times daily
Characteristics	Baseline characteristics (on patients remaining in study only - no details on 6 patients who discontinued): Male: 67; mean age (years):39 Female: 20; mean age (years): 41 Total n: 87; mean age (years): 40
Results	Pain [mean(SEM)]

Parameter	Sequence A				Sequence B				Results
	Placebo	Piroxicam	placebo	Indomethacin	Placebo	Indomethacin	Placebo	Piroxicam	

Bibliographic reference	Sydnes,O.A., Comparison of piroxicam with indomethacin in ankylosing spondylitis: a double-blind crossover trial, The British journal of clinical practice, 35, 40-44, 1981

Peripheral joint pain at rest*	3.6 (0.5)	2.5 (0.4)	3.7 (0.5)	3.2 (0.4)	3.7 (0.3)	3.2 (0.4)	4.3 (0.4)	2.4 (0.3)	P>I p>0.01
Peripheral joint pain on movement*	5.0 (0.5)	3.3 (0.4)	4.4 (0.4)	3.7 (0.4)	3.7 (0.3)	3.0 (0.4)	4.6 (0.4)	2.4 (0.3)	P>I 0.05 <p<0.1
Pain in tendon attachments*	3.8 (0.5)	2.2 (0.4)	3.7 (0.4)	2.8 (0.4)	3.6 (0.4)	3.2 (0.4)	4.2 (0.4)	2.2 (0.4)	P>I p<0.02
Back pain+	5.0 (0.4	3.2 (0.4)	4.6 (0.4)	3.7 (0.4)	5.0 (0.3)	3.8 (0.4)	5.7 (0.4)	2.8 (0.3)	P>I p<0.01
Overall condition**	3.3 (0.1)	2.3 (0.1)	3.0 (0.1)	2.4 (0.1)	3.3 (0.1)	2.6 (0.1)	3.3 (0.1)	2.1 (0.1)	P>I p<0.03

*measured on VAS scale of 0 [very good] to 10 [very bad]),
+ not reported what scale back pain was measure on)
** 5 Grades; 1= very good - 5=very bad

Withdrawals due to adverse events
n=1 withdrew during treatment with Indomethacin

Bibliographic reference	Sydnes,O.A., Comparison of piroxicam with indomethacin in ankylosing spondylitis: a double-blind crossover trial, The British journal of clinical practice, 35, 40-44, 1981
	Withdrawals due to lack of efficacy of study medication n=1 hospitalised for flare of disease activity (not stated during which intervention).
Overall Risk of Bias	The ability of the investigator to shorten any placebo period and move to active treatment is a source of bias; not reported how many participants this occurred with. Lack of information on baseline characteristics. No baseline information on 6 patients who discontinued study.
Other information	Comparisons in efficacy between the 2 medications made by using student's T test, each patient being their own control between measurements of each active treatment period.
Was the allocation sequence adequately generated?	UNCLEAR
Was allocation adequately concealed?	UNCLEAR
Was knowledge of the allocated intervention adequately prevented during the study?	YES
Were incomplete outcome data adequately addressed?	UNCLEAR
Are reports of the study free of suggestion of selective outcome reporting?	UNCLEAR
Was the study apparently free of other problems that could put it at a high risk of bias?	UNCLEAR

Table 92: Tannenbaum et al., 1984

Bibliographic reference	Tannenbaum,H., DeCoteau,W.E., Esdaile,J.M., A double blind multicenter trial comparing piroxicam and indomethacin in ankylosing spondylitis with long-term follow-up, Current Therapeutic Research - Clinical and Experimental, 36, 426-435, 1984
Country/ies where the study was carried out	Canada
Study type	Randomised, double blind parallel study
Aim of the study	To compare the efficacy and safety of piroxicam with indomethacin in the therapy of patients with AS. Compliance was also assessed.
Study dates	Not reported
Source of funding	Not reported
Sample size	n=55
Inclusion criteria	AS diagnosed by a history of morning stiffness, low back pain with limitation of motion, sacroiliitis radiologically graded according to New York criteria. Patient had to be aged between 18-65 years, and have active disease as evidenced by spinal and/or sacroiliac pain and one or more of the following:1. muscle spasm in the back; 2. decreased range of motion of some part of the spine; 3. increased ESR. A history of uveitis and detection of HLA-B27 histocompatibility antigen was also considered as positive evidence of disease (but absence of these did not preclude the diagnosis of AS).
Exclusion criteria	Patients with other arthropathies or diseases closely related to AS, such as psoriatic arthritis were excluded, as were patients with active haematological, GI, renal or hepatic disease, pregnant or nursing women.
Details	Double blind phase, 12 weeks duration. Undertaken at 4 rheumatology centres. Patients underwent a placebo washout period of up to 7 days (average length was 5 days). The washout terminated when there was an exacerbation of symptoms. Patients randomised to either indomethacin or piroxicam. As the two drugs were not identical, the double dummy technique was used. Depending on the clinical response, it was possible to increase or decrease the dose of the drug without breaking blinding.
Interventions	Indomethacin (n=27) 100mg (25mg capsules) divided into 3 doses: 25mg at 08.00 and 12.00, and 50mg at 22.00. The dose could be adjusted between 75mg - 125mg. In addition to indomethacin tablets, patients received placebo capsules identical to piroxicam.

Bibliographic reference	**Tannenbaum,H., DeCoteau,W.E., Esdaile,J.M., A double blind multicenter trial comparing piroxicam and indomethacin in ankylosing spondylitis with long-term follow-up, Current Therapeutic Research - Clinical and Experimental, 36, 426-435, 1984**
	Piroxicam (n=28) 20mg (in 10mg capsules) once a day at 8.00. The dose could be lowered to 10mg, but could not be increased beyond 20mg per day. In addition to piroxicam tablets, patients received placebo capsules identical to indomethacin. For both groups, the number of piroxicam or indomethacin capsules were increased or decreased in a parallel fashion whenever a change in dosage was required. The paper states that in 75% of patients, no adjustments from the starting dosage of indomethacin (100mg) or piroxicam (20mg) were made. No further detail supplied.
Characteristics	Baseline characteristics

	Piroxicam	indomethacin
Number	28	27
Age	35.6 (1.3)	34.0 (1.8)
Sex (m/f)	21/7	20/7
Disease duration (yrs)	8.8 (1.4)	9.7 (1.7)
Sacroiliitis on x-ray:		
Grade 1	1	1
Grade 2	11	11
Grade 3	11	12
Grade 4	5	3
HLA-B27pos:neg	22:3	22:3

Bibliographic reference	**Tannenbaum,H., DeCoteau,W.E., Esdaile,J.M., A double blind multicenter trial comparing piroxicam and indomethacin in ankylosing spondylitis with long-term follow-up, Current Therapeutic Research - Clinical and Experimental, 36, 426-435, 1984**
	Not reported | 3 | 2
Results	All values expressed as mean (SEM) Pain (VAS, using 17 point scale) Baseline | Mean change Piroxicam | Indomethacin | Piroxicam | Indomthacin Patients self-assessment of pain | 9.6 (0.6) | 9.9 (0.7) | -6.3 (1.1) | -6.8 (0.8) Withdrawals due to adverse events: Piroxicam: 0 Indomethacin: 1 Withdrawals due to lack of efficacy: Piroxicam: 1 Indomethacin: 1
Overall Risk of Bias	Not stated whether ITT or how missing data dealt with.
Other information	Unblinded investigator dispensed the medications, scheduled visits and made any required dosage adjustments. A blinded investigator performed all clinical assessments, including assessment of pain. Compliance to the dosing regimen was measured at each visit by counting the returned medications. Student's t test used to compare differences between groups. Paired t test or Wilcoxon signed rank test used to compare data within group to determine significant change from baseline. Chi squared statistic and life table analysis used to analyse dropout pattern between the 2 groups.
Was the allocation sequence adequately generated?	UNCLEAR

Bibliographic reference	Tannenbaum,H., DeCoteau,W.E., Esdaile,J.M., A double blind multicenter trial comparing piroxicam and indomethacin in ankylosing spondylitis with long-term follow-up, Current Therapeutic Research - Clinical and Experimental, 36, 426-435, 1984
Was allocation adequately concealed?	UNCLEAR
Was knowledge of the allocated intervention adequately prevented during the study?	UNCLEAR
Were incomplete outcome data adequately addressed?	UNCLEAR
Are reports of the study free of suggestion of selective outcome reporting?	UNCLEAR
Was the study apparently free of other problems that could put it at a high risk of bias?	UNCLEAR

Table 93: van der Heijde et al., 2005

Bibliographic reference	van der Heijde,Desiree, Baraf,Herbert S.B., Ramos-Remus,Cesar, Calin,Andrei, Weaver,Arthur L., Schiff,Michael, James,Margaret, Markind,Jan E., Reicin,Alise S., Melian,Agustin, Dougados,Maxime, Evaluation of the efficacy of etoricoxib in ankylosing spondylitis: results of a fifty-two-week, randomized, controlled study, Arthritis and rheumatism, 52, 1205-1215, 2005
Country/ies where the study was carried out	Europe, USA; 44 centres
Study type	Multicentre, double blind, parallel group. The first 6/52 was placebo controlled; from week 6-52 was an active comparator controlled study
Aim of the study	To assess the efficacy, safety and tolerability of etoricoxib for the treatment of AS.
Study dates	Not stated

Bibliographic reference	**van der Heijde,Desiree, Baraf,Herbert S.B., Ramos-Remus,Cesar, Calin,Andrei, Weaver,Arthur L., Schiff,Michael, James,Margaret, Markind,Jan E., Reicin,Alise S., Melian,Agustin, Dougados,Maxime, Evaluation of the efficacy of etoricoxib in ankylosing spondylitis: results of a fifty-two-week, randomized, controlled study, Arthritis and rheumatism, 52, 1205-1215, 2005**
Source of funding	Not stated
Sample size	n=387 (part 1). n=301 completed part 1. Of the 81 people who discontinued, 77 continued to part 2. n=374 (part 2), n=284 completed the study.
Inclusion criteria	Outpatients who fulfilled the modified New York criteria for AS. 18 years or older, diagnosis of AS made >6 months prior to study start, history of positive therapeutic benefit with NSAIDs, routine NSAID intake (use of NSAIDs for at least 25 of the previous 30 days prior to study enrolment), and at a therapeutic dose level for >30 days prior to study enrolment, use of approved non-study anti-rheumatic therapy at a stable dose for required time periods (MTX, SSZ for 3 months, other DMARDs for 6 months), satisfaction of flare criteria (>40mm on patients assessment of spine pain on 100mm VAS scale and increase of >30% compared with the pain rating at the screening visit) after the washout period for pre-study NSAIDs. Patients with chronic peripheral arthritis were eligible for inclusion in the study, if spine pain was the primary source of pain.
Exclusion criteria	Patients with concurrent rheumatic disease (e.g. SLE) that could confound the evaluation of efficacy, patients with acute peripheral articular disease (onset within 4 weeks prior to study or active peripheral arthritis), use of corticosteroid therapy within 1 month prior to the screening visit, use of analgesic medication within 3 days of study entry and through week 6 (acetaminophen was permitted prior to study entry), use of NSAID or selective COX-2 inhibitor, with the exception of low-dose aspirin (<100mg daily), which was allowed for cardiovascular prophylaxis.
Details	Part 1 - consisted of a 6 week, active comparator and placebo controlled treatment period. All patients who completed or discontinued part 1 (due to lack of efficacy of following at least 2 weeks of treatment during part 1) were given the opportunity to progress to part 2. Part 2 was a double blind, active comparator, 46 week period. Patients were randomly allocated to a treatment sequence using a computer generated random allocation schedule. Based on the original randomisation schedule, patients who received placebo during part 1 were reassigned 1:1:1 to etoricoxib 90mg, etoricoxib 10mg or naproxen 1g. Patients who received etoricoxib or naproxen during part 1 of the study continued to receive the same regimen for part 2 of the study.
Interventions	Etoricoxib 90mg daily Etoricoxib 120mg daily Naproxen 500mg, twice daily Placebo (part 1 only) During part 1 patients received 3 bottles of study medication at randomisation and at weeks 2 and 4. Each bottle contained active medication or matching placebo. Patients also received acetaminophen (a rescue medication for breakthrough AS pain). During part 2, study medication was dispensed in blister cards, each containing active medication or matching placebo, for 7 days.
Characteristics	Demographics / Placebo (n=93) / Etoricoxib 90mg (n=103) / Etoricoxib 120mg (n=92) / Naproxen 1g (n=99) / Total (n=387)

Bibliographic reference	van der Heijde,Desiree, Baraf,Herbert S.B., Ramos-Remus,Cesar, Calin,Andrei, Weaver,Arthur L., Schiff,Michael, James,Margaret, Markind,Jan E., Reicin,Alise S., Melian,Agustin, Dougados,Maxime, Evaluation of the efficacy of etoricoxib in ankylosing spondylitis: results of a fifty-two-week, randomized, controlled study, Arthritis and rheumatism, 52, 1205-1215, 2005

Female (%)	20.4	26.2	21.7	20.2	22.2
Age (mean, SD)	43.7 (12.1)	43.1 (12.1)	42.5 (12)	45 (11.4)	43.6 (11.9)
History of chronic peripheral arthritis (no, %)	37 (39.8)	41 (39.8)	36 (39.1)	41 (41.4)	155 (40.1)
History of corticosteroid use, no (%)	30 (32.3)	24 (23.3)	22 (23.9)	22 (22.2)	98 (25.3)
Concomitant DMARD use. no (%)	18 (19.4)	27 (26.2)	18 (19.6)	23 (23.2)	86 (22.2)
Baseline spine pain (100mm VAS), mean, (SD)	77.22 (15.24)	77.95 (13.94)	77.96 (14.16)	77.20 (16.45)	77.58 (14.92)
Patients global assessment of disease activity (100mm VAS), mean (SD)	64.26 (20.99)	63.19 (20.84)	64.29 (21.60)	64.65 (22.17)	64.08 (21.33)
BASFI (100mm VAS), mean, (SD)	54.12 (26.99)	56.89 (22.48)	55.23 (25.07)	54.09 (23.23)	55.11 (24.37)

Results

Patients assessment of spine pain on VAS

End point	Placebo (n=93)	Etoricoxib 90mg (n=100)	Etoricoxib 120mg (n=90)	Naproxen 1000mg (n=97)
Patients assessment of spine pain on VAS (100mm)				
6 weeks	-12.6 (2.3)	-41.5 (2.2)	-41.6 (2.4)	-33.7 (2.3)
1 year	-	-42.9 (2.2)	-43.7 (1.6)	-35.4 (2.3)
Patients global assessment of disease activity on VAS (100mm)				
6 weeks	-3.4 (2.2)	-27.9 (2.1)	-26.6 (2.2)	-20.9 (2.1)

<table>
<tr><th>Bibliographic reference</th><th>van der Heijde,Desiree, Baraf,Herbert S.B., Ramos-Remus,Cesar, Calin,Andrei, Weaver,Arthur L., Schiff,Michael, James,Margaret, Markind,Jan E., Reicin,Alise S., Melian,Agustin, Dougados,Maxime, Evaluation of the efficacy of etoricoxib in ankylosing spondylitis: results of a fifty-two-week, randomized, controlled study, Arthritis and rheumatism, 52, 1205-1215, 2005</th></tr>
<tr><td></td><td>
<table>
<tr><td>1 year</td><td>-</td><td>-29.5 (2.2)</td><td>-30.1(2.3)</td><td>-22.6 (2.2)</td></tr>
</table>

Discontinuations due to lack of efficacy
<table>
<tr><td></td><td>Placebo</td><td>90mg Etoricoxib</td><td>120mg Etoricoxib</td><td>1000mg Naproxen</td></tr>
<tr><td>6 weeks, n (%)</td><td>44 (47.3)</td><td>8 (7.8)</td><td>9 (9.8%)</td><td>20 (20.2)</td></tr>
<tr><td>1 year</td><td>-</td><td>10 (7.9)</td><td>12 (9.8)</td><td>22 (17.6)</td></tr>
</table>
Discontinuation due to adverse events
<table>
<tr><td></td><td>Placebo</td><td>90mg Etoricoxib</td><td>120mg etoricoxib</td><td>1000mg Naproxen</td></tr>
<tr><td>6 weeks</td><td>0</td><td>2 (1.9)</td><td>0</td><td>1 (1.0)</td></tr>
<tr><td>1 year</td><td>-</td><td>10 (7/9)</td><td>12 (9.8)</td><td>22 (17.6)</td></tr>
</table>
</td></tr>
<tr><td>Overall Risk of Bias</td><td>Allocation concealment not reported</td></tr>
<tr><td>Other information</td><td>Statistical analysis: modified intention to treat principle (i.e. inclusion of all patients in the analysis population for whom a baseline measurement and at least 1 post baseline measurement were available. Part 1 analysis undertaken on per protocol approach.
For part 1, the primary measures were a time weighted average of all measurements collected over the 6 week treatment period. The time weighted average changes from baseline and efficacy were analysed using ANOVA or ANCOVA, with treatment and presence/ absence of chronic peripheral arthritis as the main effects and baseline value as the covariate for end points measured at baseline.
Etoricoxib 120mg results reported here, but not included in final analysis as 120mg etoricoxib is not a licensed dose.</td></tr>
<tr><td>Was the allocation sequence adequately generated?</td><td>UNCLEAR</td></tr>
</table>

Bibliographic reference	van der Heijde,Desiree, Baraf,Herbert S.B., Ramos-Remus,Cesar, Calin,Andrei, Weaver,Arthur L., Schiff,Michael, James,Margaret, Markind,Jan E., Reicin,Alise S., Melian,Agustin, Dougados,Maxime, Evaluation of the efficacy of etoricoxib in ankylosing spondylitis: results of a fifty-two-week, randomized, controlled study, Arthritis and rheumatism, 52, 1205-1215, 2005
Was allocation adequately concealed?	UNCLEAR
Was knowledge of the allocated intervention adequately prevented during the study?	YES
Were incomplete outcome data adequately addressed?	YES
Are reports of the study free of suggestion of selective outcome reporting?	YES
Was the study apparently free of other problems that could put it at a high risk of bias?	YES

Table 94: Villa Alcazar et al., 1996

Bibliographic reference	Villa Alcazar,L.F., de Buergo,M., Rico Lenza,H., Montull Fruitos,E., Aceclofenac is as safe and effective as tenoxicam in the treatment of ankylosing spondylitis: a 3 month multicenter comparative trial. Spanish Study Group on Aceclofenac in Ankylosing Spondylitis, The Journal of rheumatology, 23, 1194-1199, 1996
Country/ies where the study was carried out	Spain, 16 centres involved in trial
Study type	Multicentre, double blind, parallel study
Aim of the study	To compare efficacy and safety of NSAID aceclofenac 100mg bid orally with tenoxicam 20mg orally at bedtime in treatment of people with AS
Study dates	Not reported

Bibliographic reference	**Villa Alcazar,L.F., de Buergo,M., Rico Lenza,H., Montull Fruitos,E., Aceclofenac is as safe and effective as tenoxicam in the treatment of ankylosing spondylitis: a 3 month multicenter comparative trial. Spanish Study Group on Aceclofenac in Ankylosing Spondylitis, The Journal of rheumatology, 23, 1194-1199, 1996**
Source of funding	Not reported
Sample size	n=273 (n=292 entered the washout period, n=19 withdrew because of insufficient control of symptoms or other reasons)
Inclusion criteria	Outpatients of both sexes, between 18-50 years of age, with defined clinical and radiological AS by New York criteria, eligible if at least 2 of the 3 following criteria were met: morning stiffness lasting 30 minutes or longer, pain requiring medication with NSAID and VAS pain of >40mm.
Exclusion criteria	People with other spondyloarthropathies or psoriasis, Paget's disease of the bone, gout, haemachromatosis and / or arthritis of any aetiology, patients with history of peptic ulcers of digestive haemorrhage caused by NSAID, patients with hypersensitivity to study drugs, patients with life expectancy of less than 2 years. Significant pulmonary, cardiac, cerebrovascular, hepatic or renal disease, pregnant women, nursing mothers, women of child bearing potential, anticoagulant therapy or other treatments that could interfere with the drugs under study, treatment with sulfasalazine, steroids or immunosuppressive drugs within the previous 3 months, concurrent pathologies or other circumstances that impeded the performance of trial controls.
Details	12 week trial. Suitable patients identified after a screening visit. Patients were withdrawn from all incompatible medication and thereafter started a washout period of 1 week, with the only drug allowed was paracetamol 500mg, up to 3 times daily to reduce pain. After the washout phase, patients were randomly assigned to receive Aceclofenac 100mg or tenoxicam. All medications were identical in appearance. Patients were evaluated after the washout period (baseline) days 15 and 30 and at months 2 and 3. Patients were recommended to take capsules after meals. Each medication unit was completed with emergency medication (paracetamol 500mg), presented in 3 bottles of 90 tablets, one bottle for each month of treatment.
Interventions	Aceclofenac (n=135) 100mg in morning and 100mg at bedtime. Tenoxicam (n=138)
Characteristics	Baseline characteristics: No significant differences observed between the groups regarding demographic and pre-trial AS severity data, clinical or analytical variables and frequency distribution. All patients were Caucasian.

Parameter	Aceclofenac n=135 mean, (SD) or N	Tenoxicam n=138 mean, (SD) or N

Bibliographic reference	**Villa Alcazar,L.F., de Buergo,M., Rico Lenza,H., Montull Fruitos,E., Aceclofenac is as safe and effective as tenoxicam in the treatment of ankylosing spondylitis: a 3 month multicenter comparative trial. Spanish Study Group on Aceclofenac in Ankylosing Spondylitis, The Journal of rheumatology, 23, 1194-1199, 1996**
	Age (yrs) 37.4 (8.4) 37.1 (8.1) Sex: m/f 112/23 106/32 Duration of disease (yrs) 6.3 (5.7) 5.4 (5.4)
Results	Pain (VAS), mm | | Aceclofenac (n=120) | Tenoxicam (n=115) | | Baseline (mean scores) | 57.9 | 58.1 | | Difference at end of therapy | -25.7* | -27.5* | | % change from baseline | -44.5 | -45.1 | *Significance vs baseline p<0.01 Not clear whether Difference and % change outcomes were mean values. Withdrawals due to adverse events Aceclofenac (n=135): 3 (2%) Tenoxicam (n=138): 2 (1%) Withdrawals due to lack of efficacy of study drugs: Aceclofenac (n=135): 8 (6%) Tenoxicam (n=138): 7 (5%)
Other information	Sample size calculation based on outcome of morning stiffness, mean value of 50 mins with variance of 25 min after 3 months of treatment. Not clear what n required was.
Was the allocation sequence adequately generated?	UNCLEAR
Was allocation adequately concealed?	UNCLEAR
Was knowledge of the allocated intervention	YES

Bibliographic reference	Villa Alcazar,L.F., de Buergo,M., Rico Lenza,H., Montull Fruitos,E., Aceclofenac is as safe and effective as tenoxicam in the treatment of ankylosing spondylitis: a 3 month multicenter comparative trial. Spanish Study Group on Aceclofenac in Ankylosing Spondylitis, The Journal of rheumatology, 23, 1194-1199, 1996
adequately prevented during the study?	
Were incomplete outcome data adequately addressed?	UNCLEAR
Are reports of the study free of suggestion of selective outcome reporting?	NO
Was the study apparently free of other problems that could put it at a high risk of bias?	UNCLEAR

Table 95: Walker et al., 2016

Bibliographic reference	Walker,C., Essex,M.N., Li,C., Parl,P.W., Celecoxib versus diclofenac for the treatment of ankylosing spondylitis: 12-week randomized study in Norwegian patients, Journal of International Medical Research, 44(3), 483-95, 2016
Country/ies where the study was carried out	Norway, 16 centres involved in trial
Study type	Multicentre, double blind, parallel study
Aim of the study	To compare efficacy and safety of two different doses of celecoxib and diclofenac in the treatment of Norwegian patients with ankylosis spondylitis
Study dates	September 2002 to November 2004
Source of funding	Pfizer
Sample size	n=330
Inclusion criteria	Aged 18-75 with a diagnosis of ankylosis spondylitis (modified Ney York criteria) Active symptoms requiring daily treatment with NSAIDs during the 30 days prior to study entry
Exclusion criteria	Acute peripheral articular disease and/or ongoing extra-articular signs. Ulcerative colitis or Crohn's disease Endoscopy-confirmed gastroduodenal ulcer within the past year Gastrointestinal bleeding Cardiac, renal or hepatic disease Coagulation disorders

<table>
<tr><th>Bibliographic reference</th><th>Walker,C., Essex,M.N., Li,C., Parl,P.W., Celecoxib versus diclofenac for the treatment of ankylosing spondylitis: 12-week randomized study in Norwegian patients, Journal of International Medical Research, 44(3), 483-95, 2016</th></tr>
<tr><td></td><td>History of asthma
Known hypersensitivity to celecoxib, HSAIDs of sulphonamide medication</td></tr>
<tr><td>Details</td><td>12 week trial.
Suitable patients identified after a screening visit.
There was then a washout period before beginning the study drug</td></tr>
<tr><td>Interventions</td><td>200 mg of celecoxib once a day
400 mg of celecoxib once a day
50 mg of celecoxib three times a day</td></tr>
<tr><td>Characteristics</td><td>Mean age: 48 years
72% male
Mean time since diagnosis: 10.3 years
Other disease characteristics were similar across treatment groups (data not reported in paper)</td></tr>
<tr><td>Results</td><td>Pain (VAS), mm
<table><tr><td></td><td>Celecoxib 200mg</td><td>Celecoxib 400mg</td><td>Diclofenac</td></tr><tr><td>Baseline (mean scores)</td><td>61.3 (24.2)</td><td>57.9 (23.3)</td><td>62.0 (21.7)</td></tr><tr><td>Week 12</td><td>35.9 (26.3)</td><td>27.6 (23.4)</td><td>34.4 (25.7)</td></tr><tr><td>Change from baseline</td><td>-25.9 (2.5)</td><td>-33.1 (2.5)</td><td>-28.0 (2.4)</td></tr></table>
Withdrawals due to adverse events
Celecoxib 200mg: 12 (11.2%)
Celecoxib 400mg: 14 (13.0%)
Diclofenac: 15 (13.0%)</td></tr>
<tr><td>Was the allocation sequence adequately generated?</td><td>YES</td></tr>
<tr><td>Was allocation adequately concealed?</td><td>YES</td></tr>
<tr><td>Was knowledge of the allocated intervention adequately prevented during the study?</td><td>YES</td></tr>
</table>

Bibliographic reference	Walker,C., Essex,M.N., Li,C., Parl,P.W., Celecoxib versus diclofenac for the treatment of ankylosing spondylitis: 12-week randomized study in Norwegian patients, Journal of International Medical Research, 44(3), 483-95, 2016
Were incomplete outcome data adequately addressed?	UNCLEAR
Are reports of the study free of suggestion of selective outcome reporting?	YES
Was the study apparently free of other problems that could put it at a high risk of bias?	YES

E.2.2 Pharmacological management of peripheral spondyloarthritis

Review Question 21

- What is the comparative effectiveness of the following pharmacological interventions for the management of peripheral spondyloarthritis:
  - corticosteroids
  - non-steroidal anti-inflammatory drugs (NSAIDs)
  - standard disease-modifying anti-rheumatic drugs (DMARDs)?

Table 96: Juvakoski & Lassus, 1982

Bibliographic reference	Juvakoski,T., Lassus,A., A double-blind cross-over evaluation of ketoprofen and indomethacin in Reiter's disease, Scandinavian journal of rheumatology, 11, 106-108, 1982
Country/ies where the study was carried out	Finland
Study type	RCT, double-blind, crossover (details on randomisation not reported)
Aim of the study	To compare the effect of ketoprofen and indomethacin on patients with clinically typical Reiter's disease (reactive arthritis)
Study dates	Recruited from an out-patient department 1978-79
Source of funding	Not reported
Sample size	N=50
Inclusion criteria	Reiter's disease
Exclusion criteria	None reported
Characteristics	Mean age 36years (range 23 to 68), duration of arthritis 6years (range 1 to 19), 92% male All analgesic and anti-inflammatory drugs withdrawn 1week before first treatment period, no additional analgesia or anti-inflammatory drugs allowed during study period
Interventions	N=50 (crossover), 8week treatment, 1week washout, 8week treatment Identical tablets; ketoprofen 200mg or indomethacin 100mg
Results	Assessments;

Bibliographic reference	Juvakoski,T., Lassus,A., A double-blind cross-over evaluation of ketoprofen and indomethacin in Reiter's disease, Scandinavian journal of rheumatology, 11, 106-108, 1982
	morning stiffness, joint pain, limitation of joint movement (graded 0 to 4), estimation of general condition by patient (worse, unchanged, improved) N=44 (88%) completed the study Treatment withdrawal; N=2 due to indomethacin side effects (dizziness, severe abdominal pain), N=1 intercurrent disorder Treatment discontinued; exacerbation of arthritis N=2 ketoprofen, N=1 indomethacin Results; Pain scores; ketoprofen; week 0 (71), week 9 (35), week 17 (29) indomethacin; week 0 (63), week 9 (37), week 17 (24) significant decrease in both groups after first period, NS difference between the drugs Patient assessment of response; improved (ketoprofen); 8weeks, N=11; 17weeks, N=12 improved (indomethacin); 8weeks, N=14; 17weeks, N=10 no change either treatment; 8weeks, N=12, 17 weeks, N=17 worse (ketoprofen); 8weeks, N=3; 17weeks, N=4 worse (indomethacin); 8weeks, N=4; 17weeks, N=1 Limitation in joint movement scores; ketoprofen; week 0 (64), week 9 (32), week 17 (27) indomethacin; week 0 (53), week 9 (29), week 17 (11) significant decrease in both groups after first period, NS difference between the drugs Adverse effects; diarrhoea, N=1 (ketoprofen) gastric pain, N=2 (ketoprofen), N=1 (indomethacin) stomach pain, N=1 (indomethacin) gastritis, N=1 (ketoprofen) headache, N=2 (indomethacin) vertigo, N=1 (indomethacin) dizziness, N=1 (indomethacin)

Bibliographic reference	Juvakoski,T., Lassus,A., A double-blind cross-over evaluation of ketoprofen and indomethacin in Reiter's disease, Scandinavian journal of rheumatology, 11, 106-108, 1982
Overall Risk of Bias	
Other information	No sample size calculation
Was allocation adequately concealed?	UNCLEAR
Was knowledge of the allocated intervention adequately prevented during the study?	UNCLEAR
Was the allocation sequence adequately generated?	UNCLEAR
Was the study apparently free of other problems that could put it at a high risk of bias?	NO
Were incomplete outcome data adequately addressed?	UNCLEAR
Are reports of the study free of suggestion of selective outcome reporting?	UNCLEAR

Table 97: Salvarani et al., 2001

Bibliographic reference	Salvarani,C., Macchioni,P., Olivieri,I., Marchesoni,A., Cutolo,M., Ferraccioli,G., Cantini,F., Salaffi,F., Padula,A., Lovino,C., Dovigo,L., Bordin,G., Davoli,C., Pasero,G., Alberighi,O.D., A comparison of cyclosporine, sulfasalazine, and symptomatic therapy in the treatment of psoriatic arthritis, Journal of Rheumatology, 28, 2274-2282, 2001
Country/ies where the study was carried out	Italy
Study type	RCT, open (randomisation via prearranged centralised randomisation plan, balanced for each centre)
Aim of the study	To evaluate the efficacy and safety of ciclosporin versus sulfasalazine and symptomatic therapy in the treatment of psoriatic arthritis with or without axial involvement

Bibliographic reference	**Salvarani,C., Macchioni,P., Olivieri,I., Marchesoni,A., Cutolo,M., Ferraccioli,G., Cantini,F., Salaffi,F., Padula,A., Lovino,C., Dovigo,L., Bordin,G., Davoli,C., Pasero,G., Alberighi,O.D., A comparison of cyclosporine, sulfasalazine, and symptomatic therapy in the treatment of psoriatic arthritis, Journal of Rheumatology, 28, 2274-2282, 2001**
Study dates	Not reported
Source of funding	Novastis Farma SpA, Origgio, Italy
Sample size	N=99
Inclusion criteria	psoriatic arthritis, 16 to 65years, with distal interphalangeal (DIP) joint involvement, asymmetrical peripheral arthritis, or systematic polyarthritis with or without axial involvement ≥3 swollen and tender joints, active disease ≥6 weeks duration that did not respond to NSAID those who had failed with antimalarials, gold salts, etretinate, methotrexate, or photochemotherapy could be included Steinbrocker functional and anatomical grade <IV and mild/moderate cutaneous psoriasis
Exclusion criteria	positive rheumatoid factor, psoriatic arthritis exclusively involving the DIP joints, previous treatment with ciclosporin or sulfasalazine, oral corticosteroids (daily dose >5mg prednisolone equivalent), intraarticular corticosteroid previous 3weeks, photochemotherapy previous 4weeks, retinoid therapy previous 3months uncontrolled arterial hypertension, neoplasms, active infections, thrombocytopenia, leukopenia, neutropenia, pregnancy, inadequate contraception, epilepsy, renal or hepatic dysfunction, chronic illness that would limit trial participation
Characteristics	Groups were similar for baseline demographic, clinical and lab characteristics, 37% male Age, mean (SD); ciclosporin 49 (12), sulfasalazine 46 (10), symptomatic therapy 48 (11) Disease duration, years; ciclosporin 1.9 (4.0), sulfasalazine 2.7 (4.3), symptomatic therapy 2.0 (3.1) Number with axial involvement; ciclosporin 8 (22%), sulfasalazine 4 (13%), symptomatic therapy 2.0 (3.1) Tender joint count; ciclosporin 14.8 (11.4), sulfasalazine 14.6 (9.0), symptomatic therapy 15.1 (8.0) Swollen joint count; ciclosporin 9.2 (6.1), sulfasalazine 9.6 (6.8), symptomatic therapy 8.4 (5.2)
Interventions	N=36 Ciclosporin, initial dose 3mg/kg/day - increase to maximum 5mg/kg/day allowed at weeks 4, 8 and 12 in the case of insufficient response (dose was halved if serum creatinine increased by >30% of baseline, blood ciclosporin increased by >200ng/ml at 2 consecutive visits, serum potassium increased above normal limits, liver enzymes or bilirubin were twice normal limits, SBP>160mmHg, or DBP >95mmHg at 2 consecutive visits) N=32 Sulfasalazine, enteric coated, 500mg x2/day for 1 week, increased by 500mg/day each week up to 2000mg given in 2 divided doses/day, could be increased to 3000mg/day in insufficient response

<table>
<tr><th>Bibliographic reference</th><th>Salvarani,C., Macchioni,P., Olivieri,I., Marchesoni,A., Cutolo,M., Ferraccioli,G., Cantini,F., Salaffi,F., Padula,A., Lovino,C., Dovigo,L., Bordin,G., Davoli,C., Pasero,G., Alberighi,O.D., A comparison of cyclosporine, sulfasalazine, and symptomatic therapy in the treatment of psoriatic arthritis, Journal of Rheumatology, 28, 2274-2282, 2001</th></tr>
<tr><td></td><td>(withdrawn if WBC count <3000/mm3, polymorphonuclear cell count <1500/mm3, platelet count <100,000/mm3, acute or progressive decrease in haemoglobin or haematocrit, proteinuria >500mg/24hr or significant rash)

Those in the ciclosporin or sulfasalazine groups were allowed to receive a stable dose of NSAID/corticosteroids/analgesics - those taking NSAIDs had to be taking a stable dose for 1month before study entry

N=31
Symptomatic therapy, NSAID/corticosteroids/analgesics alone - allowed full doses of NSAID, prednisolone equivalent ≤5mg/day</td></tr>
<tr><td>Missing data handling/loss to follow up</td><td>N=20 withdrew, 20%; N=6 ciclosporin, N=3 sulfasalazine, N=11 symptomatic therapy</td></tr>
<tr><td>Results</td><td>Assessment;
patient self-assessment measures; severity of pain via 100mm VAS, duration of morning stiffness, global disease assessment via graded 5-point scale, Arthritis Impact Measurement Scale (AIMS), spondylitis functional index
clinical; number of tender (57 sites) and swollen joints (54 sites), joint pain/tenderness score on a 4-point scale, number of fingers showing dactylitis (presence of tenderness and swelling of entire digits), mobility impairment related to axial involvement, physician global disease assessment on a 5-point scale
compliance; tablet/capsule count of trial medication
adverse events

Results;
Treatments;
Ciclosporin; dose increased in N=5/36, decreased in N=3, withdrawn in N=6
Sulfasalazine; dose increased in N=7/32, decreased in N=3, withdrawn in N=3

Clinical outcomes;
Change at 24weeks
<table>
<tr><td>Outcome</td><td>Ciclosporin, N=36</td><td>Sulfasalazine, N=32</td><td>Symptomatic therapy only, N=31</td></tr>
</table>
</td></tr>
</table>

Bibliographic reference	Salvarani,C., Macchioni,P., Olivieri,I., Marchesoni,A., Cutolo,M., Ferraccioli,G., Cantini,F., Salaffi,F., Padula,A., Lovino,C., Dovigo,L., Bordin,G., Davoli,C., Pasero,G., Alberighi,O.D., A comparison of cyclosporine, sulfasalazine, and symptomatic therapy in the treatment of psoriatic arthritis, Journal of Rheumatology, 28, 2274-2282, 2001

Pain score (VAS), mm (mean (SD))	-27.2 (31.9)	-17.3 (18.0)	-12.5 (22.8)
Swollen joint count (mean (SD))	-4.8 (7.5)	-4.4 (5.8)	-1.8 (5.5)
Tender joint count (mean (SD))	-7.6 (10.4)	-5.7 (6.9)	-3.5 (8.1)
Joint pain/tenderness score (mean (SD))	-6.9 (8.8)	-4.8 (6.7)	-1.5 (8.1)
CRP. mg/dl (mean (SD))	-1.6 (2.3)	-0.9 (3.4)	-0.1 (2.3)

Pain score (VAS); ciclosporin vs symptomatic therapy, p<0.05; ciclosporin vs sulfasalazine, p<0.05, sulfasalazine vs symptomatic therapy, NS difference

Swollen joint count; ciclosporin vs symptomatic therapy, p=0.05

Tender joint count; ciclosporin vs symptomatic therapy, p=0.01

Joint pain/tenderness score; ciclosporin vs symptomatic therapy, p=0.002

Not reported in detail;

patient global disease assessment decrease by at least 1 point; ciclosporin 61% vs symptomatic therapy 33%, p=0.04

physician global disease assessment decrease by at least 1 point; ciclosporin 66% vs symptomatic therapy 32%, p=0.01

physician global disease assessment decrease by at least 2 points; ciclosporin 24% vs symptomatic therapy 0%, p=0.005

physician global disease assessment decrease by at least 2 points; ciclosporin 24% vs sulfasalazine 3%, p=0.03

Response criteria;

Response criteria	ciclosporin, N=36, %	sulfasalazine, N=32, %	symptomatic therapy, N=31, %	ciclosporin vs sulfasalazine	ciclosporin vs symptomatic therapy	sulfasalazine vs symptomatic therapy
ACR20 (CRP)	44.4	37.5	32.3	NS	NS	NS
ACR50 (CRP)	27.7	12.5	3.2	NS	0.02	NS

<table>
<tr><td>Bibliographic reference</td><td>Salvarani,C., Macchioni,P., Olivieri,I., Marchesoni,A., Cutolo,M., Ferraccioli,G., Cantini,F., Salaffi,F., Padula,A., Lovino,C., Dovigo,L., Bordin,G., Davoli,C., Pasero,G., Alberighi,O.D., A comparison of cyclosporine, sulfasalazine, and symptomatic therapy in the treatment of psoriatic arthritis, Journal of Rheumatology, 28, 2274-2282, 2001</td></tr>
<tr><td></td><td>
<table>
<tr><td>ACR70 (CRP)</td><td>13.8</td><td>0.0</td><td>0.0</td><td>0.05</td><td>0.05</td><td>NS</td></tr>
</table>
ACR - American College of Rheumatology

Adverse events, over 24weeks;
<table>
<tr><td>Adverse event</td><td>ciclosporin, N=36</td><td>sulfasalazine, N=32</td><td>symptomatic therapy, N=31</td></tr>
<tr><td>Impaired renal function</td><td>10</td><td>1</td><td>1</td></tr>
<tr><td>GI intolerance</td><td>4</td><td>6</td><td>4</td></tr>
<tr><td>Neurological disturbances</td><td>7</td><td>3</td><td>3</td></tr>
<tr><td>Hypertrichosis</td><td>2</td><td>0</td><td>0</td></tr>
<tr><td>Hypertension</td><td>5</td><td>1</td><td>1</td></tr>
<tr><td>Gingival hyperplasia</td><td>2</td><td>0</td><td>0</td></tr>
<tr><td>Increased liver enzymes</td><td>1</td><td>4</td><td>1</td></tr>
<tr><td>Bacterial infections</td><td>1</td><td>0</td><td>0</td></tr>
<tr><td>Altered blood cell counts</td><td>1</td><td>0</td><td>0</td></tr>
<tr><td>Neoplasia</td><td>0</td><td>0</td><td>0</td></tr>
</table>
</td></tr>
<tr><td>Other information</td><td>ITT analysis
Within patient difference in pain score (VAS 0-100mm), primary efficacy variable for sample size calculation. For between group difference of mean pain score of ≥20±SD25, 5% significance level, power 80% - 20 patients per arm needed - increased to 99 to allow for expected drop out of 10%. (Drop-out was 20%)</td></tr>
<tr><td>Was allocation adequately concealed?</td><td>UNCLEAR</td></tr>
<tr><td>Was knowledge of the allocated intervention</td><td>UNCLEAR</td></tr>
</table>

Bibliographic reference	Salvarani,C., Macchioni,P., Olivieri,I., Marchesoni,A., Cutolo,M., Ferraccioli,G., Cantini,F., Salaffi,F., Padula,A., Lovino,C., Dovigo,L., Bordin,G., Davoli,C., Pasero,G., Alberighi,O.D., A comparison of cyclosporine, sulfasalazine, and symptomatic therapy in the treatment of psoriatic arthritis, Journal of Rheumatology, 28, 2274-2282, 2001
adequately prevented during the study?	
Was the allocation sequence adequately generated?	UNCLEAR
Was the study apparently free of other problems that could put it at a high risk of bias?	UNCLEAR
Were incomplete outcome data adequately addressed?	YES
Are reports of the study free of suggestion of selective outcome reporting?	YES

Table 98: Spadaro et al., 1995

Bibliographic reference	Spadaro,A., Riccieri,V., Sili-Scavalli,A., Sensi,F., Taccari,E., Zoppini,A., Comparison of cyclosporin A and methotrexate in the treatment of psoriatic arthritis: a one-year prospective study, Clinical & Experimental Rheumatology, 13, 589-593, 1995
Country/ies where the study was carried out	Italy
Study type	RCT, unblinded (randomised, no details reported)
Aim of the study	To compare low doses of ciclosporin A and methotrexate in the management of psoriatic arthritis
Study dates	Not reported
Source of funding	Not reported
Sample size	N=35
Inclusion criteria	Inclusion;

Bibliographic reference	Spadaro,A., Riccieri,V., Sili-Scavalli,A., Sensi,F., Taccari,E., Zoppini,A., Comparison of cyclosporin A and methotrexate in the treatment of psoriatic arthritis: a one-year prospective study, Clinical & Experimental Rheumatology, 13, 589-593, 1995
	• psoriatic arthritis with active arthritis affecting ≥5 peripheral joints (painful and/or swollen) • not adequately controlled with NSAIDs, NSAID dosage had to be stable for ≥1month prior to study entry • disease duration >6months, age 16 to 65years • had stopped taking slow acting anti-rheumatic drugs for ≥3months
Exclusion criteria	Exclusion; • previous treatment with ciclosporin A or methotrexate, systemic steroids within last 8weeks prior to study • abnormal renal or hepatic function, medical or surgical conditions that would compromise the absorption, metabolism or excretion of either drug • platelet count <150,000 cells/mm^3, WBC count <3500 cells/mm^3, malignancy, infections, alcohol abuse, SBP >160mmHg, DBP >95mmHg, pregnancy, breast feeding, not taking appropriate contraception
Characteristics	Mean age CsA (45, range 30-65), MTX (52, range 28-64), mean duration of arthritis CsA (9 years, range 1-32), MTX (8, range 1-21), 63% male Baseline assessment of the clinical and lab parameters did not show any significant difference between the groups
Interventions	N=17 ciclosporin A 3mg/kg/day, increments of 1mg/kg/day at monthly intervals to maximum dose of 5mg/kg/day - reduced by 1mg/kg/day if an increase of >30% of baseline creatinine, transaminases more than twice upper limit of normal or persistent hypertension N=18 methotrexate oral, 2.5mg every 12hours for 3 consecutive doses x1/week, increments of 2.5mg/weekly to maximum dose of 15mg/weekly - temporarily discontinued if WBC decreased to <3500mm^3, PMN to 1200mm^3, platelets to 150,000mm^3, liver enzymes to more than twice
Missing data handling/loss to follow up	Withdrawals; • Ciclosporin A (N=7, 41%) - N=3 uncontrolled hypertension, N=1 abnormal renal function, N=1 GI discomfort, N=2 unsatisfactory response • Methotrexate (N=4, 22.2%) - N=2 GI symptoms, N=1 liver enzymes, N=1 intercurrent infections • At 6months 17.6% ciclosporin A, 22.2% methotrexate • After 1year therapy stopped 41.2% ciclosporin A, 27.8% methotrexate
Results	Assessment;

Bibliographic reference	Spadaro,A., Riccieri,V., Sili-Scavalli,A., Sensi,F., Taccari,E., Zoppini,A., Comparison of cyclosporin A and methotrexate in the treatment of psoriatic arthritis: a one-year prospective study, Clinical & Experimental Rheumatology, 13, 589-593, 1995

- number of painful joints, number of swollen joints, Ritchie index, duration of morning stiffness, grip strength, patient's assessment of PsA activity (100mm analogue scale), physician's assessment of PsA (100mm analogue scale), psoriasis area and severity index (PASI)

Results;

- changes from baseline for both interventions at 6 and 12months reported in this paper, not included in this evidence table

Comparison of clinical and lab values at 12months:

Outcome	Ciclosporin A	Methotrexate	p
painful joints (number)	4.6±1.2	6.6±0.9	NS
swollen joints (number)	2.6±0.9	3.5±0.5	NS
Ritchie index	14.0±4.2	11.1±1.7	NS
Morning stiffness (min)	1.95±5.8	55.4±14.7	NS
Grip strength, right (mmHg)	-14±5	-51±15	NS
Grip strength, left (mmHg)	-9±5	-17±23	NS
Physician's assessment (mm)	16.0±4.9	30.8±4.0	NS
Patient's assessment (mm)	30.0±5.6	22.7±9.8	NS
PASI	7.6±2.0	2.6±0.6	NS
ESR (mm/hr)	9.3±6.1	19.5±6.3	NS
CRP (mg/l)	17.5±7.1	13.3±4.1	NS
Creatinine (mg/dl)	-0.14±0.06	-0.01±0.1	NS
AST (U/l)	1.0±3.4	-10.9±4.4	0.05
ALT (U/l)	3.8±4.4	-29.2±19.3	0.05

other lab values reported not extracted in this evidence table (no differences between the groups)

Bibliographic reference	Spadaro,A., Riccieri,V., Sili-Scavalli,A., Sensi,F., Taccari,E., Zoppini,A., Comparison of cyclosporin A and methotrexate in the treatment of psoriatic arthritis: a one-year prospective study, Clinical & Experimental Rheumatology, 13, 589-593, 1995
Other information	No sample size consideration
Was allocation adequately concealed?	UNCLEAR
Was knowledge of the allocated intervention adequately prevented during the study?	UNCLEAR
Was the allocation sequence adequately generated?	UNCLEAR
Was the study apparently free of other problems that could put it at a high risk of bias?	NO
Were incomplete outcome data adequately addressed?	UNCLEAR
Are reports of the study free of suggestion of selective outcome reporting?	UNCLEAR

E.2.3 Switching or augmenting pharmacological interventions for spondyloarthritis

Review Question 23

- When a first-line treatment has failed, what is the effectiveness of the following for managing spondyloarthritis:
  - switching to a different pharmacological intervention?
  - augmenting with a second pharmacological intervention?

Table 99: Fraser et al., 2005

Bibliographic reference	Fraser,A.D.,vanKuijk,A.W.R.,Westhovens,R.,Karim,Z.,Wakefiled,R.,Gerards,A.H.,Landewe,R.,Steinfeld,S.D.,Emery,P.,Dijkmans,B.A.C.,Veale,D.J., A randomised, double blind, placebo controlled, multicentre trial of combination therapy with methotrexate plus ciclosporin in patients with active psoriatic arthritis, Ann Rheum Dis., 64,859-864, 2005
Country/ies where the study was carried out	5 centres, 3 European countries including the UK
Study type	Double blind, placebo controlled RCT (no randomisation details)
Aim of the study	To assess combination therapy of methotrexate plus ciclosporin for the treatment of those with active psoriatic arthritis
Study dates	Recruited from 5 clinical centres, dates not reported
Source of funding	Novartis Pharma AG
Sample size	N=72
Inclusion criteria	Inclusion; • between 18 and 70years • minimum disease duration of 24weeks, evidence of skin and/or nail psoriasis, seronegative for rheumatoid factor • active psoriatic arthritis (≥3 tender joints), incomplete response to 15mg of methotrexate weekly (or lower if unable to tolerate a higher dose) Could be taking oral prednisolone (≤10mg/day) or NSAIDs, or both, dose had to be stable for 1month before baseline
Exclusion criteria	Exclusion: • abnormal; hepatic or renal function, blood dyscrasia, severe cardiac or respiratory disease

Bibliographic reference	Fraser,A.D.,vanKuijk,A.W.R.,Westhovens,R.,Karim,Z.,Wakefiled,R.,Gerards,A.H.,Landewe,R.,Steinfeld,S.D.,Emery,P.,Dijkmans,B.A.C.,Veale,D.J., A randomised, double blind, placebo controlled, multicentre trial of combination therapy with methotrexate plus ciclosporin in patients with active psoriatic arthritis, Ann Rheum Dis., 64,859-864, 2005
Characteristics	Baseline; - female N=19, 56% (placebo), N=27, 71% (ciclosporin) - age, mean (SD), 47.1 (10.8) placebo, 46.8 (11.5) ciclosporin - disease duration in months, mean (SD), 42.4 (41.9) placebo, 40.8 (33.0) ciclosporin - concomitant NSAIDs, N=26 (76%) placebo, N=30 (79%) ciclosporin - concomitant prednisolone, N=0 placebo, N=2 (5%) ciclosporin - tender joint count, mean (SD), mean (SD), 28.3 (19.2) placebo, 22.6 (15.9) ciclosporin - swollen joint count, mean (SD), mean (SD), 11.7 (8.6) placebo, 11.7 (9.7) ciclosporin
Interventions	N=38 Ciclosporin (initial dose 2.5mg/kg/day, increased by 0.5mg/kg/day at weeks 4, 8, 12 to a maximum dose of 4mg/kg/day), in addition to methotrexate N=34 Placebo, in addition to methotrexate If serum creatinine increased during treatment by 30% ciclosporin reduced via titration table Methotrexate reduced by 50% increase in aspartate aminotransferase or alanine aminotransferase Mean dose of methotrexate, ciclosporin group 16.2mg/week (baseline), 15.9mg/week (final assessment) Mean dose of methotrexate, placebo group 15.8mg/week (baseline), 15.7mg/week (final assessment)
Results	Primary endpoint; change from baseline to final visit (12months) in joint tenderness, via Ritchie index Secondary endpoint; tender joint count, swollen joint count, ESR and/or CRP, change in psoriasis severity, change in pain, change in patient assessment, QoL, The measures of arthritis disease activity; • tender joint count • swollen joint count • psoriasis area and severity index (PASI) • pain, 100mm VAS • physician's global assessment of disease activity (100mm VAS) • patient's global assessment of disease activity (100mm VAS) • quality of life (HAQ) • change in Larsen and Dale damage score (x-ray)

Bibliographic reference	Fraser,A.D.,vanKuijk,A.W.R.,Westhovens,R.,Karim,Z.,Wakefiled,R.,Gerards,A.H.,Landewe,R.,Steinfeld,S.D.,Emery,P.,Dijkmans,B.A.C.,Veale,D.J., A randomised, double blind, placebo controlled, multicentre trial of combination therapy with methotrexate plus ciclosporin in patients with active psoriatic arthritis, Ann Rheum Dis., 64,859-864, 2005

- synovitis (high resolution ultrasounds, 1 site only)

Results;
Outcomes,

Outcome	Placebo, baseline	Placebo, 48weeks	Ciclosporin, baseline	Ciclo 48we
Tender joint count, mean (SD)	28.3 (19.2)	19.7 (17.9)*	22.6 (15.9)	15.3
Swollen joint count, mean (SD)	11.7 (8.6)	7.9 (5)	11.7 (9.7)	6.7 (6
CRP (mg/l), mean (SD)	15.4 (13.3)	12.6 (9)	17.4 (14.5)	12.7
PASI, mean (SD)	2.2 (2.7)	1.9 (2.8)	2 (2.3)	0.8 (1
Patient's global pain, mean (SD)	5.1 (2.3)	4.9 (2.9)	4.7 (2.2)	3.9 (2
Patient's global assessment of disease activity, mean (SD)	5.4 (2.2)	4.9 (2.80)	5.1 (2.30)	4.1 (2
HAQ score, mean (SD)	1.1 (0.45)	0.9 (0.52)	1.0 (0.62)	0.9 (0

*p<0.001, difference from baseline
#p<0.05, difference from baseline
~p<0.05 between group differences

Adverse effects;

Adverse effect, number (%)	Placebo, N=34	Ciclospor
Nausea	6 (18%)	15 (39%)
Headache	2 (6%)	9 (24%)
Burning sensation	0	5 (13%)

Bibliographic reference	Fraser,A.D.,vanKuijk,A.W.R.,Westhovens,R.,Karim,Z.,Wakefiled,R.,Gerards,A.H.,Landewe,R.,Steinfeld,S.D.,Emery,P.,Dijkmans,B.A.C.,Veale,D.J., A randomised, double blind, placebo controlled, multicentre trial of combination therapy with methotrexate plus ciclosporin in patients with active psoriatic arthritis, Ann Rheum Dis., 64,859-864, 2005

	Paraesthesia	0	4 (11%)
	Muscle cramps	0	4 (11%)
	Hypertrichosis	0	3 (8%)
	Serious adverse event	1 (3%)	4 (11%)

Other information	Response rates of 25% treatment and 5% placebo used for sample size calculation, sample of 112 calculated (N=72 in the study) to have 80% power to detect a difference at 5% significance and 20% drop-out rate ITT analysis
Was allocation adequately concealed?	UNCLEAR
Was knowledge of the allocated intervention adequately prevented during the study?	UNCLEAR
Was the allocation sequence adequately generated?	UNCLEAR
Was the study apparently free of other problems that could put it at a high risk of bias?	NO
Were incomplete outcome data adequately addressed?	UNCLEAR
Are reports of the study free of suggestion of selective outcome reporting?	UNCLEAR

Table 100: Coates et al, 2015

Bibliographic reference	Coates,L.C.,Moverley,A.R.,McParland,L.,Brown,S.,Navarro-Coy,N.,O'Dwyer,J.L.,Meads,D.M.,Emery,P.,Conaghan,P.G.,Helliwell,P.S., Effect of tight control on inflammation in early psoriatic arthritis (TICOPA): a UK multicentre, open-label, randomised controlled trial, The Lancet., S0140-6736, 2015 (protocol paper; Coates,L.C.,Navarroro-Coy,N., Brown,S.R., Brown,S., McParland,L.,Collier,H.,Skinner,E.,Law,J., Moverley,A.R.,Pavitt,S.,Hulme,C.,Emery,P. Conaghan,P.G.,Helliwell,P.S., The TICOPA protocol (TIght COntrol of Psoriatic Arthritis): a randomised controlled trial to compare intensive management versus standard care in early psoriatic arthritis, BMC Musculoskeletal Disorders, 14,101,2013)
Country/ies where the study was carried out	UK
Study type	Open-label multicentre RCT (randomisation via automated telephone system, ensured treatment groups were balanced for randomising centre and pattern of arthritis, oligoarticular vs polyarticular. Follow-up assessments undertaken by research nurse masked to the allocated treatment group)
Aim of the study	To study the effect of tight control of early psoriatic arthritis using a treat-to-target approach
Study dates	May 2008 to March 2012
Source of funding	Arthritis Research UK, Pfizer
Sample size	N=206
Inclusion criteria	Inclusion; ≥18years, recent onset (<24months symptom duration), psoriatic arthritis diagnosed by consultant rheumatologist No previous treatment with DMARDs
Exclusion criteria	Exclusion: previous DMARD treatment for articular disease with (including but not limited to) methotrexate, sulfasalazine, leflunomide
Characteristics	Baseline; male N=53, 53% (tight control), N=55, 52% (standard care) age, median (IQR), 46 (38 to 55) tight control, 45 (36 to 51) standard care disease duration, median (IQR), 0.9 (0.5 to 2.1) tight control, 0.7 (0.4 to 1.8) standard care n
Interventions	N=101 Tight control; seen by study physician every 4weeks and treated according to treatment protocol minimal disease activity (MDA) criteria assessed at each visit, considered to have achieved MDA with 5/7 of the criteria DMARDs increased to maximum dose or highest tolerated dose if they had not achieved MDA Treatment protocol;

Bibliographic reference	**Coates,L.C.,Moverley,A.R.,McParland,L.,Brown,S.,Navarro-Coy,N.,O'Dwyer,J.L.,Meads,D.M.,Emery,P.,Conaghan,P.G.,Helliwell,P.S., Effect of tight control on inflammation in early psoriatic arthritis (TICOPA): a UK multicentre, open-label, randomised controlled trial, The Lancet., S0140-6736, 2015** **(protocol paper; Coates,L.C.,Navarroro-Coy,N., Brown,S.R., Brown,S., McParland,L.,Collier,H.,Skinner,E.,Law,J., Moverley,A.R.,Pavitt,S.,Hulme,C.,Emery,P. Conaghan,P.G.,Helliwell,P.S., The TICOPA protocol (TIght COntrol of Psoriatic Arthritis): a randomised controlled trial to compare intensive management versus standard care in early psoriatic arthritis, BMC Musculoskeletal Disorders, 14,101,2013)**
	initially methotrexate (if not MDA), then methotrexate and sulfasalazine (if not MDA and <3 tender/swollen joints) then methotrexate and ciclosporin A or leflunomide (if not MDA and ≥3 tender/swollen joints) then first-line anti-TNFα (if not MDA) then second-line anti-TNFα MDA criteria (minimal disease activity criteria developed as a potential target for therapy); Tender joint count ≤1;swollen joint count ≤1, PASI ≤1, patient pain VAS ≤15mm, patient global disease activity VAS ≤20mm, HAQ score ≤0.5; ≤1 tender entheseal points N=105 Standard care Treated in a general rheumatology clinic by consultant rheumatologist Generally reviewed every 12weeks, more often if needed No formal measures of disease activity used in clinical decision-making All participants were required to meet the NICE criteria for use of biologics in psoriatic arthritis before receiving them
Missing data handling/loss to follow up	48weeks of treatment, safety follow-up to 52weeks N=33/206 (16%) had missing data needed for the derivation of ACR20 (N=12 in the tight control group, N=12 in the standard control group)
Results	Primary endpoint; proportion of each treatment group achieving the ACR20 response at 48weeks Secondary endpoint; ACR50 response, ACR70 response, PASI 75%, modified Sharp-van der Heijde x-ray score, at 48weeks Additional physician-assessed secondary outcomes Additional patient-assessed secondary outcomes

Bibliographic reference	**Coates,L.C.,Moverley,A.R.,McParland,L.,Brown,S.,Navarro-Coy,N.,O'Dwyer,J.L.,Meads,D.M.,Emery,P.,Conaghan,P.G.,Helliwell,P.S., Effect of tight control on inflammation in early psoriatic arthritis (TICOPA): a UK multicentre, open-label, randomised controlled trial, The Lancet., S0140-6736, 2015** **(protocol paper; Coates,L.C.,Navarroro-Coy,N., Brown,S.R., Brown,S., McParland,L.,Collier,H.,Skinner,E.,Law,J., Moverley,A.R.,Pavitt,S.,Hulme,C.,Emery,P. Conaghan,P.G.,Helliwell,P.S., The TICOPA protocol (TIght COntrol of Psoriatic Arthritis): a randomised controlled trial to compare intensive management versus standard care in early psoriatic arthritis, BMC Musculoskeletal Disorders, 14,101,2013)**

Treatment used

Treatment	Tight control, N=101	Standard control, N=105
Methotrexate monotherapy, throughout the trial	27 (27%)	63 (60%)
Combination DMARDs, throughout the trial	74 (73%)	30 (29%)
Biological therapies, throughout the trial	39 (39%)	7 (7%)
Methotrexate dose of ≥15mg by week 12	101 (100%)	70 (67%)
Methotrexate dose of ≥20mg by week 12	91 (90%)	31 (30%)
Methotrexate dose of ≥25mg by week 12	83 (82%)	8 (8%)
Methotrexate monotherapy at week 12	57 (56%)	72 (69%)
Moving unto combination DMARDs at week 12	37 (37%)	4 (4%)
Methotrexate monotherapy by week 48	26 (26%)	51 (49%)
Combination DMARDs by week 48	24 (24%)	11 (11%)
Biological therapies by week 48	37 (37%)	7 (7%)

Escalation;

Week 12, 83 (83%) reached methotrexate 25mg/week

Week 12, 24 (24%) reached MDA, of the 75 who hadn't treatment was escalated in 53 (71%)

Week 12 to week 48, 73 (72%) reached MDA at least once, 57 (56%) reached MDA on at least 2 consecutive visits

On average participants reached MDA at 41% of assessments attended

Where MDA not met treatment escalated 37% of the time

Reasons for non-escalation; on current DMARD for <12weeks, concurrent disease, on maximum therapy already, recent missed treatment, unable to tolerate maximum therapy

Results;

Outcomes,

Bibliographic reference	**Coates,L.C.,Moverley,A.R.,McParland,L.,Brown,S.,Navarro-Coy,N.,O'Dwyer,J.L.,Meads,D.M.,Emery,P.,Conaghan,P.G.,Helliwell,P.S., Effect of tight control on inflammation in early psoriatic arthritis (TICOPA): a UK multicentre, open-label, randomised controlled trial, The Lancet., S0140-6736, 2015** **(protocol paper; Coates,L.C.,Navarroro-Coy,N., Brown,S.R., Brown,S., McParland,L.,Collier,H.,Skinner,E.,Law,J., Moverley,A.R.,Pavitt,S.,Hulme,C.,Emery,P. Conaghan,P.G.,Helliwell,P.S., The TICOPA protocol (TIght COntrol of Psoriatic Arthritis): a randomised controlled trial to compare intensive management versus standard care in early psoriatic arthritis, BMC Musculoskeletal Disorders, 14,101,2013)**

Multivariable logistic regression for the effect of treatment on the primary endpoint, ITT, N=206

	OR (95%CI)	P value
Tight control vs standard care	1.91 (1.03 to 3.55)	0.0392
Oligoarthritis vs polyarthritis	0.62 (0.31 to 1.24)	0.1733

Secondary endpoint, ITT, N=206, 48weeks
ACR50; OR 2.36 (95%CI, 1.25 to 4.47), p=0.0081
ACR70; OR 2.64 (95%CI, 1.32 to 5.26), p=0.0058
PASI 75; OR 2.92 (95%CI, 1.51to 5.65), p=0.0015

Univariable analysis for the proportion of evaluable patients (N=173) achieving a response at 48weeks for key secondary endpoints

	Tight control	Standard care	% difference in proportions (95%CI)	P value
ACR20	55/89 (62%)	37/84 (44%)	17.8% (3.1 to 32.4)	0.0194
ACR50	44/86 (51%)	21/84 (25%)	26.2% (12.1 to 40.2)	0.0004
ACR70	33/87 (38%)	15/86 (17%)	20.5% (7.5 to 33.5)	0.0026
PASI 75	44/75 (59%)	27/81 (33%)	25.3% (10.2 to 40.5)	0.0015

Measures of disease activity, proportion of evaluable patients, 48weeks

Measure	Tight control	Standard control
Total joint count, median improvement (IQR)	N=92 4.0 (1.0 to 11.0)	N=92 3.0 (-1.0 to 9.5)
Swollen joint count, median improvement (IQR)	N=92 4.0 (2.0 to 7.5)	N=92 2.5 (1.0 to 6.0)

Bibliographic reference	**Coates,L.C.,Moverley,A.R.,McParland,L.,Brown,S.,Navarro-Coy,N.,O'Dwyer,J.L.,Meads,D.M.,Emery,P.,Conaghan,P.G.,Helliwell,P.S., Effect of tight control on inflammation in early psoriatic arthritis (TICOPA): a UK multicentre, open-label, randomised controlled trial, The Lancet., S0140-6736, 2015** **(protocol paper; Coates,L.C.,Navarroro-Coy,N., Brown,S.R., Brown,S., McParland,L.,Collier,H.,Skinner,E.,Law,J., Moverley,A.R.,Pavitt,S.,Hulme,C.,Emery,P. Conaghan,P.G.,Helliwell,P.S., The TICOPA protocol (TIght COntrol of Psoriatic Arthritis): a randomised controlled trial to compare intensive management versus standard care in early psoriatic arthritis, BMC Musculoskeletal Disorders, 14,101,2013)**

Patient reported outcomes, proportion of evaluable patients, 48weeks (RR calculated by analyst)

Measure	Tight control	Standard control	RR (95%CI)
BASDAI MCID, n(%)	57/81 (70.4)	44/79 (55.7)	1.26 (1.00 to 1.61)
BASFI MCID, n(%)	49/81 (60.5)	32/80 (40.0)	1.51 (1.10 to 2.09)
HAQ MCID, n(%)	53/91 (58.2)	37/90 (41.1)	1.42 (1.05 to 1.92)
ASAS20, n(%)	49/80 (61.3)	33/79 (41.8)	1.47 (1.07 to 2.01)
ASAS40, n(%)	37/80 (46.3)	25/81 (30.9)	1.50 (1.00 to 2.24)

Serious adverse events;
Tight control N=25 SAEs in N=14 patients (14%)
Standard care N=8 SAEs in N=6 patients (6%)

Considered related to drug treatment N=10 SAEs
N=8 tight control; N=2 cellulitis, N=2 pneumonia, N=1 musculoskeletal chest pain, N=1 raised LFTs, N=1 collapse and pancytopenia, N=1 anaphylaxis
N=2 standard care; N=1 migraine, N=1 septic arthritis

Adverse events;
Reported in N=179 (87%) of patients
Tight control, N=98 (97%), 68% considered related to drug treatment
Standard care, N=81 (77%), 73% considered related to drug treatment

Commonly reported adverse events;

AE	Tight control, no. of patients (%)	Standard care, no. of patients (%)	Total
Abdominal/GI upset	31 (30.7%)	12 (11.4%)	43 (20.9%)

Bibliographic reference	**Coates,L.C.,Moverley,A.R.,McParland,L.,Brown,S.,Navarro-Coy,N.,O'Dwyer,J.L.,Meads,D.M.,Emery,P.,Conaghan,P.G.,Helliwell,P.S., Effect of tight control on inflammation in early psoriatic arthritis (TICOPA): a UK multicentre, open-label, randomised controlled trial, The Lancet., S0140-6736, 2015** **(protocol paper; Coates,L.C.,Navarroro-Coy,N., Brown,S.R., Brown,S., McParland,L.,Collier,H.,Skinner,E.,Law,J., Moverley,A.R.,Pavitt,S.,Hulme,C.,Emery,P. Conaghan,P.G.,Helliwell,P.S., The TICOPA protocol (TIght COntrol of Psoriatic Arthritis): a randomised controlled trial to compare intensive management versus standard care in early psoriatic arthritis, BMC Musculoskeletal Disorders, 14,101,2013)**

Fatigue (asthenia, lethargy, malaise)	22 (21.8%)	8 (7.6%)	30 (14.6%)
Headache/migraine	20 (19.8%)	7 (6.7%)	27 (13.1%)
Infection (common cold)	34 (33.7%)	13 (12.4%)	47 (22.8%)
Liver enzyme abnormalities	23 (22.8%)	28 (26.7%)	51 (24.8%)
Musculoskeletal pain	22 (21.8%)	6 (5.7%)	28 (13.6%)
Nausea	36 (35.6%)	27 (25.7%)	63 (30.6%)

Other information	Sample size of 93 per group would provide 80% power to detect a 20% difference in the primary outcome, under the assumption of a 50% response rate in the standard care group, 5% significance level To allow for 10% drop-out 206 recruited ITT analysis of primary endpoint
Was allocation adequately concealed?	N/A
Was knowledge of the allocated intervention adequately prevented during the study?	N/A
Was the allocation sequence adequately generated?	Yes
Was the study apparently free of other problems that could put it at a high risk of bias?	No
Were incomplete outcome data adequately addressed?	Yes
Are reports of the study free of suggestion of selective outcome reporting?	Yes

E.2.4 Biological DMARDs for spondyloarthritis

Review questions 24, 25, and 26

- What is the effectiveness of systemic biological disease-modifying anti-rheumatic drugs for managing symptoms of enteropathic arthritis?
- What is the effectiveness of systemic biological disease-modifying anti-rheumatic drugs for managing symptoms of reactive arthritis?
- What is the effectiveness of systemic biological disease-modifying anti-rheumatic drugs for managing symptoms of undifferentiated spondyloarthritis, excluding non-radiographic ankylosing spondylitis?

Table 101: Paramarta et al., 2013

Bibliographic reference	**Paramarta, Jacqueline E., De Rycke,Leen, Heijda,Tanja F., Ambarus,Carmen A., Vos,Koen, Dinant,Huib J., Tak,Paul P., Baeten,Dominique L., Efficacy and safety of adalimumab for the treatment of peripheral arthritis in spondyloarthritis patients without ankylosing spondylitis or psoriatic arthritis, Annals of the rheumatic diseases, 72, 1793-1799, 2013**
Country/ies where the study was carried out	Netherlands
Study type	Randomised double blind clinical trial
Aim of the study	To assess the efficacy and safety of adalimumab in patients with peripheral spondyloarthritis not fulfilling the criteria for ankylosing spondylitis (AS) or psoriatic arthritis (PsA).
Study dates	Not reported.
Source of funding	None. Medication for study was supplied by Abbott.
Sample size	40 (20 in intervention group, 20 in control group)
Diagnostic criteria	Participants were required to fulfil either the ESSG or Amor criteria for spondyloarthritis for at least 3 months, and not fulfil the criteria for AS or PsA. 31 fulfilled both sets of criteria, 6 only fulfilled the ESSG criteria, and 3 only the Amor criteria.
Inclusion criteria	Aged between 18-70 years old Have an active arthritis (at least one swollen and tender joint) despite treatment with NSAIDs. Female participants: a negative pregnancy test and adequate contraception during the study and for 150 days thereafter.
Exclusion criteria	Serious infections in previous 4 weeks History of malignancy in the past 10 years Significant history of other severe diseases or uncontrolled concomitant disease Active tuberculosis People with latent tuberculosis had to receive at least 3 months of isoniazide before enrolment.

<table>
<tr><th>Bibliographic reference</th><td>Paramarta, Jacqueline E., De Rycke,Leen, Heijda,Tanja F., Ambarus,Carmen A., Vos,Koen, Dinant,Huib J., Tak,Paul P., Baeten,Dominique L., Efficacy and safety of adalimumab for the treatment of peripheral arthritis in spondyloarthritis patients without ankylosing spondylitis or psoriatic arthritis, Annals of the rheumatic diseases, 72, 1793-1799, 2013</td></tr>
<tr><td>Characteristics</td><td>
<table>
<tr><td>Characteristic</td><td>Adalimumab (n=20)</td><td>Placebo (n=20)</td></tr>
<tr><td>age, years (mean (sd))</td><td>41.5 (12.8)</td><td>44.4 (11.1)</td></tr>
<tr><td>disease duration, years (mean (sd))</td><td>7.9 (9.3)</td><td>6.7 (6.2)</td></tr>
<tr><td>n men/women</td><td>9/11</td><td>12/8</td></tr>
<tr><td>HLA-B27 positive (n(%))</td><td>11 (55)</td><td>17 (85)</td></tr>
<tr><td>SpA subtype (n(%))
uSpA
ReA
IBD-SpA</td><td>
15 (75)
4 (20)
1 (5)</td><td>
17 (85)
0 (0)
3 (15)</td></tr>
<tr><td>Concomitant drugs* (n(%))
NSAIDs
corticosteroids
methotrexate
sulphasalazine</td><td>
13 (65)
0 (0)
5 (25)
7 (35)</td><td>
14 (70)
2 (10)
6 (30)
4 (20)</td></tr>
<tr><td>Previous anti-TNF treatment** (n(%))</td><td>1 (5)</td><td>2 (10)</td></tr>
</table>
*Participants allowed to continue with existing NSAIDs, corticosteroids (≤10 mg/day prednisone or equivalent), methotrexate or sulphasalazine as long as dosage was stable for >=4 weeks before baseline and during study. Where methotrexate or sulphasalazine were taken, these had to be initiated at least 3 months before inclusion. Intra-articular corticosteroids and other DMARDs were not permitted and had to cease >=4 weeks prior to baseline.
**Prior use of anti-TNF therapy/investigational drugs was allowed if stopped >2 months before baseline</td></tr>
<tr><td>Details</td><td>Recruitment and randomisation:
Single centre study in which 40 participants were randomised on a 1:1 basis to receive either adalimumab or placebo in a double blind trial with an open label extension of adalimumab. The primary endpoint was improvement in patient global assessment at week 12. Participants provided written consent and initiated treatment within 3 weeks where eligible to do so.
Clinical evaluation:
Participants were evaluated at 0, 6, 12, 18 and 24 weeks. The following assessments were carried out at each time point:</td></tr>
</table>

Bibliographic reference	**Paramarta, Jacqueline E., De Rycke,Leen, Heijda,Tanja F., Ambarus,Carmen A., Vos,Koen, Dinant,Huib J., Tak,Paul P., Baeten,Dominique L., Efficacy and safety of adalimumab for the treatment of peripheral arthritis in spondyloarthritis patients without ankylosing spondylitis or psoriatic arthritis, Annals of the rheumatic diseases, 72, 1793-1799, 2013**
	• Patient's and physician's global assessment of disease activity (each a 100 mm visual analogue scale) • 68 tender joint count • 66 swollen joint count • BASDAI • ASDAS (Ankylosing Spondylitis Disease Activity Score) • Modified Schober index • Erythrocyte sedimentation rate • C-reactive protein • Self-reporting of side effects • Routine laboratory testing for safety evaluation • Physical examination for safety evaluation • In addition the following were measured at weeks 12 and 24 to assess improvement • ASDAS improvement criteria • BASDAI150 response • The following were also measured, but it is unclear at which time points: • Health assessment questionnaire Disability Index (HAQ-DI) • Health Utility Index Mark 3 (HUI-3) Statistical analysis: A sample size calculation was carried out using information from previous trials of anti-TNF therapies (including studies on peripheral SpA). It was estimated that the change in patient global assessment VAS at week 12 would be -48(±24)mm in the intervention group and -21(±32)mm in the placebo group. Power was set at 80% and α level at 0.05. Results were presented at mean ± standard deviation (SD) or SEM, after checking for normal distribution. ANCOVA was used to compare change from baseline to week 12 between treatment groups. Intra-group analysis (changes from baseline were also assessed with paired t-tests. Comparison of the characteristics of the two treatment groups was done by t test for continuous variables and $\chi 2$ test for categorical variables.
Interventions	Study drug was provided in pre-filled syringes containing Adalimumab 40g or an equivalent placebo. Phase 1: Adalimumab or placebo subcutaneously every other week for 12 weeks. Phase 2: Open label extension with adalimumab for an additional 12 weeks.

Bibliographic reference	**Paramarta, Jacqueline E., De Rycke,Leen, Heijda,Tanja F., Ambarus,Carmen A., Vos,Koen, Dinant,Huib J., Tak,Paul P., Baeten,Dominique L., Efficacy and safety of adalimumab for the treatment of peripheral arthritis in spondyloarthritis patients without ankylosing spondylitis or psoriatic arthritis, Annals of the rheumatic diseases, 72, 1793-1799, 2013**
Missing data handling/loss to follow up	In the initial RCT phase, one patient dropped out of each group (adalimumab group: death due to suicide; placebo group: arthroscopy-related septic arthritis). The mean changes in disease activity from week 0 to week 12 were calculated on the 38 remaining people.
Results	Phase 1: change in mean values for Adalimumab vs Control Weeks 0-12

	Adalimumab			Placebo		
	Week 0 (n=20)	Week 12 (n=19)	Change* (mean(SD))	Week 0 (n=20)	Week 12 (n=19)	Change* (mean(SD))
Pain	Back pain reported in graphical form only, assessed by BASDAI Q2					
Swollen joint count (0-66 joints)	4.3 (4.2)	1.9 (2.2)	-2.5 (4.0)	2.5 (1.9)	2.2 (1.1)	-0.4(1.8)
Tender joint count (0-68 joints)	9.4 (8.2)	7.9 (14.0)	-1.8 (9.2)	10.6 (5.9)	12.6 (8.8)	1.7(6.5)
BASDAI	5.5 (2.3)	3.8 (3.2)	-1.8 (2.6)	6.0 (1.4)	5.7 (1.7)	-0.3(1.5)
CRP (mg/l)	7.8 (13.3)	2.5 (2.2)	-5.7 (12.4)	13.5 (26.4)	12.8 (24.7)	4.0(22.9)
ESR (mm/h)	11.6 (13.5)	6.1 (7.2)	-6.0 (12.5)	15.7 (23.1)	13.1 (13.7)	1.7(9.3)
Quality of life: HAQ-DI	0.8 (0.6)	0.6 (0.7)	** -0.2 (0.7)	1.1 (0.5)	1.0 (0.4)	** -0.1 (0.7)
Quality of life: HUI-3	0.48 (0.35)	0.60 (0.40)	** 0.12 (0.4)	0.38 (0.28)	0.46 (0.34)	** 0.08 (0.4)
Adverse events	See below					
Imaging changes	Not reported					

*Values as reported by study authors in separate table, based on n participants remaining at week 12

**Manually calculated by analyst as (mean value at week 24)-(mean value at week 12), with SDs imputed (selected as the largest SD from either before or after values for either treatment group for that variable)

Authors also reported:

- Patient and physician global health of disease activity
- ASDAS score

These are not reported here as they are outside the scope of the pre-specified outcome measures.

Bibliographic reference	**Paramarta, Jacqueline E., De Rycke,Leen, Heijda,Tanja F., Ambarus,Carmen A., Vos,Koen, Dinant,Huib J., Tak,Paul P., Baeten,Dominique L., Efficacy and safety of adalimumab for the treatment of peripheral arthritis in spondyloarthritis patients without ankylosing spondylitis or psoriatic arthritis, Annals of the rheumatic diseases, 72, 1793-1799, 2013**

Secondary phase: change in mean values for Adalimumab vs Control

Weeks 12-24

**Manually calculated by analyst (KMc) as (mean value at week 24)-(mean value at week 12), with SDs imputed (selected as the largest SD from either before or after values for either treatment group for that variable)

	Adalimumab continuation			Adalimumab initiation following placebo		
	Week 12 (n=19)	Week 24 (n=19)	Change**(mean(SD))	Week 12 (n=19)	Week 24 (n=17)	Change**(mean(SD))
Pain	Back pain reported in graphical form only, assessed by BASDAI Q2					
Swollen joint count (0-66 joints)	1.9 (2.2)	0.6 (1.0)	-1.3 (2.2)	2.2 (1.1)	1.3 (0.8)	-0.9 (2.2)
Tender joint count (0-68 joints)	7.9 (14.0)	4.6 (6.9)	-3.3 (14.0)	12.6 (8.8)	7.8 (7.0)	-4.8 (14.0)
BASDAI	3.8 (3.2)	2.5 (2.1)	-1.3(3.2)	5.7 (1.7)	3.6 (2.4)	-2.1 (3.2)
CRP (mg/l)	2.5 (2.2)	2.1 (2.8)	-0.4 (24.7)	12.8 (24.7)	7.9 (24.0)	-4.9 (24.7)
ESR (mm/h)	6.1 (7.2)	4.9 (2.7)	-1.2 (13.7)	13.1 (13.7)	4.1 (2.6)	-9.0 (13.7)
Quality of life: HAQ-DI	0.8 (0.6)	0.6 (0.7)	-0.2 (0.7)	1.0 (0.4)	0.6 (0.4)	-0.1 (0.7)
Quality of life: HUI-3	0.48 (0.35)	0.60 (0.40)	0.07 (0.4)	0.46 (0.34)	0.59 (0.31)	0.13 (0.4)

Adverse events

AE = adverse event, SAE = Serious adverse event

Weeks 0-12

	Adalimumab	Placebo
Total AEs (n)	10	10
Infections		

Bibliographic reference	Paramarta, Jacqueline E., De Rycke,Leen, Heijda,Tanja F., Ambarus,Carmen A., Vos,Koen, Dinant,Huib J., Tak,Paul P., Baeten,Dominique L., Efficacy and safety of adalimumab for the treatment of peripheral arthritis in spondyloarthritis patients without ankylosing spondylitis or psoriatic arthritis, Annals of the rheumatic diseases, 72, 1793-1799, 2013

common cold	4	3
gingivitis	0	1
cystitis	0	2
septic arthritis	0	1
dermatomycosis	0	1
Skin		
diffuse rash	2	0
other	0	2
Gastrointestinal (nausea)	1	0
Psychological (depression)	1	0
Other	4	2
Total SAEs (n)	1	1
Death	1*	0
Hospital admission	0	1**

*Death due to suicide, not considered related to the study drug

**Arthroscopy-related septic arthritis

Weeks 12-24

	Adalimumab (continuation)	Adalimumab (initiation following placebo)
Total AEs (n)	8	11
Infections		
common cold	3	3
sinusitis	0	1

Bibliographic reference	Paramarta, Jacqueline E., De Rycke,Leen, Heijda,Tanja F., Ambarus,Carmen A., Vos,Koen, Dinant,Huib J., Tak,Paul P., Baeten,Dominique L., Efficacy and safety of adalimumab for the treatment of peripheral arthritis in spondyloarthritis patients without ankylosing spondylitis or psoriatic arthritis, Annals of the rheumatic diseases, 72, 1793-1799, 2013

otitis	0	1
tooth abscess	1	1
cystitis	0	3
Skin		
injection site reaction	0	1
other	0	1
Gastrointestinal		
diarrhoea	0	1
bloating	1	0
Psychological		
depression	1	0
psychosis	0	1
Other	3	0
Total SAEs (n)	0	1
Hospital admission	0	1*

* admission due to acute psychosis, not considered related to study drug

Swollen joints

Swollen joints

	Mean	SD	Total
Experimental	-2.50	4.00	19
Control	-0.40	1.80	19

Painful/tender joints/arthralgia

Painful/tender joints/arthralgia

	Mean	SD	Total
Experimental	-1.80	9.20	19

Bibliographic reference	Paramarta, Jacqueline E., De Rycke,Leen, Heijda,Tanja F., Ambarus,Carmen A., Vos,Koen, Dinant,Huib J., Tak,Paul P., Baeten,Dominique L., Efficacy and safety of adalimumab for the treatment of peripheral arthritis in spondyloarthritis patients without ankylosing spondylitis or psoriatic arthritis, Annals of the rheumatic diseases, 72, 1793-1799, 2013
	Control 1.70 6.50 19
BASDAI	BASDAI Mean SD Total Experimental -1.80 2.60 19 Control -0.30 1.50 19
ESR	ESR Mean SD Total Experimental -6.00 12.50 19 Control 1.70 9.30 19
CRP	CRP Mean SD Total Experimental -5.70 12.40 19 Control 4.00 22.90 19
QoL: HAQ-DI	QoL: HAQ-DI Mean SD Total Experimental -0.20 0.70 19 Control -0.10 0.70 19
QoL: HUI-3	QoL: HUI-3 Mean SD Total Experimental 0.12 0.40 19 Control 0.08 0.40 19
Overall Risk of Bias	Some risk of bias due to lack of detail regarding trial methodology

Bibliographic reference	Paramarta, Jacqueline E., De Rycke,Leen, Heijda,Tanja F., Ambarus,Carmen A., Vos,Koen, Dinant,Huib J., Tak,Paul P., Baeten,Dominique L., Efficacy and safety of adalimumab for the treatment of peripheral arthritis in spondyloarthritis patients without ankylosing spondylitis or psoriatic arthritis, Annals of the rheumatic diseases, 72, 1793-1799, 2013
Other information	N/A
Was allocation adequately concealed?	UNCLEAR
Was knowledge of the allocated intervention adequately prevented during the study?	UNCLEAR
Was the allocation sequence adequately generated?	UNCLEAR
Was the study apparently free of other problems that could put it at a high risk of bias?	YES
Were incomplete outcome data adequately addressed?	YES
Are reports of the study free of suggestion of selective outcome reporting?	YES

E.2.5 Long-term antibiotics for reactive arthritis

Review Question 19

- What is the effectiveness of long-term (4 weeks or longer) treatment with antibiotics for first-line management of reactive arthritis compared with standard treatment?

Randomised controlled trials

Table 102: Carter 2010

Bibliographic reference	Carter,J.D., Espinoza,L.R., Inman,R.D., Sneed,K.B., Ricca,L.R., Vasey,F.B., Valeriano,J., Stanich,J.A., Oszust,C., Gerard,H.C., Hudson,A.P., Combination antibiotics as a treatment for chronic Chlamydia-induced reactive arthritis: a double-blind, placebo-controlled, prospective trial, Arthritis and rheumatism, 62, 1298-1307, 2010
Country/ies where the study was carried out	USA and Canada
Study type	Randomised controlled trial
Aim of the study	To investigate whether a six month course of combination antibiotics is effective in the treatment of patients with chronic Chlamydia-induced ReA.
Study dates	April 2006-October 2008
Source of funding	National Institute of Arthritis and Musculoskeletal and Skin Diseases grants AR-053646 and AR-52541. ClinicalTrials.gov identifier NCT00351273
Sample size	42 were enrolled and randomised.
Diagnostic criteria	ESSG preliminary criteria for diagnosis of SpA, modified to increase the likelihood of specifically recruiting patients with post-chlamydial ReA.
Inclusion criteria	18-70 years old disease duration of >= 6 months
Exclusion criteria	current psoriasis history of ankylosing spondylitis or inflammatory bowel disease

Bibliographic reference	Carter,J.D., Espinoza,L.R., Inman,R.D., Sneed,K.B., Ricca,L.R., Vasey,F.B., Valeriano,J., Stanich,J.A., Oszust,C., Gerard,H.C., Hudson,A.P., Combination antibiotics as a treatment for chronic Chlamydia-induced reactive arthritis: a double-blind, placebo-controlled, prospective trial, Arthritis and rheumatism, 62, 1298-1307, 2010
	previous exposure to antibiotics (>2 weeks) as a potential treatment for their ReA history of sensitivity or allergic reaction to rifampin, doxycycline or azithromycin
Characteristics	Group 1 (doxycycline+rifampin+placebo) and Group 2 (azithromycin+rifampin+placebo) combined (n=27) age, years (mean(SD)): 44.2(12.3) men, n(%): 15 (56) disease duration, years (mean(SD)): 10.4(12.1) swollen joint count, 0-76 range (mean(SD)): 3.4(2.4) tender joint count, 0-78 range (mean(SD)): 5.0(4.3) duration of morning low back stiffness, hours (mean(SD)): 1.7(1.4) axial arthritis, n: 20 peripheral arthritis, n: 26 history of Chlamydia trachomatis at any time point, n: 14 history of Chlamydia trachomatis within 1 month of arthritis, n: 3 known history of C. pneumoniae infection, n: 0 Use of NSAIDs, n: 20 Use of corticosteroids, n: 4 Use of DMARDs, n: 7 Radiographic sacroiliitis, n: 19 of 20 HLA-B27 positive, n: 11 of 24 Group 3 (triple placebo) (n=15) age, years (mean(SD)): 49.0(16.4) men, n(%): 9(60) disease duration, years (mean(SD)): 14.2(14.2) swollen joint count, 0-76 range (mean(SD)): 3.8(2.7) tender joint count, 0-78 range (mean(SD)): 7.9(7.4) duration of morning low back stiffness, hours (mean(SD)): 1.0(0.9) axial arthritis, n: 12 peripheral arthritis, n: 13

Bibliographic reference	Carter,J.D., Espinoza,L.R., Inman,R.D., Sneed,K.B., Ricca,L.R., Vasey,F.B., Valeriano,J., Stanich,J.A., Oszust,C., Gerard,H.C., Hudson,A.P., Combination antibiotics as a treatment for chronic Chlamydia-induced reactive arthritis: a double-blind, placebo-controlled, prospective trial, Arthritis and rheumatism, 62, 1298-1307, 2010
	history of Chlamydia trachomatis at any time point, n: 5 history of Chlamydia trachomatis within 1 month of arthritis, n: 1 known history of C. pneumoniae infection, n: 0 Use of NSAIDs, n: 11 Use of corticosteroids, n: 0 Use of DMARDs, n: 3 Radiographic sacroiliitis, n: 8 of 10 HLA-B27 positive, n: 3 of 13
Interventions	Randomisation was stratified by age and disease duration. Participants randomly allocated (1:1:1) to one of 3 treatment groups as follows: Group 1 100mg doxycycline by mouth twice daily and 300mg rifampin by mouth daily plus placebo instead of azithromycin Group 2 500mg azithromycin by mouth daily for 5 days, then 500mg azithromycin by mouth twice weekly and 300mg rifampin by mouth daily, plus placebo instead of doxycycline Group 3 3 placebos instead of azithromycin, doxycycline and rifampin Duration of treatment was 6 months for all 3 groups, with an additional 3 months of follow up after completion of treatment. Participants were additionally permitted to take oral corticosteroids (<=10mg/day prednisone or equivalent) and/or NSAIDs if they had been receiving stable doses for >4 weeks prior to randomisation. DMARDs and biologics were permitted if participants had been receiving stable doses for >12 weeks prior to randomisation. Dosages of these could not be increased during the study but they could be reduced if clinical improvement was shown.
Randomisation, allocation, blinding	Randomisation was stratified by age and disease duration, with a 1:1:1 ratio across the three treatment groups. Study reported as double blind. No additional detail on allocation method given.
Details	Study conducted across 4 centres in the US and Canada. Participant medical history collected at baseline. In addition, data were collected on: physical examination, swollen joint count, tender joint count, questionnaire responses relating to duration and severity of lower back and peripheral joint pain,

Bibliographic reference	Carter,J.D., Espinoza,L.R., Inman,R.D., Sneed,K.B., Ricca,L.R., Vasey,F.B., Valeriano,J., Stanich,J.A., Oszust,C., Gerard,H.C., Hudson,A.P., Combination antibiotics as a treatment for chronic Chlamydia-induced reactive arthritis: a double-blind, placebo-controlled, prospective trial, Arthritis and rheumatism, 62, 1298-1307, 2010
	HAQ disability index score, HLA-B27 status, history of known chlamydial exposure. Blood sample was obtained at the screening visit. In patients with synovitis who consented, synovial tissue was obtained by blind synovial biopsy, using a Parker-Pearson needle.
Missing data handling/loss to follow up	One participant (placebo) discontinued study due to gastrointestinal adverse events. Analysis was conducted on an intention to treat basis.
Results	Joint count Modified Swollen Joint Count (Estimated from 3D bar graph) Group 1+Group 2 (combined antibiotics): baseline: 4.4; 1 month: 1.9; 3 months: 0.9; 6 months: 0.9; 9 months:0.6 Group 3 (triple placebo): baseline: 4.9; 1 month: 4.1; 3 months: 4.9; 6 months: 5.4; 9 months: 5.5 Tender joint count (Estimated from 3D bar graph) Group 1+Group 2 (combined antibiotics): baseline: 7.2; 1 month: 4.8; 3 months: 3.1; 6 months: 1.9; 9 months: 1.9 Group 3 (triple placebo): baseline: 9.1; 1 month: 10.6; 3 months: 10.8; 6 months: 11.8; 9 months: 10.8 Physical function HAQ Disability index score Group 1+Group 2 (combined antibiotics): baseline: 0.84; 1 month: 0.79; 3 months: 0.68; 6 months: 0.71; 9 months: 0.57 Group 3 (triple placebo): baseline: 1.1; 1 month: 0.92; 3 months: 0.87; 6 months: 0.99; 9 months:0.92 Inflammatory markers ESR (mm/hr) Group 1+Group 2 (combined antibiotics): baseline: 25.1; 1 month: 17.8; 3 months: 17.7; 6 months: 12.7; 9 months: 14.0 Group 3 (triple placebo): baseline: 18.9; 1 month: 25.2; 3 months: 19.8; 6 months: 17; 9 months: 18.4 hsCRP (mg/litre) Group 1+Group 2 (combined antibiotics): baseline: 1.07; 1 month: 0.56; 3 months: 0.63; 6 months: 0.41; 9 months: not measured Group 3 (triple placebo): baseline: 0.42; 1 month: 0.27; 3 months: 0.55; 6 months: 0.34; 9 months: not measured Adverse events Group 1+Group 2 (combined antibiotics): severe adverse events: 0, any adverse event: 22, nausea: 6, abdominal pain: 3, diarrhoea: 5, GORD: 2, Arthralgia: 2, Rash: 2, Viral/upper respiratory infection: 3, vaginal candidiasis: 2 of 12 Group 3 (triple placebo): baseline:

Bibliographic reference	Carter,J.D., Espinoza,L.R., Inman,R.D., Sneed,K.B., Ricca,L.R., Vasey,F.B., Valeriano,J., Stanich,J.A., Oszust,C., Gerard,H.C., Hudson,A.P., Combination antibiotics as a treatment for chronic Chlamydia-induced reactive arthritis: a double-blind, placebo-controlled, prospective trial, Arthritis and rheumatism, 62, 1298-1307, 2010
	severe adverse events: 2, any adverse event: 10, nausea: 1, abdominal pain: 1, diarrhoea: 1, GORD: 0, Arthralgia: 1, Rash: 0, Viral/upper respiratory infection: 1, vaginal candidiasis: 1 of 6
UG_swollen joints	<table><tr><td></td><td>Mean</td><td>SD</td><td>Total</td></tr><tr><td>Experimental</td><td>-3.80</td><td>4.90</td><td>27</td></tr><tr><td>Control</td><td>-3.00</td><td>4.90</td><td>15</td></tr></table>
UG_painful/tender joints/arthralgia	<table><tr><td></td><td>Mean</td><td>SD</td><td>Total</td></tr><tr><td>Experimental</td><td>-5.30</td><td>2.20</td><td>27</td></tr><tr><td>Control</td><td>1.70</td><td>2.20</td><td>15</td></tr></table>
UG_CRP	<table><tr><td></td><td>Mean</td><td>SD</td><td>Total</td></tr><tr><td>Experimental</td><td>-0.66</td><td>3.00</td><td>27</td></tr><tr><td>Control</td><td>-0.08</td><td>3.00</td><td>15</td></tr></table>
UG_ESR	<table><tr><td></td><td>Mean</td><td>SD</td><td>Total</td></tr><tr><td>Experimental</td><td>11.10</td><td>17.33</td><td>27</td></tr><tr><td>Control</td><td>-0.50</td><td>17.33</td><td>15</td></tr></table>
Swollen joints	<table><tr><td></td><td>Mean</td><td>SD</td><td>Total</td></tr><tr><td>Experimental</td><td>-3.80</td><td>4.90</td><td>27</td></tr><tr><td>Control</td><td>-3.00</td><td>4.90</td><td>15</td></tr></table>

<table>
<tr><th>Bibliographic reference</th><th>Carter,J.D., Espinoza,L.R., Inman,R.D., Sneed,K.B., Ricca,L.R., Vasey,F.B., Valeriano,J., Stanich,J.A., Oszust,C., Gerard,H.C., Hudson,A.P., Combination antibiotics as a treatment for chronic Chlamydia-induced reactive arthritis: a double-blind, placebo-controlled, prospective trial, Arthritis and rheumatism, 62, 1298-1307, 2010</th></tr>
<tr><td>Painful/tender joints/arthralgia</td><td><table><tr><td></td><td>Mean</td><td>SD</td><td>Total</td></tr><tr><td>Experimental</td><td>-5.30</td><td>2.20</td><td>27</td></tr><tr><td>Control</td><td>1.70</td><td>2.20</td><td>15</td></tr></table></td></tr>
<tr><td>ESR</td><td><table><tr><td></td><td>Mean</td><td>SD</td><td>Total</td></tr><tr><td>Experimental</td><td>11.10</td><td>17.33</td><td>27</td></tr><tr><td>Control</td><td>-0.50</td><td>17.33</td><td>15</td></tr></table></td></tr>
<tr><td>CRP</td><td><table><tr><td></td><td>Mean</td><td>SD</td><td>Total</td></tr><tr><td>Experimental</td><td>-0.66</td><td>3.00</td><td>27</td></tr><tr><td>Control</td><td>-0.08</td><td>3.00</td><td>15</td></tr></table></td></tr>
<tr><td>Overall Risk of Bias</td><td>Limited information about randomisation, allocation and blinding makes it difficult to assess risk of bias. Data on swollen/tender joint count was manually extracted by the reviewer from graphs.</td></tr>
<tr><td>Other information</td><td>n/a</td></tr>
<tr><td>Was the allocation sequence adequately generated?</td><td>UNCLEAR</td></tr>
<tr><td>Was allocation adequately concealed?</td><td>UNCLEAR</td></tr>
<tr><td>Was knowledge of the allocated intervention</td><td>UNCLEAR</td></tr>
</table>

Bibliographic reference	Carter,J.D., Espinoza,L.R., Inman,R.D., Sneed,K.B., Ricca,L.R., Vasey,F.B., Valeriano,J., Stanich,J.A., Oszust,C., Gerard,H.C., Hudson,A.P., Combination antibiotics as a treatment for chronic Chlamydia-induced reactive arthritis: a double-blind, placebo-controlled, prospective trial, Arthritis and rheumatism, 62, 1298-1307, 2010
adequately prevented during the study?	
Were incomplete outcome data adequately addressed?	YES
Are reports of the study free of suggestion of selective outcome reporting?	YES
Was the study apparently free of other problems that could put it at a high risk of bias?	YES

Table 103: Hoogkamp-Korstanje 2000

Bibliographic reference	Hoogkamp-Korstanje,J.A., Moesker,H., Bruyn,G.A., Ciprofloxacin v placebo for treatment of Yersinia enterocolitica triggered reactive arthritis, Annals of the Rheumatic Diseases, 59, 914-917, 2000
Country/ies where the study was carried out	Netherlands
Study type	Randomised controlled trial
Aim of the study	To assess the clinical and microbial efficacy of ciprofloxacin treatment in patients with proven yersinia-triggered arthritis.
Study dates	Not reported. Study published 2000
Source of funding	Not reported
Sample size	18 participants (7 received ciprofloxacin, 11 placebo)
Diagnostic criteria	Yersinia infection diagnosed by demonstration of specific serum IgA and IgG antibodies against Yersinia outer proteins (yops), positive culture of faeces or biopsy specimen, and/or demonstration of Y. entereocolitica. No details on diagnostic criteria of arthritis were reported.
Inclusion criteria	aged over 18 proven yersinia-triggered arthritis arthritis duration of fewer than five years
Exclusion criteria	People with rheumatic disease, arthritis associated with other bacterial infections, rheumatic fever, psoriasis, Crohn's disease, ulcerative colitis, or lupus erythematodes.

Bibliographic reference	Hoogkamp-Korstanje,J.A., Moesker,H., Bruyn,G.A., Ciprofloxacin v placebo for treatment of Yersinia enterocolitica triggered reactive arthritis, Annals of the Rheumatic Diseases, 59, 914-917, 2000
	Patients receiving antibiotics with a spectrum of activity similar to ciprofloxacin Patients receiving corticosteroids, sulfasalazine, antacids and theophylline derivatives
Characteristics	Ciprofloxacin (n=7) female, n: 5 age, years (median (range)): 33 (18-52) HLA-B27 positive, n: 2 Duration of disease, years (SD): 1.9 (1.4) Placebo (n=11) female, n: 3 age, years (median (range)): 45 (26-72) HLA-B27 positive, n: 3 Duration of disease, years (SD): 2.0 (1.5)
Interventions	Antibiotic group Ciprofloxacin 500mg twice a day, orally, for three months Placebo group Placebo, orally for three months
Randomisation, allocation, blinding	Study described as double blinded. No further detail given on allocation, randomisation or blinding.
Details	Participants were assessed at 1, 2 (during), 3 (end), 4, 6, 8, 10 and 12 months after the start of treatment. Clinical measures included: articular index score (each joint assessed for tenderness to pressure on a 0-3 scale), visual analogue pain scale (0-10), and patient's impression. A joint swelling scale (0-3) and pain at rest scale (0-10) were also used. In addition, participants had a full physical examination, radiographs of the thoracic and lumbar vertebrae, and blood screening tests (haematology, HLA-B27, chemistry, CRP). Faeces and biopsy specimens were collected at baseline and regular intervals thereafter. These were cultured for Y enterocolitica. Further microbial profiling was conducted to confirm yersinia infection and rule out other bacterial infections.
Missing data handling/loss to follow up	Two patients receiving placebo were excluded due to protocol violations. No other loss to follow up was reported.
Results	Pain

<table>
<tr><th>Bibliographic reference</th><th>Hoogkamp-Korstanje,J.A., Moesker,H., Bruyn,G.A., Ciprofloxacin v placebo for treatment of Yersinia enterocolitica triggered reactive arthritis, Annals of the Rheumatic Diseases, 59, 914-917, 2000</th></tr>
<tr><td></td><td>VAS (mm) [ESTIMATED FROM GRAPH]
Ciprofloxacin: baseline: 41; 1 month: 40; 2 months: 37; 3 months: 27.5; 12 months: 5
Placebo: baseline: 42; 1 month; 38 ; 2 months: 35; 3 months: 32.5; 12 months: 9

Joint count
Joint tenderness (mean, 0-3 scale per joint) [ESTIMATED FROM GRAPH]
Ciprofloxacin: baseline: 3.1; 1 month: 2.5; 2 months: 1.9; 3 months: 1.4; 12 months: 0.2
Placebo: baseline: 3.5; 1 month: 2.3; 2 months: 2.0; 3 months: 1.9; 12 months: 0.9

Adverse events
Authors state: "Ciprofloxacin was well tolerated in all patients and there were no significant side effects."</td></tr>
<tr><td>GI_painful/tender joints/arthralgia</td><td><table><tr><td></td><td>Mean</td><td>SD</td><td>Total</td></tr><tr><td>Experimental</td><td>-2.90</td><td>2.20</td><td>7</td></tr><tr><td>Control</td><td>-2.60</td><td>2.20</td><td>11</td></tr></table></td></tr>
<tr><td>Painful/tender joints/arthralgia</td><td><table><tr><td></td><td>Mean</td><td>SD</td><td>Total</td></tr><tr><td>Experimental</td><td>-2.90</td><td>2.20</td><td>7</td></tr><tr><td>Control</td><td>-2.60</td><td>2.20</td><td>11</td></tr></table></td></tr>
<tr><td>Overall Risk of Bias</td><td>Article was a brief report which lacked some of the information needed to assess risk of bias (e.g. allocation method).
Paper states in the discussion: "It was difficult to include sufficient patients, because rheumatologists who were already convinced that antibiotics are of benefit in yersinia triggered arthritis were not willing to deliver patients for a double blind study, and rheumatologists who thought that antibiotics are of no value did not recruit patients."
Outcome data had to be estimated from graphs.</td></tr>
<tr><td>Other information</td><td>n/a</td></tr>
<tr><td>Was the allocation sequence adequately generated?</td><td>UNCLEAR</td></tr>
<tr><td>Was allocation adequately concealed?</td><td>UNCLEAR</td></tr>
</table>

Bibliographic reference	Hoogkamp-Korstanje,J.A., Moesker,H., Bruyn,G.A., Ciprofloxacin v placebo for treatment of Yersinia enterocolitica triggered reactive arthritis, Annals of the Rheumatic Diseases, 59, 914-917, 2000
Was knowledge of the allocated intervention adequately prevented during the study?	UNCLEAR
Were incomplete outcome data adequately addressed?	YES
Are reports of the study free of suggestion of selective outcome reporting?	NO
Was the study apparently free of other problems that could put it at a high risk of bias?	YES

Table 104: Kuuliala et al., 2013

Bibliographic reference	Kuuliala,Antti, Julkunen,Heikki, Paimela,Leena, Peltomaa,Ritva, Kautiainen,Hannu, Repo,Heikki, Leirisalo-Repo,Marjatta, Double-blind, randomized, placebo-controlled study of three-month treatment with the combination of ofloxacin and roxithromycin in recent-onset reactive arthritis, Rheumatology international, 33, 2723-2729, 2013
Country/ies where the study was carried out	Finland
Study type	Randomised controlled trial
Aim of the study	To evaluate the efficacy of a 3-month course of the combination of ofloxacin and roxithromycin in recent-onset ReA.
Study dates	Not stated. Submitted and published 2013
Source of funding	Helsinki University Central Hospital research funds
Sample size	56 participants (26 on combination therapy, 30 on control)
Diagnostic criteria	No diagnostic criteria for ReA were reported. Infection triggering the ReA episode was confirmed (see 'inclusion criteria')
Inclusion criteria	typical clinical picture of ReA preceding infection verified by positive culture and/or serology or with a history of urethritis or gastroenteritis within the previous 2 months have had other inflammatory arthritides excluded by clinical examination and relevant laboratory tests
Exclusion criteria	allergy to quinolones or macrolides treatment with systemic corticosteroids within 2 weeks

Bibliographic reference	Kuuliala,Antti, Julkunen,Heikki, Paimela,Leena, Peltomaa,Ritva, Kautiainen,Hannu, Repo,Heikki, Leirisalo-Repo,Marjatta, Double-blind, randomized, placebo-controlled study of three-month treatment with the combination of ofloxacin and roxithromycin in recent-onset reactive arthritis, Rheumatology international, 33, 2723-2729, 2013
	serum creatinine level elevated about upper limit of normal current or planned pregnancy or lack of contraception known HIV positivity blood leukocyte count<4.0x10^9/l blood platelet count less than 100 x10^9/l lack of co-operation Previous use of antimicrobial drugs for the infection preceding ReA was not considered as an exclusion criterion.
Characteristics	Combination therapy (n=26) age, years (mean(sd)): 40(14) female, n: 8 duration of arthritis, weeks (median (range)): 5 (1-14) previous reactive arthritis, n: 3 Fever> 37.5°, n: 19 low back pain, n: 12 enthesopathy, n: 10 urethritis, n: 1 eye inflammation, n: 1 mucocutaneous lesions, n: 0 Microbial triggers Salmonella, n: 8 Yersinia, n: 6 Campylobacter, n: 3 C. trachomatis, n: 4 Enteritis (unspecified), n: 5 Urethritis (unspecified), n: 0 Placebo (n=30) age, years (mean(sd)): 38(11) female, n: 11 duration of arthritis, weeks (median (range)): 4 (0-19) previous reactive arthritis, n: 8

Bibliographic reference	Kuuliala,Antti, Julkunen,Heikki, Paimela,Leena, Peltomaa,Ritva, Kautiainen,Hannu, Repo,Heikki, Leirisalo-Repo,Marjatta, Double-blind, randomized, placebo-controlled study of three-month treatment with the combination of ofloxacin and roxithromycin in recent-onset reactive arthritis, Rheumatology international, 33, 2723-2729, 2013
	Fever> 37.5°, n: 24 low back pain, n: 18 enthesopathy, n: 10 urethritis, n: 0 eye inflammation, n: 0 mucocutaneous lesions, n: 1 Microbial triggers Salmonella, n: 10 Yersinia, n: 4 Campylobacter, n: 6 C. trachomatis, n: 3 Enteritis (unspecified), n: 5 Urethritis (unspecified), n: 2
Interventions	Combination therapy 200mg ofloxacin and 150mg roxithromycin twice daily for 3 months, or until complete recovery if earlier than three months. Placebo As above, with placebo replacing the combination therapy Patients diagnosed with C. trachomatis-triggered ReA initially received roxithromycin 150mg twice daily for 2 weeks and were subsequently randomised to blinded treatment with combination therapy or placebo. Concomitant use of NSAIDs and administration of intra-articular corticosteroids was allowed. If ReA was severe with persistent disease activity, the treatment was considered to have failed and the patient could thereafter be treated with systemic corticosteroids or DMARDs. If there was an additional intervening infection occurring during the study, participants were allowed to receive appropriate antibiotics, while the study drugs were temporarily discontinued.
Randomisation, allocation, blinding	Randomisation was performed centrally with a block size of five. Study drugs were prepared and labelled specifically for the study by the pharmacy at one of the participating hospitals. No further details given with respect to randomisation, allocation or blinding.
Details	Recruitment Patients were recruited from participating hospital clinics. Primary care physicians were asked to identify eligible patients and refer them on to these clinics. Assessment

Bibliographic reference	**Kuuliala,Antti, Julkunen,Heikki, Paimela,Leena, Peltomaa,Ritva, Kautiainen,Hannu, Repo,Heikki, Leirisalo-Repo,Marjatta, Double-blind, randomized, placebo-controlled study of three-month treatment with the combination of ofloxacin and roxithromycin in recent-onset reactive arthritis, Rheumatology international, 33, 2723-2729, 2013**
	Baseline measures included comprehensive history, physical examination, and routine laboratory tests (including microbial stool cultures, C. trachomatis isolation from urethra and antibody tests for C. trachomatis, Salmonella, Yersinia and Campylobacter). The Ritchie index was used for swollen and tender joint counts. Pain was assessed on a 100mm VAS. Laboratory testing was used to assess disease activity (ESR, CRP) and drug safety (alanine aminotransferase, alkaline phosphatase, creatinine, blood haemoglobin level, white blood cell count, urinalysis). Follow up visits were at 2 weeks and 1, 2, 3 and 6 months after entering the study, or ceasing earlier if the patient recovered. Statistical analysis Results expressed as mean or median (with SD or IQR or CI). Mann-Whitney test used for comparisons between characteristics of groups at baseline. Differences between groups in recovery were measured with Fisher's exact test. Median regression models with baseline value as covariate were used to compared differences in the changes of clinical and laboratory parameters between groups. No adjustment was made for multiple testing.
Missing data handling/loss to follow up	In the combination therapy group, 6 patients discontinued treatment (2 requested to stop, 4 had adverse events). A total of 3 patients in this group were lost to follow up. In the placebo group, 6 patients discontinued treatment (4 requested to stop, 2 had adverse events). 1 patient in this group was lost to follow up. An intention to treat analysis was performed, with last-observation carried forward.
Results	Data were reported on pain, joint count and inflammatory markers at baseline, 3 months and 6 months. However, these were only reported as median values with interquartile ranges, which are considered likely by Cochrane to be non-normally distributed, and therefore unsuitable for met-analysis; they are therefore not presented here. Adverse events (n) Combination therapy (n=26): gastrointestinal: 21 across 14 patients; neurological: 11 across 5 patients; cutaneous: 6 across 5 patients; infections: 5 across 3 patients; miscellaneous: 2 across 2 patients Placebo (n=30): gastrointestinal: 11 across 8 patients; neurological: 5 across 4 patients; cutaneous: 1 across 1 patients; infections: 3 across 3 patients; miscellaneous: 1 across 1 patient
Overall Risk of Bias	Limited detail on allocation and blinding makes it difficult to assess risk of bias in these areas.
Other information	n/a
Was the allocation sequence adequately generated?	UNCLEAR
Was allocation adequately concealed?	UNCLEAR
Was knowledge of the allocated intervention	UNCLEAR

Bibliographic reference	Kuuliala,Antti, Julkunen,Heikki, Paimela,Leena, Peltomaa,Ritva, Kautiainen,Hannu, Repo,Heikki, Leirisalo-Repo,Marjatta, Double-blind, randomized, placebo-controlled study of three-month treatment with the combination of ofloxacin and roxithromycin in recent-onset reactive arthritis, Rheumatology international, 33, 2723-2729, 2013
adequately prevented during the study?	
Were incomplete outcome data adequately addressed?	YES
Are reports of the study free of suggestion of selective outcome reporting?	UNCLEAR
Was the study apparently free of other problems that could put it at a high risk of bias?	YES

Table 105: Kvien et al., 2004

Bibliographic reference	Kvien,T.K., Gaston,J.S.H., Bardin,T., Butrimiene,I., Dijkmans,B.A.C., Leirisalo-Repo,M., Solakov,P., Altwegg,M., Mowinckel,P., Plan,P.A., Vischer,T., EULAR, Three month treatment of reactive arthritis with azithromycin: a EULAR double blind, placebo controlled study, Annals of the rheumatic diseases, 63, 1113-1119, 2004
Country/ies where the study was carried out	12 European countries (Austria, Bulgaria, Denmark, Finland, France, Germany, Hungary, Lithuania, Norway, Slovakia, the Netherlands, UK)
Study type	Multi-centre randomised controlled trial
Aim of the study	To investigate whether a 3 month course of antibiotic treatment could hasten recovery or diminish severity of ReA or both.
Study dates	Not reported. Article accepted 2003, published 2004.
Source of funding	Research grant from Pfizer to EULAR. Additional logistic support for meetings and data management from Pfizer.
Sample size	186 patients were randomised, 152 were included in analysis (34 failed entry criteria)
Diagnostic criteria	Not explicitly stated. Patients were required to have a reasonable possibility of ReA (see 'inclusion criteria')
Inclusion criteria	aged 16 to 55

Bibliographic reference	Kvien,T.K., Gaston,J.S.H., Bardin,T., Butrimiene,I., Dijkmans,B.A.C., Leirisalo-Repo,M., Solakov,P., Altwegg,M., Mowinckel,P., Plan,P.A., Vischer,T., EULAR, Three month treatment of reactive arthritis with azithromycin: a EULAR double blind, placebo controlled study, Annals of the rheumatic diseases, 63, 1113-1119, 2004
	presenting with an acute unexplained inflammatory arthritis enrolling physician considered the diagnosis of ReA a reasonable possibility (i.e. alternative causes of acute arthropathy had been excluded). duration of symptoms <=2 months involvement of <= single swollen joints
Exclusion criteria	patients whose symptoms may be attributed to spondyloarthropathies other than ReA, osteoarthritis, rheumatoid arthritis, or systemic lupus erythematosus were also excluded patients with trauma or orthopaedic conditions pregnancy and lactation known sensitivity to macrolides or azithromycin use of ergotamine or digitalis estimated creatinine clearance of <40ml/min serum values of alanine aminotransferase, aspartate aminotransferase and alkaline phosphatase higher than twice the upper limit use of antibiotics for 10 days or more within 30 days before enrolment Administration of corticosteroids (oral, intravenous, intramuscular) or disease modifying anti-rheumatic drugs (DMARDs) within 2 months before enrolment Intra-articular corticosteroid injection within 2 weeks before enrolment Infections requiring antibiotic treatment in addition to the study drug History of peptic ulceration, gastrectomy, or any other gastrointestinal condition that might affect absorption of the study drug Evidence of drug abuse or alcoholism Immunodeficiency from any cause (but known HIV positive patients could be enrolled, provided that they had no evidence of being immunosuppressed).
Characteristics	Azithromycin (n=81) age, years (mean(SD)): 33.0 (9.8) duration of arthritis, days (mean(SD)): 30.1(17.3) women, n: 25 previous similar episode, n: 17 recent intra-articular steroid injection, n: 20 heel enthesopathy, n: 28 urethritis, n: 13

Bibliographic reference	Kvien,T.K., Gaston,J.S.H., Bardin,T., Butrimiene,I., Dijkmans,B.A.C., Leirisalo-Repo,M., Solakov,P., Altwegg,M., Mowinckel,P., Plan,P.A., Vischer,T., EULAR, Three month treatment of reactive arthritis with azithromycin: a EULAR double blind, placebo controlled study, Annals of the rheumatic diseases, 63, 1113-1119, 2004
	diarrhoea, n: 5 skin abnormalities, n: 11 eye abnormalities, n: 17 genitourinary abnormalities, n: 19 HLA-B27, n: 22 Placebo (n=71) age, years (mean(SD)): 34.7(8.9) duration of arthritis, days (mean(SD)): 30.7(17.9) women, n: 24 previous similar episode, n: 15 recent intra-articular steroid injection, n: 17 heel enthesopathy, n: 30 urethritis, n: 12 diarrhoea, n: 2 skin abnormalities, n: 10 eye abnormalities, n: 14 genitourinary abnormalities, n: 17 HLA-B27, n: 12
Interventions	The study was of 6 months' duration, including a 12 week study drug administration period (azithromycin or placebo after 1 g single dose of azithromycin). 1g oral azithromycin was given weekly (two tablets of 500 mg) for 12 weeks in the intervention group, starting one week after a 1g single dose of azithromycin. Patients in either group were allowed to take piroxicam 20mg once a day as needed for pain/inflammation relief, or an alternative NSAID if intolerant. Paracetamol was additionally allowed if required. Patients needing oral corticosteroids or DMARDs during the study period were removed from the study. Intra-articular corticosteroids were avoided where possible and only permitted during study assessment visits.
Randomisation, allocation, blinding	Participants were randomised and the trial was described as double-blind. No further detail on randomisation, allocation method or blinding was provided.
Details	Assessment Measures relating to disease activity and therapeutic efficacy were collected at baseline then every 4 weeks for 24 weeks. Patient reported measures: overall disease activity (5 point scale), pain site assessment (various sites, each on 5 point

Bibliographic reference	**Kvien,T.K., Gaston,J.S.H., Bardin,T., Butrimiene,I., Dijkmans,B.A.C., Leirisalo-Repo,M., Solakov,P., Altwegg,M., Mowinckel,P., Plan,P.A., Vischer,T., EULAR, Three month treatment of reactive arthritis with azithromycin: a EULAR double blind, placebo controlled study, Annals of the rheumatic diseases, 63, 1113-1119, 2004**
	scale). Clinical assessment: number of swollen or tender joints (both 56 point scale, dactylitis counted as one joint, presence/absence of enthesopathies at the heel, overall disease activity (5 point scale), presence of extra-articular manifestations. Laboratory measures at each visit: CRP, serum alanine aminotransferase, aspartate aminotransferase, alkaline phosphatase, creatinine, haemoglobin, packed cell volume, white blood cell count with differential, platelets, CRP. Urinalysis was also conducted to test for C trachomatis DNA. Rheumatoid factor and HLA-B27 were also tested for. Adverse drug reactions were measured at every visit. Statistical analysis Patients not fulfilling exclusion/inclusion criteria were removed from analysis; otherwise remaining patients were analysed even if they did not complete the study (see 'Missing data handling', below). Summary statistics were used for demographic and disease variables. T tests were used for changes from baseline to end of study, ANOVA for time-dependent changes, and Kaplan-Meier survival analyses and log rank tests for assessing time to resolution of arthritis and other end points.
Missing data handling/loss to follow up	34 patients were excluded after enrolment no swollen joint at baseline (n=5) swollen joint count >6 (n=11) not fulfilling all inclusion criteria (n=1) one or more exclusion criteria present (n=3) duration of symptoms >60 days (n=10) missing information on swollen joint count or duration of symptoms (n=4) positive rheumatoid factor test (n=3) (some patients had more than one reason for being excluded). Patients who had received at least one dose of study drug were included in the analysis on an intention to treat basis, with last observation carried forward. A further analysis was carried out in the 'completer population' i.e. those who completed the entire 24 week study period.
Results	Pain Joint pain, 5 point scale (mean) Azithromycin: baseline: 2.20(SD 0.73); change: decrease of 1.32 (95% CI 1.06 to 1.41) Placebo: baseline: 1.99(SD 0.84); change: decrease of 1.23(95% CI 0.96 to 1.49) Back pain, 5 point scale Azithromycin: baseline: 0.52(SD 0.85); change: 0.38(95% CI 0.19 to 0.57) [Direction of effect unclear; assumed to be decrease] Placebo: baseline: 0.38(SD 0.72); change: 0.21(95% CI 0.03 to 0.39) [Direction of effect unclear; assumed to be decrease] Heel pain, 5 point scale Azithromycin: baseline: 0.62(SD 0.98); change: 0.33(95% CI 0.12 to 0.55) [Direction of effect unclear; assumed to be decrease]

Bibliographic reference	Kvien,T.K., Gaston,J.S.H., Bardin,T., Butrimiene,I., Dijkmans,B.A.C., Leirisalo-Repo,M., Solakov,P., Altwegg,M., Mowinckel,P., Plan,P.A., Vischer,T., EULAR, Three month treatment of reactive arthritis with azithromycin: a EULAR double blind, placebo controlled study, Annals of the rheumatic diseases, 63, 1113-1119, 2004
	Placebo: baseline: 0.73(SD 1.00); change: 0.35(95% CI 0.09 to 0.61) [Direction of effect unclear; assumed to be decrease] Joint count Swollen joint count (0-56): Azithromycin: baseline: 2.63(SD 1.53); change: 1.44(95% CI 0.95 to 1.94) Placebo: baseline: 2.25(SD 1.28); change: 1.44(95% CI 1.01 to 1.86) Tender joint count (0-56) Azithromycin: baseline: 3.69(SD 3.31); change: 1.79(95% CI 0.92 to 2.65) Placebo: baseline: 3.52(SD 3.31); change: 1.79(95% CI 0.92 to 2.65) Inflammatory markers CRP Azithromycin: baseline: 43(SD 49); change: 25(95% CI 11 to 38) Placebo: baseline: 47(SD 55); change: 35(95% CI 20 to 50) Adverse events Azithromycin: Number of patients experiencing adverse events was as follows: gastrointestinal=30, fungal infections=2, respiratory=10, cutaneous=5, stomatitis=2, neurological=2, headache=3, urogenital=1, laboratory abnormalities=1, miscellaneous=13. Placebo: Number of patients experiencing adverse events was as follows: gastrointestinal=12, fungal infections=1, respiratory=9, cutaneous=3, stomatitis=1, neurological=1, headache=0, urogenital=2, laboratory abnormalities=3, miscellaneous=10.
Swollen joints	Swollen joints <table><tr><td></td><td>Mean</td><td>SD</td><td>Total</td></tr><tr><td>Experimental</td><td>-1.44</td><td>2.27</td><td>81</td></tr><tr><td>Control</td><td>-1.44</td><td>1.83</td><td>71</td></tr></table>

<table>
<tr><th>Bibliographic reference</th><th>Kvien,T.K., Gaston,J.S.H., Bardin,T., Butrimiene,I., Dijkmans,B.A.C., Leirisalo-Repo,M., Solakov,P., Altwegg,M., Mowinckel,P., Plan,P.A., Vischer,T., EULAR, Three month treatment of reactive arthritis with azithromycin: a EULAR double blind, placebo controlled study, Annals of the rheumatic diseases, 63, 1113-1119, 2004</th></tr>
<tr><td>Painful/tender joints/arthralgia</td><td>Painful/tender joints/arthralgia<table><tr><td></td><td>Mean</td><td>SD</td><td>Total</td></tr><tr><td>Experimental</td><td>-1.79</td><td>3.97</td><td>81</td></tr><tr><td>Control</td><td>-1.76</td><td>7.57</td><td>71</td></tr></table></td></tr>
<tr><td>CRP</td><td>CRP<table><tr><td></td><td>Mean</td><td>SD</td><td>Total</td></tr><tr><td>Experimental</td><td>-25.00</td><td>61.99</td><td>81</td></tr><tr><td>Control</td><td>-35.00</td><td>64.50</td><td>71</td></tr></table></td></tr>
<tr><td>Overall Risk of Bias</td><td>Lack of detail on randomisation, allocation and blinding makes it difficult to assess risk of bias in these areas. Some ambiguity about direction of change in reported outcome measures.</td></tr>
<tr><td>Other information</td><td>n/a</td></tr>
<tr><td>Was the allocation sequence adequately generated?</td><td>UNCLEAR</td></tr>
<tr><td>Was allocation adequately concealed?</td><td>UNCLEAR</td></tr>
<tr><td>Was knowledge of the allocated intervention adequately prevented during the study?</td><td>UNCLEAR</td></tr>
</table>

Bibliographic reference	Kvien,T.K., Gaston,J.S.H., Bardin,T., Butrimiene,I., Dijkmans,B.A.C., Leirisalo-Repo,M., Solakov,P., Altwegg,M., Mowinckel,P., Plan,P.A., Vischer,T., EULAR, Three month treatment of reactive arthritis with azithromycin: a EULAR double blind, placebo controlled study, Annals of the rheumatic diseases, 63, 1113-1119, 2004
Were incomplete outcome data adequately addressed?	YES
Are reports of the study free of suggestion of selective outcome reporting?	YES
Was the study apparently free of other problems that could put it at a high risk of bias?	YES

Table 106: Sieper et al 1999

Bibliographic reference	Sieper,J., Fendler,C., Laitko,S., Sorensen,H., Gripenberg-Lerche,C., Hiepe,F., Alten,R., Keitel,W., Groh,A., Uksila,J., Eggens,U., Granfors,K., Braun,J., No benefit of long-term ciprofloxacin treatment in patients with reactive arthritis and undifferentiated oligoarthritis: a three-month, multicenter, double-blind, randomized, placebo-controlled study, Arthritis and rheumatism, 42, 1386-1396, 1999
Country/ies where the study was carried out	Germany
Study type	Multicentre randomised controlled trial
Aim of the study	To investigate the effect of long-term antibiotic treatment in patients with reactive arthritis (ReA) and undifferentiated oligoarthritis.
Study dates	Submitted 1998, accepted and published 1999
Source of funding	Bayer Leverkusen, Leverkusen, Germany
Sample size	126 patients were enrolled, of whom 104 were eligible for evaluation and 55 had reactive arthritis.
Diagnostic criteria	ReA was diagnosed if patients presented with a clinical picture of asymmetric arthritis plus one of the following conditions: a preceding symptomatic urethritis on enteritis not longer than 4 weeks before the onset of arthritis, positive findings on examination of a urogenital swab for C trachomatis, positive findings on stool cultures for Yersinia, Salmonella, Shigella, or Campylobacter. other diagnoses were excluded by appropriate tests.

Bibliographic reference	Sieper,J., Fendler,C., Laitko,S., Sorensen,H., Gripenberg-Lerche,C., Hiepe,F., Alten,R., Keitel,W., Groh,A., Uksila,J., Eggens,U., Granfors,K., Braun,J., No benefit of long-term ciprofloxacin treatment in patients with reactive arthritis and undifferentiated oligoarthritis: a three-month, multicenter, double-blind, randomized, placebo-controlled study, Arthritis and rheumatism, 42, 1386-1396, 1999
Inclusion criteria	No additional inclusion criteria were reported beyond those described in 'Diagnostic criteria' above.
Exclusion criteria	None reported
Characteristics	Characteristics of the 55 patients with reactive arthritis: Ciprofloxacin (n=27) age, years (mean(range)): 37.3 (19-58) female, n: 13 disease duration, weeks (median (range)): 9 (1-208) % with disease duration<3 months: 59.3% % HLA-B27 positive: 53.8% Placebo (n=28) age, years (mean(range)): 35.5 (19-60) female, n: 14 disease duration, weeks (median (range)): 11 (1-260) % with disease duration<3 months: 57.1% % HLA-B27 positive: 50.0%
Interventions	Patients who tested positive for C. trachomatis or enterobacteria, had a pre-study treatment of 1000mg ciprofloxacin (2x 500mg) for 10 days. The study intervention was then as follows: Ciprofloxacin 500mg orally twice a day for 90 days Placebo Oral placebo for 90 days No medications other than NSAIDs were permitted throughout the study. Previous injections of glucocorticoids into joints and treatment with disease-modifying anti-rheumatic drugs were allowed until 4 weeks before the start of the study; no previous antibiotic treatment was permitted.
Randomisation, allocation, blinding	Study described as double-blind, randomised controlled study. Patients with ReA and undifferentiated oligoarthritis were separately randomised for treatment. No further detail on randomisation, allocation method or blinding was reported.
Details	Laboratory testing.

Bibliographic reference	**Sieper,J., Fendler,C., Laitko,S., Sorensen,H., Gripenberg-Lerche,C., Hiepe,F., Alten,R., Keitel,W., Groh,A., Uksila,J., Eggens,U., Granfors,K., Braun,J., No benefit of long-term ciprofloxacin treatment in patients with reactive arthritis and undifferentiated oligoarthritis: a three-month, multicenter, double-blind, randomized, placebo-controlled study, Arthritis and rheumatism, 42, 1386-1396, 1999**
	Participants were tested for antibodies against C trachomatis using the micro-immunofluorescence test. Anti–Yersinia enterocolitica and anti–Yersinia pseudotuberculosis antibodies were tested using an enzyme-linked immunosorbent assay (ELISA) and agglutination test; anti–Salmonella enteritidis, anti–Salmonella typhimurium, and anti–Campylobacter jejuni antibodies antibodies were tested by ELISA. Stool samples tested for Yersinia, Salmonella, Shigella, and C jejuni using established cultural methods. Urogenital swabs were tested for the presence of C trachomatis, Chlamydia was cultured on McCoy cell monolayers, and inclusion bodies were identified by immunofluorescence-labelled anti-Chlamydia antibodies. A lymphocyte proliferation assay was performed, where synovial fluid samples were available, with the following heat-inactivated bacteria used as antigens: C trachomatis, Y enterocolitica and Y pseudotuberculosis, S enteritidis, S flexneri, and C jejuni. At months 1, 2, and 3, laboratory testing was carried out for side effects of treatment (complete blood cell count including platelets, gamma glutamyl transferase, serum glutamic oxaloacetic transaminase, alkaline phosphatase, serum creatinine and urinalysis). Clinical evaluation CRP and ESR were measured at months 0, 1, 2, 3, 6, and 12, along with the Articular Index score, patient's assessment of pain, patient's global assessment of health, physician's assessment of treatment success, and assessment for the presence/absence of remission. The Articular Index score assessed each affected joint separately for tenderness to pressure (0=not tender, 1=tender, 2=tender and the patient winced, 3=tender and the patient winced and withdrew), joint swelling (0=not swollen, 1=swollen, but swelling hardly visible, 2=clearly swollen, joint shape still visible, 3=swollen, joint shape no longer visible), and pain at rest (0=no pain; 1=pain). The three scores were added to give the articular index. Patient assessment of pain used a 0-10 visual analogue scale (VAS), as did patient global assessment of health. Statistical analysis The Cochran-Mantel-Haenszel test was used to assess the percentage of patients in remission and the percentage of patients with a 50% decrease in the Articular Index score. The other secondary efficacy variables were evaluated descriptively. Quantitative variables were analysed in a 3-way ANCOVA with pre-treatment values as covariates.
Missing data handling/loss to follow up	Only the results from the patients who were valid for clinical evaluation are presented. Patients were considered ineligible for analysis for the following reasons: treatment of less than 70 days (12 patients across whole study) lack of compliance (5 patients across whole study) concurrent treatment with a drug that was not permitted (5 patients across whole study)

<table>
<tr><th>Bibliographic reference</th><th>Sieper,J., Fendler,C., Laitko,S., Sorensen,H., Gripenberg-Lerche,C., Hiepe,F., Alten,R., Keitel,W., Groh,A., Uksila,J., Eggens,U., Granfors,K., Braun,J., No benefit of long-term ciprofloxacin treatment in patients with reactive arthritis and undifferentiated oligoarthritis: a three-month, multicenter, double-blind, randomized, placebo-controlled study, Arthritis and rheumatism, 42, 1386-1396, 1999</th></tr>
<tr><td>Results</td><td>Results were reported separately for reactive vs undifferentiated arthritis. There were also sub group analyses according to confirmed diagnosis of microbial infection. All patients confirmed as having either Yersinia or Salmonella infections had been classed at study outset as ReA patients, and this subgroup analysis is presented below. The patients who had a confirmation of C. trachomatis infection had a mixture of ReA and undifferentiated SpA diagnoses, so these results were excluded.

Joint count (all ReA patients)
Articular Index (joint tenderness, improvement from baseline) [ESTIMATED FROM GRAPH]
Ciprofloxacin: 3 months: 5; 6 months: 2.4; 12 months: 4.6
Placebo: 3 months: 4.6; 6 months: 6.2; 12 months: 7.3

Joint count (GI infection patients only)
Articular Index (joint tenderness, improvement from baseline) [ESTIMATED FROM GRAPH]
Ciprofloxacin: 3 months: 1.4 ; 6 months: 3.6; 12 months: 2.2 (4.5)
Placebo: 3 months: 3.6; 6 months: 5.8; 12 months: 6.75 (3.7)

Adverse events
Adverse events were not reported separately by indication. Across all study participants (ReA and undifferentiated) the adverse events were as follows:
Ciprofloxacin: mild abdominal symptoms=10, mild neurological symptoms=8, non-specific symptoms=2, granulocytopenia=1, other symptoms=7
Placebo: mild abdominal symptoms=14, mild neurological symptoms=5, non-specific symptoms=1, granulocytopenia=0, other symptoms=5</td></tr>
<tr><td>GI_painful/tender joints/arthralgia</td><td>GI_painful/tender joints/arthralgia<table><tr><td></td><td>Mean</td><td>SD</td><td>Total</td></tr><tr><td>Experimental</td><td>-2.20</td><td>4.50</td><td>14</td></tr><tr><td>Control</td><td>-6.75</td><td>3.70</td><td>25</td></tr></table></td></tr>
<tr><td>Painful/tender joints/arthralgia</td><td>Painful/tender joints/arthralgia</td></tr>
</table>

Bibliographic reference	**Sieper,J., Fendler,C., Laitko,S., Sorensen,H., Gripenberg-Lerche,C., Hiepe,F., Alten,R., Keitel,W., Groh,A., Uksila,J., Eggens,U., Granfors,K., Braun,J., No benefit of long-term ciprofloxacin treatment in patients with reactive arthritis and undifferentiated oligoarthritis: a three-month, multicenter, double-blind, randomized, placebo-controlled study, Arthritis and rheumatism, 42, 1386-1396, 1999**
	<table><tr><td></td><td>Mean</td><td>SD</td><td>Total</td></tr><tr><td>Experimental</td><td>-4.60</td><td>4.20</td><td>27</td></tr><tr><td>Control</td><td>-7.30</td><td>4.90</td><td>28</td></tr></table>
Overall Risk of Bias	Limited information available on randomisation, allocation and blinding, making it difficult to assess risk of bias in these domains. Some results were presented only as graphs, necessitating visual estimation of effect sizes, leading to a risk of error.
Other information	n/a
Was the allocation sequence adequately generated?	UNCLEAR
Was allocation adequately concealed?	UNCLEAR
Was knowledge of the allocated intervention adequately prevented during the study?	UNCLEAR
Were incomplete outcome data adequately addressed?	NO
Are reports of the study free of suggestion of selective outcome reporting?	YES
Was the study apparently free of other problems that could put it at a high risk of bias?	NO

Table 107: Toivanen et al 1993

Bibliographic reference	**Toivanen,A., Yli-Kerttula,T., Luukkainen,R., Merilahti-Palo,R., Granfors,K., Seppala,J., Effect of antimicrobial treatment on chronic reactive arthritis, Clinical & Experimental Rheumatology, 11, 301-307, 1993**
Country/ies where the study was carried out	Finland

Bibliographic reference	Toivanen,A., Yli-Kerttula,T., Luukkainen,R., Merilahti-Palo,R., Granfors,K., Seppala,J., Effect of antimicrobial treatment on chronic reactive arthritis, Clinical & Experimental Rheumatology, 11, 301-307, 1993
Study type	Randomised controlled trial
Aim of the study	To assess the effect of a three month course of ciprofloxacin on chronic reactive arthritis.
Study dates	Submitted 1992, published 1993
Source of funding	Sigrid Juseliux Foundation
Sample size	36 participants (17 Ciprofloxacin, 19 control)
Diagnostic criteria	No overall diagnostic criteria were reported. Many participants had had the triggering microbial organism identified.
Inclusion criteria	Patients at rheumatology units in Turku University Central hospital or Satalinna Hospital being treated for reactive arthritis
Exclusion criteria	Not reported
Characteristics	Ciprofloxacin (n=17) age, years (mean(range)): 43.4(22-64) Triggering microbe Yersinia, n: 15 Chlamydia, n: 2 Campylobacter, n: 0 ESR (mean, range)): 16.2(2-80) HLA-B27 positive, n: 9 Clinical diagnosis reactive arthritis, n: 13 Reiter's triad, n: 1 Arthralgia, n: 3 Disease duration, years (mean (range)): 4.8 (2 mo-14yr) Placebo (n=19)

Bibliographic reference	Toivanen,A., Yli-Kerttula,T., Luukkainen,R., Merilahti-Palo,R., Granfors,K., Seppala,J., Effect of antimicrobial treatment on chronic reactive arthritis, Clinical & Experimental Rheumatology, 11, 301-307, 1993
	age, years (mean(range)): 44.1(25-66) Triggering microbe Yersinia, n: 16 Chlamydia, n: 2 Campylobacter, n: 1 ESR (mean, range)): 22.4 (6-50) HLA-B27 positive, n: 13 Clinical diagnosis reactive arthritis, n: 16 Reiter's triad, n: 2 Arthralgia, n: 1 Disease duration, years (mean (range)): 4.9 (2 mo. - 16yr)
Interventions	Intervention 500mg Ciprofloxacin twice daily for 90 days Placebo Twice daily for 90 days
Randomisation, allocation, blinding	Randomisation by alternating numbers to one treatment arm or the other. The code was not broken until the end of the study. No further detail regarding blinding was provided.
Details	Laboratory measures Before treatment the following laboratory measures were taken: HLA-B27 antigen, ESR, CRP, haemoglobin, blood leukocyte count, leukocyte differential count, platelet count, alanine amino transferase, alkaline phosphatase, serum creatinine, Waaler-Rose test for rheumatoid factor, urine sediment analysis, stool culture. A serum sample was taken at each visit and stored; after study completion antibody titre was determined. Antibodies against Yersinia, Chlamydia and Campylobacter were measured using ELISA. Clinical measures Clinical investigator assessed patients for joint swelling and insertitis (pain on palpating, 0-3 scale). Each joint was assessed using the Ritchie Index, and the scores for each joint were summed. Patient's assessed their general condition, pain at rest, pain at movement, and morning stiffness using VAS (0-10) with a physician present. Statistical analysis ANOVA was used, with one grouping factor (treatment), and one repeated measures factor with 3 levels (0, 3, 9 months).

Bibliographic reference	Toivanen,A., Yli-Kerttula,T., Luukkainen,R., Merilahti-Palo,R., Granfors,K., Seppala,J., Effect of antimicrobial treatment on chronic reactive arthritis, Clinical & Experimental Rheumatology, 11, 301-307, 1993
Missing data handling/loss to follow up	One patient in the ciprofloxacin group withdrew due to adverse effects of treatment.
Results	Joint count Joint swelling, 0-3 scale (mean(SD)): Ciprofloxacin: baseline: 2.71(4.15); 3 months: 1.35(2.67); last assessment: 1.47(1.97) Placebo: baseline: 1.26(2.08); 3 months: 0.63(2.09); last assessment: 1.16(1.86) Pain Pain at movement, linear 0-10 scale (mean(SD)): Ciprofloxacin: baseline: 5.41(2.32); 3 months: 4.18(2.60); last assessment: 3.76(2.61) Placebo: baseline: 5.42(2.89); 3 months: 3.95(2.82); last assessment: 4.16(2.99) Arthralgia, linear 0-10 scale (mean(SD)): Ciprofloxacin: baseline: 5.0(2.65); 3 months: 3.67(2.66); last assessment: 3.24(2.46) Placebo: baseline: 3.0(1.97); 3 months: 2.63(2.56); last assessment: 2.84(2.95) Morning stiffness, linear 0-10 scale (mean(SD)): Ciprofloxacin: baseline: 5.12(3.08); 3 months: 4.24(2.73); last assessment: 2.94(2.68) Placebo: baseline: 3.53(2.93); 3 months: 3.05(3.01); last assessment: 3.0(3.20) Inflammatory markers ESR, no units given (mean(SD)): Ciprofloxacin: baseline: 16.24(17.33); 3 months: 14.88(18.88); last assessment: 14.13(13.20) Placebo: baseline: 22.37(14.20); 3 months: 21.32(16.16); last assessment: 19.38(11.93) CRP, no units given (mean(SD)): Ciprofloxacin: baseline: 11.5(6.00); 3 months: 10.47(1.33); last assessment: 10.2(0.77) Placebo: baseline: 14.11(10.11); 3 months: 15.26(10.79); last assessment: 17.27(15.60) Adverse events Ciprofloxacin: 1 patient rash, leading to study discontinuation; 1 patient with malaise, leading to interruption of treatment for 2 weeks Placebo: authors report that none were detected
Swollen joints	Swollen joints

Bibliographic reference	Toivanen,A., Yli-Kerttula,T., Luukkainen,R., Merilahti-Palo,R., Granfors,K., Seppala,J., Effect of antimicrobial treatment on chronic reactive arthritis, Clinical & Experimental Rheumatology, 11, 301-307, 1993
	<table><tr><td></td><td>Mean</td><td>SD</td><td>Total</td></tr><tr><td>Experimental</td><td>-1.24</td><td>4.15</td><td>17</td></tr><tr><td>Control</td><td>-0.10</td><td>4.15</td><td>19</td></tr></table>
Painful/tender joints/arthralgia	Painful/tender joints/arthralgia <table><tr><td></td><td>Mean</td><td>SD</td><td>Total</td></tr><tr><td>Experimental</td><td>-1.76</td><td>2.95</td><td>17</td></tr><tr><td>Control</td><td>-0.16</td><td>2.95</td><td>19</td></tr></table>
ESR	ESR <table><tr><td></td><td>Mean</td><td>SD</td><td>Total</td></tr><tr><td>Experimental</td><td>-2.11</td><td>17.33</td><td>17</td></tr><tr><td>Control</td><td>-2.99</td><td>17.33</td><td>19</td></tr></table>
CRP	CRP <table><tr><td></td><td>Mean</td><td>SD</td><td>Total</td></tr><tr><td>Experimental</td><td>-1.30</td><td>15.60</td><td>17</td></tr><tr><td>Control</td><td>3.16</td><td>15.60</td><td>19</td></tr></table>
Pain (general)	Pain (general)

Bibliographic reference	**Toivanen,A., Yli-Kerttula,T., Luukkainen,R., Merilahti-Palo,R., Granfors,K., Seppala,J., Effect of antimicrobial treatment on chronic reactive arthritis, Clinical & Experimental Rheumatology, 11, 301-307, 1993**
	<table><tr><td></td><td>Mean</td><td>SD</td><td>Total</td></tr><tr><td>Experimental</td><td>-1.65</td><td>2.99</td><td>17</td></tr><tr><td>Control</td><td>-1.26</td><td>2.99</td><td>19</td></tr></table>
Stiffness	Stiffness <table><tr><td></td><td>Mean</td><td>SD</td><td>Total</td></tr><tr><td>Experimental</td><td>-2.18</td><td>3.20</td><td>17</td></tr><tr><td>Control</td><td>-0.53</td><td>3.20</td><td>19</td></tr></table>
Overall Risk of Bias	Patient population contains 3 people in the antibiotic arm and 1 in the placebo arm who were described as having arthralgia rather than ReA or Reiter's triad. In the absence of reporting of diagnostic criteria, however, it is unclear whether these participants might have been classified as having ReA in another study.
Other information	n/a
Was the allocation sequence adequately generated?	UNCLEAR
Was allocation adequately concealed?	UNCLEAR
Was knowledge of the allocated intervention adequately prevented during the study?	YES
Were incomplete outcome data adequately addressed?	YES

Bibliographic reference	Toivanen,A., Yli-Kerttula,T., Luukkainen,R., Merilahti-Palo,R., Granfors,K., Seppala,J., Effect of antimicrobial treatment on chronic reactive arthritis, Clinical & Experimental Rheumatology, 11, 301-307, 1993
Are reports of the study free of suggestion of selective outcome reporting?	YES
Was the study apparently free of other problems that could put it at a high risk of bias?	YES

Table 108: Wakefield et al 1999

Bibliographic reference	Wakefield,D., McCluskey,P., Verma,M., Aziz,K., Gatus,B., Carr,G., Ciprofloxacin treatment does not influence course or relapse rate of reactive arthritis and anterior uveitis, Arthritis & Rheumatism, 42, 1894-1897, 1999
Country/ies where the study was carried out	Australia
Study type	Randomised controlled trial
Aim of the study	To assess the efficacy of ciprofloxacin in the treatment of reactive arthritis (and anterior uveitis (AU)).
Study dates	Submitted 1998, published 1999
Source of funding	Bayer Australia Pty. Ltd.
Sample size	In total there were 72 participants of whom 56 had ReA, 42 had anterior uveitis (26 had both)
Diagnostic criteria	Not stated
Inclusion criteria	Patients meeting published criteria for reactive arthritis and/or anterior uveitis. Other inclusion criteria were not stated.
Exclusion criteria	Exclusion criteria were not stated.
Characteristics	Characteristics across whole study population: Ciprofloxacin (n=38)

Bibliographic reference	Wakefield,D., McCluskey,P., Verma,M., Aziz,K., Gatus,B., Carr,G., Ciprofloxacin treatment does not influence course or relapse rate of reactive arthritis and anterior uveitis, Arthritis & Rheumatism, 42, 1894-1897, 1999
	Reactive arthritis only, n: 16 anterior uveitis only, n: 9 reactive arthritis and anterior uveitis, n: 13 Total no. with reactive arthritis: 29 female, n: 9 HLA-B27 positive, n: 23 Placebo (n=34) Reactive arthritis only, n: 14 anterior uveitis only, n: 7 reactive arthritis and anterior uveitis, n: 13 Total no. with reactive arthritis: 27 female, n: 11 HLA-B27 positive, n: 23
Interventions	Ciprofloxacin (750mg twice a day) or placebo for 12 months
Randomisation, allocation, blinding	Randomisation was stratified on HLA-B27 phenotype. Assignment code for patients was not broken until the end of the study.
Details	Patient assessment Patients were assessed at enrolment, on at least 3 occasions during the 12 months of therapy and at least 3 occasions during the 12 months of follow up. At baseline, participants were tested for present of HLA-B27 antigen; complete blood cell count; liver function test; ESR; urinalysis; serum levels of urea, electrolytes and creatinine; stool culture; rectal swabs and urethral or cervical swabs. Participants with uveitis were examined by an ophthalmologist at each clinic visit. ReA symptoms were assessed by a physician at baseline and each clinic visit. A symptom score was used comprising number of joints involved as well as the following measures graded on a 0-3 scale: amount of swelling, pain and morning stiffness, limitation of movement. Statistical analysis Analysis was carried out separately for people with ReA and those with AU (with the patients who had both conditions included in both analyses). Time to first relapse assessed with Kaplan-Meier curves and log rank statistics. Non-parametric (Wilcoxon's 2-tailed test) was used to compare the changes in the 2 treatment groups.
Missing data handling/loss to follow up	Analysis was conducted on both the intention to treat population and the efficacy population (patients listed as compliant, as assessed by a physician).

<table>
<tr><th>Bibliographic reference</th><th>Wakefield,D., McCluskey,P., Verma,M., Aziz,K., Gatus,B., Carr,G., Ciprofloxacin treatment does not influence course or relapse rate of reactive arthritis and anterior uveitis, Arthritis & Rheumatism, 42, 1894-1897, 1999</th></tr>
<tr><td></td><td>Patients withdrew for the following reasons (across whole study):
non-compliance (6 ciprofloxacin, 8 placebo)
loss to follow up (1 in ciprofloxacin, 3 placebo)
patient request to withdraw (6 ciprofloxacin, 8 placebo)</td></tr>
<tr><td>Results</td><td>Joint Count
Joint score (composite measure) (mean(sd))
Ciprofloxacin: baseline: 10.7(11.9); 6 months: 3.44(3.34); change from baseline to 6 months: -7.74(12.95)
Placebo: baseline: 11.26(14.2); 6 months: 5.32(6.08); change from baseline to 6 months: -6.68(11.68)

Adverse events
3 patients were reported to have withdrawn due to adverse events in the placebo group. It is not clear whether these were patients with reactive arthritis, or anterior uveitis only.</td></tr>
<tr><td>Painful/tender joints/arthralgia</td><td>Painful/tender joints/arthralgia
<table>
<tr><td></td><td>Mean</td><td>SD</td><td>Total</td></tr>
<tr><td>Experimental</td><td>-7.74</td><td>12.95</td><td>27</td></tr>
<tr><td>Control</td><td>-6.68</td><td>11.68</td><td>22</td></tr>
</table></td></tr>
<tr><td>Overall Risk of Bias</td><td>Intervention duration was 12 months with an additional 12 months of follow up but table results were only reported as far as 6 months post-baseline. Aside from time to relapse, results for reactive arthritis patients were only presented on the efficacy population, rather than intention to treat.</td></tr>
<tr><td>Other information</td><td>n/a</td></tr>
<tr><td>Was the allocation sequence adequately generated?</td><td>UNCLEAR</td></tr>
<tr><td>Was allocation adequately concealed?</td><td>UNCLEAR</td></tr>
<tr><td>Was knowledge of the allocated intervention adequately prevented during the study?</td><td>YES</td></tr>
</table>

Bibliographic reference	Wakefield,D., McCluskey,P., Verma,M., Aziz,K., Gatus,B., Carr,G., Ciprofloxacin treatment does not influence course or relapse rate of reactive arthritis and anterior uveitis, Arthritis & Rheumatism, 42, 1894-1897, 1999
Were incomplete outcome data adequately addressed?	NO
Are reports of the study free of suggestion of selective outcome reporting?	NO
Was the study apparently free of other problems that could put it at a high risk of bias?	UNCLEAR

Table 109: Whaley et al. 1969

Bibliographic reference	Whaley,K., Downie,W.W., Dick,W.C., Nuki,G., Schofield,C.B., Anderson,J., Clinical trial of lincomycin hydrochloride in Reiter's disease, British Medical Journal, 2, 421-422, 1969
Country/ies where the study was carried out	UK
Study type	Randomised controlled trial
Aim of the study	To assess the effectiveness of lincomycin hydrochloride in the treatment of Reiter's Disease
Study dates	Not reported. Published 1969
Source of funding	Arthritis and Rheumatism Council for Research (UK); study medications provided by Boots Pure Drug Company; additional personal funding of one investigator by CIBA clinical research fellowship.
Sample size	22 patients
Diagnostic criteria	Specific criteria were not reported. All were seronegative for rheumatoid factor and had no radiologic evidence of bony erosion.
Inclusion criteria	Not reported
Exclusion criteria	Not reported
Characteristics	Lyncomycin group (n=11) age, years (mean(range)): 25.5 (18-32) duration of disease (mean (range)): 1 year (1 week-5 years) articular index (mean (range)): 17.8 (3-46) urethritis (n): 7 balanitis (n): 6 conjunctivitis (n): 4

Bibliographic reference	Whaley,K., Downie,W.W., Dick,W.C., Nuki,G., Schofield,C.B., Anderson,J., Clinical trial of lincomycin hydrochloride in Reiter's disease, British Medical Journal, 2, 421-422, 1969
	oral lesions (n): 4 keratodermia blenorrhagica (n): 2 nail changes (n): 4 white cell count, cu.mm (mean (range)): 9,880 (6,500-15,800) ESR Westergreen mm/1st hour (mean (range)): 66.2 (27-123) Placebo group (n=11) age, years (mean(range)): 31.9 (20-52) duration of disease (mean (range)): 1.4 years (1 week-10 years) articular index (mean (range)): 19.8 (0-43) urethritis (n): 10 balanitis (n): 5 conjunctivitis (n): 9 oral lesions (n): 1 keratodermia blenorrhagica (n): 3 nail changes (n): 3 white cell count, cu.mm (mean (range)): 9,670 (6,300-13,500) ESR Westergreen mm/1st hour (mean (range)): 59.7 (2-122)
Interventions	Intervention group: lincomycin hydrochloride 2g/day for 4 weeks Placebo group: identical capsules containing lactose for 4 weeks
Randomisation, allocation, blinding	Alternate patients were allocated treatment or placebo. Study described as 'double blind'. Clinical measures were made by a physician who was unaware of treatment allocation.
Details	Participants were examined clinically at baseline and twice weekly during the duration of therapy. Measurements were collected on articular index, joint tenderness (Ritchie et al, 1968), ESR, white blood cell count and presence of urethritis, circinate balanitis, keratodermia blenorrhagica, nail changes, oral ulceration and conjunctivitis.
Missing data handling/loss to follow up	No loss to follow up or missing data reported.
Results	Inflammatory markers (ESR) mean (SE) fall per week, relative to baseline Lincomycin: week 1: 9.20 (1.003); week 2: 7.457(1.212); week 3: 6.300 (1.362); week 4: 6.950 (1.586) Placebo: week 1: 9.35(1.441); week 2: 7.986(2.139); week 3: 6.429(1.623); week 4: 5.300 (1.125)

<table>
<tr><th>Bibliographic reference</th><th>Whaley,K., Downie,W.W., Dick,W.C., Nuki,G., Schofield,C.B., Anderson,J., Clinical trial of lincomycin hydrochloride in Reiter's disease, British Medical Journal, 2, 421-422, 1969</th></tr>
<tr><td></td><td>Articular index
Ritchie index (tenderness) mean (SE) fall per week, relative to baseline
Lincomycin: week 1: 7.564(1.218); week 2: 8.818(2.100); week 3: 4.491(1.510); week 4: 3.218(1.417)
Placebo: week 1: 5.689(1.054); week 2: 5.144(1.691); week 3: 4.511(1.641); week 4: 4.394(1.362)

Adverse Events
None reported</td></tr>
<tr><td>Painful/tender joints/arthralgia</td><td>Painful/tender joints/arthralgia<table><tr><td></td><td>Mean</td><td>SD</td><td>Total</td></tr><tr><td>Experimental</td><td>-3.20</td><td>4.70</td><td>11</td></tr><tr><td>Control</td><td>-4.39</td><td>4.51</td><td>11</td></tr></table></td></tr>
<tr><td>ESR</td><td>ESR<table><tr><td></td><td>Mean</td><td>SD</td><td>Total</td></tr><tr><td>Experimental</td><td>-6.95</td><td>5.26</td><td>11</td></tr><tr><td>Control</td><td>-5.30</td><td>3.73</td><td>11</td></tr></table></td></tr>
<tr><td>Overall Risk of Bias</td><td>Brief report, lacking in detail on various aspects of study design. Bias likely to arise from allocating treatment or placebo to alternate participants.

Various clinical measures were made but most were not reported numerically as there was 'no change noted'.</td></tr>
<tr><td>Other information</td><td>n/a</td></tr>
<tr><td>Was the allocation sequence adequately generated?</td><td>NO</td></tr>
</table>

Bibliographic reference	Whaley,K., Downie,W.W., Dick,W.C., Nuki,G., Schofield,C.B., Anderson,J., Clinical trial of lincomycin hydrochloride in Reiter's disease, British Medical Journal, 2, 421-422, 1969
Was allocation adequately concealed?	NO
Was knowledge of the allocated intervention adequately prevented during the study?	UNCLEAR
Were incomplete outcome data adequately addressed?	YES
Are reports of the study free of suggestion of selective outcome reporting?	NO
Was the study apparently free of other problems that could put it at a high risk of bias?	YES

Table 110: Yli-Kerttula et al., 2000

Bibliographic reference	Yli-Kerttula,T., Luukkainen,R., Yli-Kerttula,U., Mottonen,T., Hakola,M., Korpela,M., Sanila,M., Parviainen,J., Uksila,J., Vainionpaa,R., Toivanen,A., Effect of a three month course of ciprofloxacin on the outcome of reactive arthritis, Annals of the Rheumatic Diseases, 59, 565-570, 2000
Country/ies where the study was carried out	Finland
Study type	(Multicentre) randomised controlled trial
Aim of the study	To evaluate the effect of a three month course of ciprofloxacin on ReA
Study dates	Accepted and published 2000
Source of funding	Emil Aaltonen foundation and the EVO grant of Turku University Central Hospital. Bayer Finland Oy provided the ciprofloxacin used in the study, and supported the statistical analysis.
Sample size	71 patients recruited (36 in antibiotic group, 35 in placebo)
Diagnostic criteria	ReA diagnosed if patients presented with a clinical picture of an asymmetrical arthritis and symptomatic enteritis or urethritis a few days to a few weeks before the onset of arthritis.
Inclusion criteria	Aged 18 or over Outpatients or inpatients at one of the study hospitals

Bibliographic reference	Yli-Kerttula,T., Luukkainen,R., Yli-Kerttula,U., Mottonen,T., Hakola,M., Korpela,M., Sanila,M., Parviainen,J., Uksila,J., Vainionpaa,R., Toivanen,A., Effect of a three month course of ciprofloxacin on the outcome of reactive arthritis, Annals of the Rheumatic Diseases, 59, 565-570, 2000
	clinically evident acute ReA
Exclusion criteria	pregnancy, lactation, or women in whom pregnancy could not be ruled out patients requiring concomitant antimicrobial treatment for more than 10 days during or before the study patients receiving anti-rheumatic drugs or systemic steroids patients with other inflammatory joint diseases.
Characteristics	The following patients were eligible for efficacy and safety analysis: Ciprofloxacin (n=30) age, years (mean(sd)): 37.1(13.4) duration of disease, days (mean(sd)): 39(27) female, n: 13 swollen joints, (mean(sd)): 3.7(1.8) joint tenderness score, Ritchie index (mean(sd)): 6.7(3.3) joint swelling score (mean(sd)): 5.5(2.7) morning stiffness, mins (mean(sd)): 48(29) ESR, mm/1st h (mean(sd)): 55(28) CRP, mg/l (mean(sd)): 67(56) HB, g/l (mean(sd)): 130(14) Leucocytes (10^9/l) (mean(sd)): 8.9(2.1) HLA-B27 positive (%): 22(73) Placebo (n=32) age, years (mean(sd)): 35.7(11.2) duration of disease, days (mean(sd)): 52(69) female, n: 14 swollen joints, n: 3.3 (1.6) joint tenderness score, Ritchie index (mean(sd)): 5.9(2.9) joint swelling score (mean(sd)): 5.1(2.9) morning stiffness, mins (mean(sd)): 49(28) ESR, mm/1st h (mean(sd)): 67(26) CRP, mg/l (mean(sd)): 52(40)

Bibliographic reference	Yli-Kerttula,T., Luukkainen,R., Yli-Kerttula,U., Mottonen,T., Hakola,M., Korpela,M., Sanila,M., Parviainen,J., Uksila,J., Vainionpaa,R., Toivanen,A., Effect of a three month course of ciprofloxacin on the outcome of reactive arthritis, Annals of the Rheumatic Diseases, 59, 565-570, 2000
	HB, g/l (mean(sd)): 123(15) Leucocytes (10^9/l) (mean(sd)): 8.9(2.3) HLA-B27 positive (%): 27(84)
Interventions	Ciprofloxacin 500mg orally twice daily for 3 months Placebo Identical looking placebo orally twice daily for 3 months Patients were allowed to continue or receive other drugs except DMARDs or immunosuppressive drugs. Concomitant treatment with an appropriate other antimicrobial drug, if needed, was allowed for up to 10 days (patients were excluded if this continued for more than 10 days). Antacids containing aluminium or bismuth were allowed to be taken only if they were given two hours before or after the test drug administration. All concomitant drugs were identified and recorded in the case report form at each visit.
Randomisation, allocation, blinding	Study described as randomised, double blind, controlled trial. No further detail was given regarding randomisation, allocation or blinding.
Details	Clinical measures Patients were assessed at study entry, at 6 weeks, 3 months, 6 months, and 12 months for the following: Ritchie articular index number and scoring of swollen joints duration of morning stiffness global assessment (100 mm VAS) articular pain at movement (100 mm VAS) articular pain at rest (100 mm VAS) difficulty of movement and severity of morning stiffness (100 mm VAS) overall improvement as evaluated (100 mm VAS) Laboratory measures HLA-B27 typing At each visit: ESR, CRP, blood Hb concentration, white blood cell count, thrombocyte count, serum antibody titres against triggering microbe, urine analysis Serum antibodies against salmonella, yersinia and campylobacter were determined by immunoassay.

Bibliographic reference	Yli-Kerttula,T., Luukkainen,R., Yli-Kerttula,U., Mottonen,T., Hakola,M., Korpela,M., Sanila,M., Parviainen,J., Uksila,J., Vainionpaa,R., Toivanen,A., Effect of a three month course of ciprofloxacin on the outcome of reactive arthritis, Annals of the Rheumatic Diseases, 59, 565-570, 2000
	synovial fluid from swollen joints was assessed, as were faecal samples at start of study. Radiography Sacroiliac joints if patient had chronic lower back pain; peripheral joints in cases of severe, prolonged joint swelling Statistical analysis Descriptive statistics (mean, standard deviation, range, median, frequency counts and percentages). Outcome variables analysed with ANOVA with repeat measures. Complete recovery was treated as the end point in a Kaplan-Meier survival analysis. The differences between the survival curves for each treatment were analysed using log rank statistics. All tests were evaluated as two sided with $p<0.05$. significant difference between the treatment groups
Missing data handling/loss to follow up	Patient's participation was terminated if there was an interruption in therapy of more than two weeks, less than 85% of medication was taken, the participant experienced severe side effects, was reluctant to continue, or had medical or surgical conditions which required removal from the study. An intention to treat analysis was carried out.
Results	Joint count Number of swollen joints [ESTIMATED FROM GRAPHS] Ciprofloxacin (n=30): baseline: 3.75(0.35); 1.5mo: 2.15(0.45); 3mo: 1.65(0.45); 6mo: 0.8(0.4); 12mo: 0.6(0.3) Placebo (n=32): baseline: 3.3(0.35); 1.5mo: 1.85(0.3); 3mo: 0.8(0.25); 6mo: 0.3(0.1); 12mo: 0.4(0.1) Inflammatory markers ESR (mm/1st h), (mean(SE)) [ESTIMATED FROM GRAPHS] Ciprofloxacin (n=30): baseline: 55.5 (5.8); 1.5mo: 38.0(5.5); 3mo: 23.5(4.5); 6mo: 9.5 (1.5); 12mo: 10.5 (1.5) Placebo (n=32): baseline: 67.5 (5.5); 1.5mo: 34.0(5.0); 3mo: 18(4.0); 6mo: 12.5 (2.5); 12mo: 11.5 (1.5) Adverse events The number of adverse events per group was as follows: Ciprofloxacin (n=36): Abdominal=14, infections=11 (bacterial=1, viral=8, other infections=2), nervous system=5, skin reactions=3, miscellaneous=7 Placebo (n=35): Abdominal=8, infections=14 (bacterial=6, viral=5, other infections=3), nervous system=2, skin reactions=4, miscellaneous=6

<table>
<tr><th>Bibliographic reference</th><th>Yli-Kerttula,T., Luukkainen,R., Yli-Kerttula,U., Mottonen,T., Hakola,M., Korpela,M., Sanila,M., Parviainen,J., Uksila,J., Vainionpaa,R., Toivanen,A., Effect of a three month course of ciprofloxacin on the outcome of reactive arthritis, Annals of the Rheumatic Diseases, 59, 565-570, 2000</th></tr>
<tr><td>Swollen joints</td><td>Swollen joints<table><tr><td></td><td>Mean</td><td>SD</td><td>Total</td></tr><tr><td>Experimental</td><td>-3.15</td><td>2.46</td><td>30</td></tr><tr><td>Control</td><td>-2.90</td><td>2.55</td><td>32</td></tr></table></td></tr>
<tr><td>ESR</td><td>ESR<table><tr><td></td><td>Mean</td><td>SD</td><td>Total</td></tr><tr><td>Experimental</td><td>-45.00</td><td>31.77</td><td>30</td></tr><tr><td>Control</td><td>-56.00</td><td>32.80</td><td>32</td></tr></table></td></tr>
<tr><td>Overall Risk of Bias</td><td>Lack of detail on randomisation, allocation and blinding makes it difficult to assess risk of bias in these areas. Some results were estimated from graphs leading to potential for bias.</td></tr>
<tr><td>Other information</td><td>n/a</td></tr>
<tr><td>Was the allocation sequence adequately generated?</td><td>UNCLEAR</td></tr>
<tr><td>Was allocation adequately concealed?</td><td>UNCLEAR</td></tr>
<tr><td>Was knowledge of the allocated intervention adequately prevented during the study?</td><td>UNCLEAR</td></tr>
<tr><td>Were incomplete outcome data adequately addressed?</td><td>YES</td></tr>
</table>

Bibliographic reference	Yli-Kerttula,T., Luukkainen,R., Yli-Kerttula,U., Mottonen,T., Hakola,M., Korpela,M., Sanila,M., Parviainen,J., Uksila,J., Vainionpaa,R., Toivanen,A., Effect of a three month course of ciprofloxacin on the outcome of reactive arthritis, Annals of the Rheumatic Diseases, 59, 565-570, 2000
Are reports of the study free of suggestion of selective outcome reporting?	NO
Was the study apparently free of other problems that could put it at a high risk of bias?	YES

Table 111: Putschky et al., 2006

Bibliographic reference	Putschky,N., Pott,H.G., Kuipers,J.G., Zeidler,H., Hammer,M., Wollenhaupt,J., Comparing 10-day and 4-month doxycycline courses for treatment of Chlamydia trachomatis-reactive arthritis: a prospective, double-blind trial, Annals of the rheumatic diseases, 65, 1521-1524, 2006
Country/ies where the study was carried out	Germany
Study type	Randomised controlled trial
Aim of the study	To compare the efficacy of a 10-day and 4 month doxycycline course for the treatment of Chlamydia trachomatis-reactive arthritis (Ct-ReA
Study dates	Conducted 1990 to 1994. Published 2006
Source of funding	Doxycycline(Vibramycin) provided by Pfizer
Sample size	37 patients recruited; 32 completed and analysed
Diagnostic criteria	At least one tender and swollen joint not explained by another rheumatological condition. Evidence of urogenital infection with C trachomatis (either immunofluorescence detection OR clinical symptoms plus raised anti-chlamydial antibodies).
Inclusion criteria	aged 18 to 65 presenting for the first time and diagnosed with active Ct-ReA
Exclusion criteria	pregnant women doxycycline or tetracycline intolerance
Characteristics	Doxycycline (n=17) age, years (mean(sd)): 42.6(13.7) female, n: 9 duration of disease (range): 17.1 (2-42) history of urinogenital infection (months): 8

Bibliographic reference	**Putschky,N., Pott,H.G., Kuipers,J.G., Zeidler,H., Hammer,M., Wollenhaupt,J., Comparing 10-day and 4-month doxycycline courses for treatment of Chlamydia trachomatis-reactive arthritis: a prospective, double-blind trial, Annals of the rheumatic diseases, 65, 1521-1524, 2006**
	Urinogenital detection of chlamydia, n: 11 inflammatory lower back pain, n: 7 of 14 enthesopathy, n: 4 of 13 HLA-B27 positive, n: 3 of 9 Placebo (n=15) age, years (mead(sd)): 40.5(12.11) female, n: 8 duration of disease (range): 16.0(5-49) history of urinogenital infection (months): 10 Urinogenital detection of chlamydia, n: 12 inflammatory lower back pain, n: 4/11 enthesopathy, n: 2/11 HLA-B27 positive, n: 8/15
Interventions	Doxycycline 100mg twice daily for 4 months Placebo Identical capsules twice daily for 4 months Participants in both groups (and their sexual partners) received a 10 day course of doxycycline (100mg twice daily) prior to the study start. DMARDs, or intra-articular or systemic corticosteroids were not permitted 2 weeks before baseline or during the study.
Randomisation, allocation, blinding	Study described as double blind; no further detail of blinding was presented. Patients were randomly assigned in blocks of 10 to either treatment arm.
Details	Patients were clinically evaluated at baseline and end of study. Measurements were taken on patient global assessment, intensity of pain (both VAS), during of morning stiffness and fatigue (mins), number of tender joints and number of swollen joints (denominator/scale not specified). Prior to study start, first void urine samples or genitourinary smears of the cervix and urethra in women and urethral smears in men were taken. Smears considered +ve if >7 inclusion bodies identified. ESR and CRP (plus IgA and IgG antibodies to C trachomatis) were measured at baseline and end of study. HLA-B27 tests were available in a subset of patients (n=24) Statistical analysis Sample size calculation (16 patients per group) assumed rate of spontaneous remission not >25% in patients with >6

Bibliographic reference	Putschky,N., Pott,H.G., Kuipers,J.G., Zeidler,H., Hammer,M., Wollenhaupt,J., Comparing 10-day and 4-month doxycycline courses for treatment of Chlamydia trachomatis-reactive arthritis: a prospective, double-blind trial, Annals of the rheumatic diseases, 65, 1521-1524, 2006
	months disease duration, rate of prolonger antibiotic treatment of at least 75% alpha-error of 0.05 and statistical power of 80%. Chi-squared tests (with Yate's correction), Fisher's exact test or t-test for unmatched pairs, or the Mann-Whitney U test were used on baseline characteristics. Before- and after- comparisons were made using t-test for matched pairs and the Mann-Whitney U test. The Bonferroni adjustment for multiple testing was used.
Missing data handling/loss to follow up	5 patients did not complete the study (2 lost to follow up, 1 withdrew consent to participate, 2 had diagnosis changed).
Results	Joint count Swollen joints Doxycycline (4 months treatment): baseline: 2.5; end: 1.9; change (sd): -0.6(1.7) Placebo (+10 days pre-trial doxy treatment): baseline: 2.8; end: 0.8; change (sd): -2.1(1.7) Tender joints Doxycycline (4 months treatment): baseline: 2.3; end: 2.4; change (sd): 0.1(1.8) Placebo (+10 days pre-trial doxy treatment): baseline: 3.8; end: 1.7; change (sd): -2.2(2.2) Inflammatory markers ESR (mm at end of first hour) Doxycycline (4 months treatment): baseline: 21; end: 14; change (sd): -7(14) Placebo (+10 days pre-trial doxy treatment): baseline: 25; end: 11; change (sd): -14(18) CRP (mg/l) Doxycycline (4 months treatment): baseline: 1.5; end: 0.9; change (sd): -0.8(2.3) Placebo (+10 days pre-trial doxy treatment): baseline: 2.9; end: 0.7; change (sd): -2.1(3.0) Pain Pain intensity (VAS, 0-10) Doxycycline (4 months treatment): baseline: 4.5; end: 3.1; change (sd): -1.1(2.6) Placebo (+10 days pre-trial doxy treatment): baseline: 4.8; end: 2.3; change (sd): -2.5(2.1) Morning stiffness (min) Doxycycline (4 months treatment): baseline: 72; end: 48; change (sd): -17(73) Placebo (+10 days pre-trial doxy treatment): baseline: 48; end: 19; change (sd): -33(50) Fatigue Fatigue intensity (min)

<table>
<tr><th>Bibliographic reference</th><th>Putschky,N., Pott,H.G., Kuipers,J.G., Zeidler,H., Hammer,M., Wollenhaupt,J., Comparing 10-day and 4-month doxycycline courses for treatment of Chlamydia trachomatis-reactive arthritis: a prospective, double-blind trial, Annals of the rheumatic diseases, 65, 1521-1524, 2006</th></tr>
<tr><td></td><td>Doxycycline (4 months treatment): baseline: 144; end: 81; change (sd): -21(45)
Placebo (+10 days pre-trial doxy treatment): baseline: 188; end: 140; change (sd): -61(262)

Adverse events
No adverse events were reported. Article states that no drop outs were due to adverse events but does not state whether any occurred</td></tr>
<tr><td>UG_swollen joints</td><td>UG_swollen joints<table><tr><td></td><td>Mean</td><td>SD</td><td>Total</td></tr><tr><td>Experimental</td><td>-0.60</td><td>1.70</td><td>17</td></tr><tr><td>Control</td><td>-2.10</td><td>1.70</td><td>15</td></tr></table></td></tr>
<tr><td>UG_painful/tender joints/arthralgia</td><td>UG_painful/tender joints/arthralgia<table><tr><td></td><td>Mean</td><td>SD</td><td>Total</td></tr><tr><td>Experimental</td><td>0.10</td><td>1.80</td><td>17</td></tr><tr><td>Control</td><td>-2.20</td><td>2.20</td><td>15</td></tr></table></td></tr>
<tr><td>UG_Fatigue</td><td>UG_Fatigue<table><tr><td></td><td>Mean</td><td>SD</td><td>Total</td></tr><tr><td>Experimental</td><td>-21.00</td><td>45.00</td><td>17</td></tr></table></td></tr>
</table>

Bibliographic reference	Putschky,N., Pott,H.G., Kuipers,J.G., Zeidler,H., Hammer,M., Wollenhaupt,J., Comparing 10-day and 4-month doxycycline courses for treatment of Chlamydia trachomatis-reactive arthritis: a prospective, double-blind trial, Annals of the rheumatic diseases, 65, 1521-1524, 2006
	Control | -61.00 | 262.00 | 15
UG_pain (general)	UG_pain (general) Experimental | -1.10 | 2.60 | 17 Control | -2.50 | 2.10 | 15
UG_morning stiffness	UG_morning stiffness Experimental | -17.00 | 73.00 | 17 Control | -33.00 | 50.00 | 15
UG_CRP	UG_CRP Experimental | -0.80 | 2.30 | 17 Control | -2.10 | 3.00 | 15

Bibliographic reference	Putschky,N., Pott,H.G., Kuipers,J.G., Zeidler,H., Hammer,M., Wollenhaupt,J., Comparing 10-day and 4-month doxycycline courses for treatment of Chlamydia trachomatis-reactive arthritis: a prospective, double-blind trial, Annals of the rheumatic diseases, 65, 1521-1524, 2006
UG_ESR	
Swollen joints	
Painful/tender joints/arthralgia	
ESR	

	Mean	SD	Total
Experimental	-7.00	14.00	17
Control	-14.00	18.00	15

	Mean	SD	Total
Experimental	-0.60	1.70	17
Control	-2.10	1.70	15

	Mean	SD	Total
Experimental	0.10	1.80	17
Control	-2.20	2.20	15

	Mean	SD	Total
Experimental	-7.00	14.00	17
Control	-14.00	18.00	15

Bibliographic reference	Putschky,N., Pott,H.G., Kuipers,J.G., Zeidler,H., Hammer,M., Wollenhaupt,J., Comparing 10-day and 4-month doxycycline courses for treatment of Chlamydia trachomatis-reactive arthritis: a prospective, double-blind trial, Annals of the rheumatic diseases, 65, 1521-1524, 2006
CRP	
Pain (general)	
Stiffness	
Fatigue	

	Mean	SD	Total
Experimental	-0.80	2.30	17
Control	-2.10	3.00	15

	Mean	SD	Total
Experimental	-1.10	2.60	17
Control	-2.50	2.10	15

	Mean	SD	Total
Experimental	-17.00	73.00	17
Control	-33.00	50.00	15

	Mean	SD	Total
Experimental	-21.00	45.00	17
Control	-61.00	262.00	15

Bibliographic reference	Putschky,N., Pott,H.G., Kuipers,J.G., Zeidler,H., Hammer,M., Wollenhaupt,J., Comparing 10-day and 4-month doxycycline courses for treatment of Chlamydia trachomatis-reactive arthritis: a prospective, double-blind trial, Annals of the rheumatic diseases, 65, 1521-1524, 2006
Overall Risk of Bias	Some lack of detail on treatment allocation strategy and maintenance of blinding means that assessment of risk of bias is partially restricted.
Other information	n/a
Was the allocation sequence adequately generated?	UNCLEAR
Was allocation adequately concealed?	UNCLEAR
Was knowledge of the allocated intervention adequately prevented during the study?	UNCLEAR
Were incomplete outcome data adequately addressed?	NO
Are reports of the study free of suggestion of selective outcome reporting?	YES
Was the study apparently free of other problems that could put it at a high risk of bias?	YES

Long-term follow up of an included randomised controlled trial

Table 112: Yli-Kerttula et al., 2003

Bibliographic reference	Yli-Kerttula,T., Luukkainen,R., Yli-Kerttula,U., Mottonen,T., Hakola,M., Korpela,M., Sanila,M., Uksila,J., Toivanen,A., Effect of a three month course of ciprofloxacin on the late prognosis of reactive arthritis, Annals of the Rheumatic Diseases, 62, 880-884, 2003
Country/ies where the study was carried out	Finland
Study type	Long term follow up of included RCT (Yli-Kerttula 2000)
Aim of the study	To analyse the long term outcome of patients with ReA treated with a three month course of ciprofloxacin or placebo

Bibliographic reference	**Yli-Kerttula,T., Luukkainen,R., Yli-Kerttula,U., Mottonen,T., Hakola,M., Korpela,M., Sanila,M., Uksila,J., Toivanen,A., Effect of a three month course of ciprofloxacin on the late prognosis of reactive arthritis, Annals of the Rheumatic Diseases, 62, 880-884, 2003**
Study dates	Original study recruited patients from 1992 to 1996, with up to 1 year follow up. This study published 2003 with 4-7 years follow up on original population
Source of funding	EVO Grant of Turku University Central Hospital
Sample size	69 out of 71 participants were contacted. 53 attended a clinic appointment and were included in this analysis
Diagnostic criteria	See extract of original study (Yli-Kerttula 2000)
Inclusion criteria	Participants from the original study were invited for a check-up visit at the clinic. 53 attended in person and 16 were interviewed by telephone. Only the 53 participants to attend in person were included in the final analysis.
Exclusion criteria	16 participants who underwent telephone interview only 2 patients who could not be contacted by either method
Characteristics	See extract of original study (Yli-Kerttula 2000) for characteristics of patients at recruitment. Characteristics of patients attending clinic follow up appointment(n=53) age, years (mean(sd)): 36.8 (12.4) duration of disease, days: 34.9(23.7) female, n: 23(43) number of swollen joints (mean(sd)): 3.6(1.7) joint tenderness score (mean(sd)): 6.1(2.8) joint swelling score: 5.4(2.7) ESR (mm/1st h)(mean(sd)): 62.7(27.1) CRP (mg/l)(mean(sd)): 62.2(45.2) HLA-B27 positive, n: 45 Characteristics of patients participating in telephone interview (n=17) age, years (mean(sd)): 34.5(12.7) duration of disease, days: 43.9(29.2) female, n: 5 number of swollen joints (mean(sd)): 2.8(1.4) joint tenderness score (mean(sd)): 6.6(3.2) joint swelling score: 4.4(2.4) ESR (mm/1st h): 54.7(25.7) CRP (mg/l): 67.0(62.6) HLA-B27 positive, n: 11 Characteristics of patients at follow up were not presented separately for intervention and control groups
Interventions	See extract of original study (Yli-Kerttula 2000) for trial details.

Bibliographic reference	Yli-Kerttula,T., Luukkainen,R., Yli-Kerttula,U., Mottonen,T., Hakola,M., Korpela,M., Sanila,M., Uksila,J., Toivanen,A., Effect of a three month course of ciprofloxacin on the late prognosis of reactive arthritis, Annals of the Rheumatic Diseases, 62, 880-884, 2003
Randomisation, allocation, blinding	See extract of original study (Yli-Kerttula 2000) Blinding of investigators at follow up was not possible as the intervention allocation code had been opened during analysis of the previous study.
Details	In this follow up study, patients attending the clinic were asked about medical history after the acute episode of ReA after the previous study. History taking including focus on possible signs of chronic spondyloarthropathy. Complete recovery was defined as normal findings by the patient's global assessment, EST, CRP, white blood cell counts and clinical examination. Clinical examination included general clinical and joint examination (No. swollen joints, joint swelling score, joint tenderness score (Ritchie index)). Also measured were: Schober test, finger-floor distance, chest expansion. Both doctor and patient assessed disease activity on a 100mm VAS. Lab tests included ESR, CRP, blood cell counts, alanine aminotransferase, alkaline phosphatase, creatinine and urine analysis. Levels of serum antibodies for the triggering microbe was determined individually for each patient. Statistical analysis Means and standard deviations were used where data were normally distributed. Otherwise median and interquartile ranges were used. Comparisons were made using Mann Whitney U test, chi-squared tests or Fisher's exact test. Statistical significance was set at the 5% level.
Missing data handling/loss to follow up	Two patients were lost to follow up in the original study. 16 patients who were contacted in the follow up study did not attend clinic appointments and were reached by telephone only.
Results	Inflammatory markers ESR, mm/1st hour (mean(sd)) Ciprofloxacin (n=26): baseline of original study: 56.6(27.1); end of follow up study: 8.0(7.7) Placebo (n=27): baseline of original study: 68.6(26.2); end of follow up study: 9.8(8.5) Number of patients with chronic rheumatic disease at the end of the follow up study Ciprofloxacin (n=26): Clinical findings ankylosing spondylitis: 0 inflammatory back pain: 0 enthesitis: 0 chronic oligoarthritis: 0 psoriatic arthritis:1 seronegative polyarthritis: 1 recurrent anterior uveitis: 0 Total: 2

Bibliographic reference	Yli-Kerttula,T., Luukkainen,R., Yli-Kerttula,U., Mottonen,T., Hakola,M., Korpela,M., Sanila,M., Uksila,J., Toivanen,A., Effect of a three month course of ciprofloxacin on the late prognosis of reactive arthritis, Annals of the Rheumatic Diseases, 62, 880-884, 2003
	Diagnostic imaging plain radiographs sacroiliitis and AS: 0 OA of spine: 1 MRI sacroiliitis: 0 HLA-B27 positive All: 20 Patients with chronic disease: 0 Placebo (n=27) Clinical findings ankylosing spondylitis: 2 inflammatory back pain: 4 enthesitis: 2 chronic oligoarthritis: 1 psoriatic arthritis: 0 seronegative polyarthritis: 0 recurrent anterior uveitis: 3 Total: 11 Diagnostic imaging plain radiographs sacroiliitis and AS: 2 OA of spine: 1 MRI sacroiliitis: 3 HLA-B27 positive All: 25 Patients with chronic disease: 10 Other reported outcomes: Patient's global assessment, Ritchie index (mixture of mean and median values), complete recovery
Long term_ESR	Long term_ESR

Bibliographic reference	**Yli-Kerttula,T., Luukkainen,R., Yli-Kerttula,U., Mottonen,T., Hakola,M., Korpela,M., Sanila,M., Uksila,J., Toivanen,A., Effect of a three month course of ciprofloxacin on the late prognosis of reactive arthritis, Annals of the Rheumatic Diseases, 62, 880-884, 2003**
	<table><tr><td></td><td>Mean</td><td>SD</td><td>Total</td></tr><tr><td>Experimental</td><td>-48.60</td><td>27.10</td><td>26</td></tr><tr><td>Control</td><td>-58.80</td><td>27.10</td><td>27</td></tr></table>
Long term_clinical findings of SpA	Long term_clinical findings of SpA <table><tr><td></td><td>Events</td><td>Total</td></tr><tr><td>Experimental</td><td>2</td><td>26</td></tr><tr><td>Control</td><td>11</td><td>27</td></tr></table>
Long term_radiographic findings	Long term_radiographic findings <table><tr><td></td><td>Events</td><td>Total</td></tr><tr><td>Experimental</td><td>1</td><td>5</td></tr><tr><td>Control</td><td>3</td><td>6</td></tr></table>
Long term_MRI findings	Long term_MRI findings <table><tr><td></td><td>Events</td><td>Total</td></tr><tr><td>Experimental</td><td>0</td><td>3</td></tr><tr><td>Control</td><td>3</td><td>3</td></tr></table>
Overall Risk of Bias	The original trial had some areas where a risk of bias may apply.

Bibliographic reference	Yli-Kerttula,T., Luukkainen,R., Yli-Kerttula,U., Mottonen,T., Hakola,M., Korpela,M., Sanila,M., Uksila,J., Toivanen,A., Effect of a three month course of ciprofloxacin on the late prognosis of reactive arthritis, Annals of the Rheumatic Diseases, 62, 880-884, 2003
Other information	SD of change in ESR not reported; the largest SD of the individual measurements was used. Number of patients per treatment group undergoing imaging was not reported, only the total number undergoing imaging. The denominator was therefore imputed as a proportional estimate of the total, rounded to the nearest integer.
Was the allocation sequence adequately generated?	UNCLEAR
Was allocation adequately concealed?	UNCLEAR
Was knowledge of the allocated intervention adequately prevented during the study?	UNCLEAR
Were incomplete outcome data adequately addressed?	UNCLEAR
Are reports of the study free of suggestion of selective outcome reporting?	YES
Was the study apparently free of other problems that could put it at a high risk of bias?	YES

E.3 Non-pharmacological management

E.3.1 Manual therapies for spondyloarthritis

Review question 14

- What is the effectiveness of manual therapies compared with standard care for managing spondyloarthritis?

Included comparative studies (RCTs and CCTs)

Table 113: Eppeland et al., 2013

Bibliographic reference	Eppeland,Siv Grodal, Diamantopoulos,Andreas P., Soldal,Dag Magnar, Haugeberg,Glenn, Short term in-patient rehabilitation in axial spondyloarthritis - the results of a 2-week program performed in daily clinical practice, BMC research notes, 6, 185-, 2013
Country/ies where the study was carried out	Norway
Study type	Retrospective cross-sectional study
Aim of the study	Using routinely collected hospital data, to evaluate the short term effects of a 2 week inpatient rehabilitation programme in people with axial spondyloarthritis
Study dates	January 2007 to June 2011
Source of funding	Not reported
Sample size	87 adults
Diagnostic criteria	Assessment of Spondyloarthritis International Society (ASAS) diagnostic criteria for axial spondyloarthritis; 64/87 fulfilled the modified New York criteria for ankylosing spondylitis
Inclusion criteria	· At least 18 years old · Diagnosed axial spondyloarthritis with imaging (X-ray, CT and/or MRI) confirmed sacroiliitis · On the hospital database, having been referred by rheumatologist as likely to benefit and completed a 2-week inpatient rehabilitation programme

Bibliographic reference	**Eppeland,Siv Grodal, Diamantopoulos,Andreas P., Soldal,Dag Magnar, Haugeberg,Glenn, Short term in-patient rehabilitation in axial spondyloarthritis - the results of a 2-week program performed in daily clinical practice, BMC research notes, 6, 185-, 2013**
Exclusion criteria	· Severe comorbidities · Severe reduced exercise tolerance
Characteristics	· 60 men, 27 women · Mean (SD) age: 49.2 (10.0) · Mean (SD) disease duration in years: 14.4 (11.9) · HLA-B27 positive: 92.5% · Imaging: o X-ray: 64/72 with radiographic sacroiliitis o CT: 5 with CT-confirmed sacroiliitis o MRI: 18 with MRI-confirmed sacroiliitis · Drugs: o NSAIDs: 62.1% o anti-TNFs: 17.2% (10 etanercept, 3 infliximab, 2 adalimumab)
Interventions	· 2-week inpatient rehabilitation programme · Training programme organised by physiotherapist, performed 5 days a week in groups of 4 with consideration of individuals' goals and statuses: o water exercises (30 minutes) o basic exercises for movement, muscle strength and stability, balance and co-ordination (45 minutes) o endurance exercises (40 minutes) · Additional individual physiotherapy including massage, stretching, mobilisation/articulation and advice on specific exercises to enhance a good body posture · Multidisciplinary team (rheumatologist, physiotherapist, occupational therapist, social worker, secretary) input as needed
Randomisation, allocation, blinding	Randomisation/allocation: not relevant Physiotherapist involved in patient assessment did not analyse the data
Details	Paired Student's t-test or non-parametric Wilcoxon test. Skewed data were presented as medians (IQR) as appropriate

Bibliographic reference	**Eppeland,Siv Grodal, Diamantopoulos,Andreas P., Soldal,Dag Magnar, Haugeberg,Glenn, Short term in-patient rehabilitation in axial spondyloarthritis - the results of a 2-week program performed in daily clinical practice, BMC research notes, 6, 185-, 2013**
	Assessments were undertaken at admission and at the end of the 2 week inpatient programme. Additionally, BASDAI, BASFI and BASMI were reassessed at the first follow-up outpatient clinic visit after the intervention (mean [SD] duration in months: 9.3 [6.9])
Missing data handling/loss to follow up	95 individuals started the inpatient programme, but 8 withdrew, for various reasons. Complete data were available for BASMI at the end of the 2 week intervention. For the remaining outcomes, there was varying levels of attrition and no attempt at data imputation
Results	Pain Not reported separately; domain within BASDAI Adverse events Not reported Joint mobility Finger-floor distance, cm · n=49; mean (SD): at baseline: 15.1 (14.0); at 2 weeks: 9.1 (12.7); p<0.001 Physical function · Not reported separately; domain within BASFI · Gait velocity, timed-stand test and chest expansion not extracted Quality of life Not reported Imaging Not reported Composite measures BASFI (0-10; higher values indicate worse outcomes) · n=59; mean (SD): at baseline: 3.1 (1.9); at 2 weeks: 2.3 (2.0); p<0.001 · n=48 provided long-term follow-up data (mean [SD] time period in months: 9.3 [6.9]; mean (SD): at baseline: 3.5 (2.6); at follow-up: 3.2 (2.0); p=0.31 BASDAI (0-10; higher values indicate worse outcomes) · n=59; mean (SD): at baseline: 4.3 (2.2); at 2 weeks: 3.1 (2.1); p<0.001 · n=48 provided long-term follow-up data (mean [SD] time period in months: 9.3 [6.9]; mean (SD): at baseline: 4.4 (2.2); at follow-up: 4.1 (2.3); p=0.24 BASMI (0-10; higher values indicate worse outcomes) · n=87; mean (SD): at baseline: 3.2 (2.4); at 2 weeks: 2.3 (2.4); p<0.001 · n=48 provided long-term follow-up data (mean [SD] time period in months: 9.3 [6.9]; mean (SD): at baseline: 3.3 (2.6); at follow-up: 2.7 (2.5); p=0.02

Bibliographic reference	Eppeland,Siv Grodal, Diamantopoulos,Andreas P., Soldal,Dag Magnar, Haugeberg,Glenn, Short term in-patient rehabilitation in axial spondyloarthritis - the results of a 2-week program performed in daily clinical practice, BMC research notes, 6, 185-, 2013
Overall Risk of Bias	Participants entering the rehabilitation programme are selectively screened as those likely to benefit. In addition, only individuals who had completed the programme were included in the analysis (8 people did not complete the study because of acute infectious disease, acute low back pain, depression and vertigo). Therefore, it is likely that the analysed sample may not be representative of the overall UK clinical population of people with axial spondyloarthritis. No details were provided of the overall contribution of the manual therapy components (massage, mobilisation/articulation). It is unclear whether the same physiotherapist who administered the intervention, also undertook the baseline and follow-up outcome assessments. Moreover, for some outcomes, there were substantial missing data, with no associated reasons provided. There was no comparative group
Other information	Not relevant

Table 114: Lubrano et al., 2006

Bibliographic reference	Lubrano,Ennio, D'Angelo,Salvatore, Parsons,Wendy J., Serino,Franca, Tanzillo,Angelo Tommaso, Olivieri,Ignazio, Pappone,Nicola, Effects of a combination treatment of an intensive rehabilitation program and etanercept in patients with ankylosing spondylitis: a pilot study, The Journal of rheumatology, 33, 2029-2034, 2006
Country/ies where the study was carried out	Italy
Study type	Before-and-after study
Aim of the study	To assess the effects of etanercept plus rehabilitation compared to a 3-week intensive inpatient rehabilitation programme alone in people with active ankylosing spondylitis using the Assessment in Ankylosing Spondylitis (ASAS) Working Group response criteria
Study dates	January to March 2004
Source of funding	Not reported
Sample size	19 adults
Diagnostic criteria	Ankylosing spondylitis according to the modified New York criteria

Bibliographic reference	**Lubrano,Ennio, D'Angelo,Salvatore, Parsons,Wendy J., Serino,Franca, Tanzillo,Angelo Tommaso, Olivieri,Ignazio, Pappone,Nicola, Effects of a combination treatment of an intensive rehabilitation program and etanercept in patients with ankylosing spondylitis: a pilot study, The Journal of rheumatology, 33, 2029-2034, 2006**
Inclusion criteria	· Active disease according to the following criteria suggested by ASAS: o Uncontrolled by NSAIDs and o At least 3 of the following conditions: - Patient's global assessment at least 40mm on visual analogue scale - Inflammatory pain at least 40mm on visual analogue scale - BASFI at least 40mm - Erythrocyte sedimentation rate more than 28mm/h or raised C-reactive protein - (BASDAI at least 4 was taken into account)
Exclusion criteria	· Complete ankylosing of the spine · Previous use of anti-TNFs · Use of DMARDs (except sulfasalazine or methotrexate) in the past 4 weeks · Daily use of more than 10 mg of prednisolone · Variation of NSAIDs or prednisolone dosage in previous 2 weeks · Positive screening for tuberculosis
Characteristics	· 16 men, 3 women · Mean (SD) age: 41.3 (8.6) · Mean (SD) disease duration in years: 9.3 (6.0) · HLA-B27 positive: 84% (n=16) · Drugs: o NSAIDs: 100% o Steroids: 58% (n=11) o DMARDs: 53% (n=10) · Disease characteristics: o Clinical peripheral joint involvement: 32% (n=6) o Psoriasis: 5% (n=1) o Eye involvement: 5% (n=1)
Interventions	3-week intensive inpatient rehabilitation programme · Intensive standardised exercise programme consisting of 2 daily sessions supervised by a senior physiotherapist: o Warm-up

Bibliographic reference	Lubrano,Ennio, D'Angelo,Salvatore, Parsons,Wendy J., Serino,Franca, Tanzillo,Angelo Tommaso, Olivieri,Ignazio, Pappone,Nicola, Effects of a combination treatment of an intensive rehabilitation program and etanercept in patients with ankylosing spondylitis: a pilot study, The Journal of rheumatology, 33, 2029-2034, 2006
	o Strengthening exercises with maximal isometric pain free and dynamic contractions (30 minutes) o Stretching exercises with progressive neuromotor facilitation (15 minutes) o Endurance exercises (15 minutes cycling, 10 minutes treadmill and 10 minutes walking) o Respiratory exercises (15 minutes) · Patients target of 60% of predicted heart rate at maximal exercise for 5 days; target progressively increased to maximum of 80% until end of 3 weeks Etanercept plus 3-week intensive inpatient rehabilitation programme · Self-administered etanercept 25mg subcutaneously twice weekly, started at home for 3 weeks and continued during rehabilitation · Etanercept plus 3-week intensive inpatient rehabilitation programme as described above · Patients were recruited and assessed (Ax1) at baseline, given 3-week rehabilitation programme, re-assessed (Ax2), discharged with no home exercises and 6 months later, reassessed at baseline (Ax3), given etanercept for 3 weeks, reassessed (Ax4), admitted into the 3-week inpatient rehabilitation programme and had final reassessment (Ax5) following combination of rehabilitation and etanercept treatment · Only data from pre-post assessments for the initial 3-week rehabilitation intervention were extracted
Randomisation, allocation, blinding	Randomisation/allocation: not relevant No description of methods for outcome assessments provided in terms of blinding
Details	Pre- and post-treatment comparisons: Wilcoxon signed-rank test Assessments were undertaken as described above
Missing data handling/loss to follow up	There was no attrition
Results	Pain Not reported separately; domain within BASDAI Adverse events Not reported Joint mobility Modified Schober's test, cm · n=19; mean difference (SD) from baseline at 3 weeks: 0.48 (0.17) Tragus to wall distance, cm

Bibliographic reference	Lubrano,Ennio, D'Angelo,Salvatore, Parsons,Wendy J., Serino,Franca, Tanzillo,Angelo Tommaso, Olivieri,Ignazio, Pappone,Nicola, Effects of a combination treatment of an intensive rehabilitation program and etanercept in patients with ankylosing spondylitis: a pilot study, The Journal of rheumatology, 33, 2029-2034, 2006
	· n=19; mean difference (SD) from baseline at 3 weeks: -2.74 (1.11) Physical function · 6 minute walk test and chest expansion not extracted Quality of life EQ-5D self-rating visual analogue scale (0-100; lower values indicate worse outcomes) on patient's global health status · n=19; mean difference (SD) from baseline at 3 weeks: 6.6 (2.8) Imaging Not reported Composite measures BASFI (0-100; higher values indicate worse outcomes) · n=19; mean difference (SD) from baseline at 3 weeks: -0.71 (0.23) BASDAI (0-100; higher values indicate worse outcomes) · n=19; mean difference (SD) from baseline at 3 weeks: -0.71 (0.40) Revised Leeds Disability Questionnaire (RLDQ; 0-3; higher values indicate worse outcomes) · n=19; mean difference (SD) from baseline at 3 weeks: -0.28 (0.08)
Overall Risk of Bias	This was a small before-and-after study of patients with active ankylosing spondylitis. Limited details of the manual therapy component were provided i.e. progressive neuromotor facilitation. No details were provided of the methods of outcome assessments. There was no relevant comparative group
Other information	Not relevant

Table 115: Silva et al., 2012

Bibliographic reference	Silva,Eliane Maria, Andrade,Sandra C., Vilar,Maria J., Evaluation of the effects of Global Postural Re-education in patients with ankylosing spondylitis, Rheumatology international, 32, 2155-2163, 2012
Country/ies where the study was carried out	Brazil
Study type	Non-randomised controlled clinical trial
Aim of the study	To compare the effects of individual global stretching (global postural re-education) with standard group segmental self-stretching exercises in people with ankylosing spondylitis

Bibliographic reference	Silva,Eliane Maria, Andrade,Sandra C., Vilar,Maria J., Evaluation of the effects of Global Postural Re-education in patients with ankylosing spondylitis, Rheumatology international, 32, 2155-2163, 2012
Study dates	Not reported
Source of funding	Not reported
Sample size	38 adults
Diagnostic criteria	Ankylosing spondylitis according to the modified New York criteria
Inclusion criteria	· 18 to 65 years old · Diagnosed with ankylosing spondylitis · Clinically stable, with no other associated diseases · Treated with NSAIDs for underlying disease · Ability to perform usual self-care and vocational activities · Agreed not to undergo other physiotherapy treatment during the study · Provided informed consent Referred by rheumatologist to physiotherapy school clinic
Exclusion criteria	· Secondary fracture due to osteoporosis
Characteristics	· GPR: 14 men, 6 women; Control: 12 men, 3 women · Mean (SD) age: GPR: 35.3 (12.2); Control: 44.27 (10.55) · Mean (SD) disease duration in years: GPR: 10.1 (5.67); Control: 7.07 (4.81) · Drugs: NSAIDs: 100%
Interventions	Global postural re-education (GPR), n=22 · 4-month individualised programme, 1 hour, once a week o Series of 5 postures that evaluated shortened muscle chains (anterior – respiratory and anterolateral of the hip; posterior; anterior of the arm; anterointernal of the shoulders) o In these 5 postures (frog posture on the floor with the upper limb in adduction; frog in the air with upper limbs in abduction; seated; standing bent forward; standing against the wall), costodiaphragmatic inspiration and expiration with depression of the sternum via abdominal protrusion were undertaken

Bibliographic reference	Silva,Eliane Maria, Andrade,Sandra C., Vilar,Maria J., Evaluation of the effects of Global Postural Re-education in patients with ankylosing spondylitis, Rheumatology international, 32, 2155-2163, 2012
	o The physiotherapist used verbal commands and manual contact to maintain alignment and make postural corrections to discourage compensatory movements and optimise stretching. For 1 specific posture, the following description was provided: “manual traction was applied to the neck and sacral traction to align the curves of the spinal column” o In the first 8 weeks, supine positions were used to pain and spinal mobility. In the last 8 weeks, sitting and standing postures were used to improve proprioception, body schema, balance and strengthening of the paraspinals and lower limbs Control (standard care), n=16 · Group based conventional segmental self-stretching and breathing exercises · 4-month programme delivered in groups of 4, 40 minutes, twice a week o In sitting, maintained flexion, extension inclination and cervical and thoracic rotation; triceps stretching, active extension of the upper limb o Respiratory exercises: diaphragmatic and costodiaphragmatic respiratory exercises associated with upper limb movements o Stretching hips and lower limbs o Stretching trunk muscles o Standing stretches were introduced when individuals reported improvement in spinal pain Both groups were supervised by a physiotherapist experienced in rheumatology, and received advice on positions for sleeping, sitting, walking and carrying out daily activities
Randomisation, allocation, blinding	Randomisation/allocation: no randomisation; no details of how individuals were allocated to groups An independent physiotherapist undertook the post-treatment assessments
Details	Group comparisons: unpaired t-test Assessments were undertaken pre-treatment and at the end of the 4 month intervention programme. Physical measurements were taken 3 times and the mean used in the analysis
Missing data handling/loss to follow up	3 individuals withdrew from treatment (2 in the GPR group and 1 in the control group) and were excluded from the analysis. No further details were provided
Results	Pain · Domain within BASDAI · Cervical, dorsal and lumbar pain and morning stiffness not extracted

Bibliographic reference	Silva,Eliane Maria, Andrade,Sandra C., Vilar,Maria J., Evaluation of the effects of Global Postural Re-education in patients with ankylosing spondylitis, Rheumatology international, 32, 2155-2163, 2012
	Adverse events Not reported Joint mobility Finger-floor distance, cm [mean improvement (SD) from baseline at 4 months] · GPR: -9.7 (1.75), n=20 · Control: -7.4 (1.48), n=15 · Between group difference: p=0.12 Modified Schober test, cm [mean improvement (SD) from baseline at 4 months] · GPR: 0.8 (0.32), n=20 · Control: 0.1 (0.33), n=15 · Between group difference: p=0.02 Cervical rotation, degrees [mean improvement (SD) from baseline at 4 months] · GPR: 11.5 (0.88), n=20 · Control: 4.5 (1.19), n=15 · Between group difference: p<0.001 · Chin-to-chest distance, occiput-to-wall distance and chest expansion not extracted Physical function Not reported separately; see HAQ-S Quality of life SF36 physical component score [mean improvement (SD) from baseline at 4 months] · GPR: 32.7 (3.06), n=20 · Control: 17.2 (2.96), n=15 · Between group difference: p<0.001 SF36 emotional component score [mean improvement (SD) from baseline at 4 months] · GPR: 22.2 (4.19), n=20 · Control: 18.6 (3.93), n=15 · Between group difference: p=0.82 Imaging Not reported Composite measures BASDAI [mean improvement (SD) from baseline at 4 months] · GPR: -3.5 (0.39), n=20 · Control: -2.1 (0.26), n=15

Bibliographic reference	Silva,Eliane Maria, Andrade,Sandra C., Vilar,Maria J., Evaluation of the effects of Global Postural Re-education in patients with ankylosing spondylitis, Rheumatology international, 32, 2155-2163, 2012
	· Between group difference: p=0.73 HAQ-S [mean improvement (SD) from baseline at 4 months] · GPR: -1.4 (0.18), n=20 · Control: -0.8 (0.13), n=15 · Between group difference: p=0.10
Overall Risk of Bias	This is a small study conducted in Brazil with a high risk of bias attributed to the lack of randomisation and clarity in terms of group allocation. Age and cervical pain baseline characteristics between the groups were different. It is unclear to what extent the independent assessor was blind to interventions the groups received. The comparator consisted of group based exercises and it is unclear the extent to which the individual attention obtained in the global postural re-education programme had on the overall treatment effect. In addition, it is unclear whether there was selective reporting of outcomes for the SF36.
Other information	Not relevant
Was the allocation sequence adequately generated?	--
Was allocation adequately concealed?	--
Was knowledge of the allocated intervention adequately prevented during the study?	UNCLEAR
Were incomplete outcome data adequately addressed?	NO
Are reports of the study free of suggestion of selective outcome reporting?	UNCLEAR
Was the study apparently free of other problems that could put it at a high risk of bias?	NO

Table 116: Table 4: Widberg et al., 2009

Bibliographic reference	Widberg,Kyllikki, Karimi,Hossein, Hafstrom,Ingiald, Self- and manual mobilization improves spine mobility in men with ankylosing spondylitis--a randomized study, Clinical rehabilitation, 23, 599-608, 2009
Country/ies where the study was carried out	Sweden
Study type	Randomised controlled trial
Aim of the study	To assess the effects of a self- and manual mobilisation physiotherapeutic intervention in terms of chest expansion, vital capacity, posture and spinal mobility in people with ankylosing spondylitis
Study dates	Not reported
Source of funding	Swedish Rheumatism Association, Nacka Rehab Centre
Sample size	32 men
Diagnostic criteria	Ankylosing spondylitis according to the modified New York criteria
Inclusion criteria	· 20 to 60 years old · Diagnosed with ankylosing spondylitis · Stable pharmacological treatment with NSAIDs and DMARDs
Exclusion criteria	· High inflammatory disease activity, possibly resulting in pharmacological changes · Radiological ossification between the thoracic vertebrae · Severe concomitant illnesses e.g. post myocardial infarction, hemiplegia, pulmonary disease, psychiatric illness
Characteristics	· Median (range) age: Intervention: 36.5 (29-60); Control: 35 (23-53) · Median (range) disease duration in years: Intervention: 2.5 (0-20); Control: 3.5 (0-20) · Drugs: o NSAIDs: Intervention: 11/16; Control: 13/16 o DMARDs: Intervention: 5/16; Control: 9/16 o None: Intervention: 2/16; Control 1/16 · Home exercise:

Bibliographic reference	Widberg,Kyllikki, Karimi,Hossein, Hafstrom,Ingiald, Self- and manual mobilization improves spine mobility in men with ankylosing spondylitis--a randomized study, Clinical rehabilitation, 23, 599-608, 2009
	o Once weekly: Intervention: 3/16; Control: 4/16 o Several times weekly: Intervention: 4/16; Control: 6/16 o No exercise: Intervention: 9/16; Control: 6/16
Interventions	Individualised physiotherapeutic intervention, n=16 · 8-week individualised programme of self- and manual mobilisation for 1 hour, twice a week and individually adjusted home exercises. The intervention was administered by the same physiotherapist and consisted of: o Initially warming up of the soft tissue of the back muscles with vibrations via a vibrator and gentle mobility exercises o Active angular and passive mobility exercises in the physiological directions of the joints in the spine and chest in 3 motions (flexion/extension, lateral flexion and rotation) and in 4 starting positions (prone, sideways, supine and sitting) o Stretching of tight muscles was done using the contracting-relaxing method o Soft tissue treatment (manual massage) of the neck was performed followed by relaxation exercises in standing and resting for some minutes lying on the treatment bench o Home programme consisted of 3 individually adjusted exercises, to be done every morning, noon and if possible in the evening. Compliance was monitored by self-report at regular physiotherapy visits. Individuals were encouraged to continue home exercise programme after the 8 week intervention had ended. Control (no treatment), n=16 · Individuals were encouraged to continue their usual physical exercises during the 8 weeks and thereafter offered the same treatment as the intervention
Randomisation, allocation, blinding	Randomisation/allocation: randomisation was undertaken by drawing lots in blocks of 4+4. The text on the lots was invisible and drawn by a blinded person. Two blinded assessors measured chest expansion, posture and spinal mobility. The same assessor measured the same individual pre- and post-treatment at the same time of the day. The physiotherapist completed the BASMI and the patient completed the other 3 BAS scales. No details were provided of the individual who assessed the intervention group at 4 months follow-up
Details	Group comparisons: repeated measures ANOVA for all mobility data and vital capacity, except thoracic spinal extension which was analysed using Mann-Whitney U-test. Assessments were undertaken pre-treatment, at the end of the 8 week intervention period. Data reassessed for the intervention group only at 4 months follow-up.

Bibliographic reference	Widberg,Kyllikki, Karimi,Hossein, Hafstrom,Ingiald, Self- and manual mobilization improves spine mobility in men with ankylosing spondylitis--a randomized study, Clinical rehabilitation, 23, 599-608, 2009
Missing data handling/loss to follow up	There was 1 person that dropped out of the intervention group at 4 months follow-up. No details were provided in the study. Only 1 individual missed 1 session in the intervention group
Results	Pain Not reported separately; domain within BASDAI Adverse events Not reported Joint mobility · Reported within BASMI · Sagittal thoracic and lumbar spine mobility (flexion and extension) and chest expansion not extracted Physical function Not reported separately; domain within BASFI Quality of life Not reported Imaging Not reported Composite measures BASFI [mean improvement (SD) from baseline at 8 weeks] · Intervention: -0.7 (1.75), n=16 · Control: -0.4 (2.07), n=16 · Between group difference: p=0.14 [mean improvement (SD) from baseline at 4 months] · Intervention: -0.4 (1.8), n=15, p=0.38 BASDAI [mean improvement (SD) from baseline at 8 weeks] · Intervention: -0.5 (1.57), n=16 · Control: -0.5 (2.05), n=16 · Between group difference: p=0.55 [mean improvement (SD) from baseline at 4 months] · Intervention: -0.3 (1.8), n=15, p=0.48 BASMI [mean change (SD) from baseline at 8 weeks; negative values indicate improvement] · Intervention: -1.0 (0.76), n=16 · Control: 0.2 (2.05), n=16 · Between group difference: p=0.0002 [mean improvement (SD) from baseline at 4 months] · Intervention: -0.6 (1.0), n=15, p=0.005 · BAS-G not extracted

Bibliographic reference	Widberg,Kyllikki, Karimi,Hossein, Hafstrom,Ingiald, Self- and manual mobilization improves spine mobility in men with ankylosing spondylitis--a randomized study, Clinical rehabilitation, 23, 599-608, 2009
Overall Risk of Bias	This is a moderate-quality, small study conducted in Sweden on participants who did not have ossification of the thoracic vertebrae and/or severe concomitant illnesses. Groups were equivalent at baseline. No specific details on the blinding procedures for the independent assessors were provided.
Other information	Not relevant
Was the allocation sequence adequately generated?	UNCLEAR
Was allocation adequately concealed?	UNCLEAR
Was knowledge of the allocated intervention adequately prevented during the study?	UNCLEAR
Were incomplete outcome data adequately addressed?	NO
Are reports of the study free of suggestion of selective outcome reporting?	UNCLEAR
Was the study apparently free of other problems that could put it at a high risk of bias?	NO

Included observational studies

Table 117: Lubrano et al., 2007

Bibliographic reference	Lubrano,E., D'Angelo,S., Parsons,W.J., Corbi,G., Ferrara,N., Rengo,F., Olivieri,I., Effectiveness of rehabilitation in active ankylosing spondylitis assessed by the ASAS response criteria, Rheumatology (Oxford, England), 46, 1672-1675, 2007
Country/ies where the study was carried out	Italy
Study type	Prospective cohort

Bibliographic reference	**Lubrano,E., D'Angelo,S., Parsons,W.J., Corbi,G., Ferrara,N., Rengo,F., Olivieri,I., Effectiveness of rehabilitation in active ankylosing spondylitis assessed by the ASAS response criteria, Rheumatology (Oxford, England), 46, 1672-1675, 2007**
Aim of the study	To assess the effectiveness of a 3-week intensive inpatient rehabilitation programme in people with active ankylosing spondylitis using the Assessment in Ankylosing Spondylitis (ASAS) Working Group response criteria
Study dates	January to October 2005
Source of funding	Not reported
Sample size	52 adults
Diagnostic criteria	Ankylosing spondylitis according to the modified New York criteria
Inclusion criteria	· Active disease according to the following criteria: o Uncontrolled by NSAIDs and o At least 3 of the following conditions: - Patient's global assessment at least 40mm on visual analogue scale - Inflammatory pain at least 40mm on visual analogue scale - BASFI at least 40mm - Erythrocyte sedimentation rate more than 28mm first hour or raised C-reactive protein - (BASDAI at least 4 was taken into account)
Exclusion criteria	· Complete ankylosing of the spine · Previous inpatient physiotherapy in the past 12 months · Previous use of anti-TNFs · Use of DMARDs (except sulfasalazine or methotrexate) in the past 4 weeks · Daily use of more than 10 mg of prednisolone · Variation of NSAIDs or prednisolone dosage in previous 2 weeks
Interventions	· 3-week intensive inpatient rehabilitation programme · Intensive standardised exercise programme consisting of 2 daily sessions supervised by a senior physiotherapist with experience in ankylosing spondylitis; groups of 6 to 8 patients:

Bibliographic reference	Lubrano,E., D'Angelo,S., Parsons,W.J., Corbi,G., Ferrara,N., Rengo,F., Olivieri,I., Effectiveness of rehabilitation in active ankylosing spondylitis assessed by the ASAS response criteria, Rheumatology (Oxford, England), 46, 1672-1675, 2007
	o Warm-up o Strengthening exercises with maximal isometric pain free and dynamic contractions (30 minutes) o Stretching exercises with neuromotor facilitation (15 minutes) o Endurance exercises o Respiratory exercises (15 minutes) · Patients target of 60% of predicted heart rate at maximal exercise for 5 days; target progressively increased to maximum of 80% until end of 3 weeks · Patients discharged with daily home exercise programme consisting of 6 groups of exercise
Randomisation, allocation, blinding	Randomisation/allocation: not relevant No description of methods for outcome assessments provided
Details	Proportion of patients achieving a response based on the ASAS 20: McNemar test Continuous outcomes: Wilcoxon signed-rank test Assessments were undertaken at admission, at discharged at the end of the 3-week rehabilitation programme, and at 6 and 12 weeks ASAS 20 was calculated as a composite index: · At least 20% relative and at least 10 units of absolute improvement in at least 3 of the following 4 domains, with no worsening in the 4th domain: o Inflammation (BASDAI mean questions 5 and 6) o Function (BASFI) o Patient perception of pain (patient pain visual analogue scale) o Patient global assessment
Missing data handling/loss to follow up	There was no attrition
Results	Pain · Domain also included within ASAS 20 Visual analogue scale, 0-100 · n=52; mean (SD): at baseline: 76.6 (5.0); at 3 weeks: 51.1 (8.5); at 6 weeks: 58.8 (7.0); at 12 weeks: 66.3 (6.3); p<0.001 at all timepoints compared to baseline Adverse events Not reported Joint mobility Modified Schober's test, cm

Bibliographic reference	**Lubrano,E., D'Angelo,S., Parsons,W.J., Corbi,G., Ferrara,N., Rengo,F., Olivieri,I., Effectiveness of rehabilitation in active ankylosing spondylitis assessed by the ASAS response criteria, Rheumatology (Oxford, England), 46, 1672-1675, 2007**
	· n=52; mean (SD): at baseline: 1.9 (0.6); at 3 weeks: 2.4 (0.7); at 6 weeks: 2.3 (0.6); at 12 weeks: 2.2 (0.6); p<0.001 at all timepoints compared to baseline Tragus to wall distance, cm · n=52; mean (SD): at baseline: 21.5 (4.3); at 3 weeks: 16.3 (3.8); at 6 weeks: 16.6 (3.1); at 12 weeks: 18.2 (5.1); p<0.001 at all timepoints compared to baseline Physical function · Domain within ASAS 20; not extracted separately · Chest expansion not extracted Quality of life Not reported Imaging Not reported Composite measures BASFI (0-100; higher values indicate worse outcomes) · Domain also included within ASAS 20 · n=52; mean (SD): at baseline: 67.1 (7.9); at 3 weeks: 49.5 (7.4); at 6 weeks: 53.7 (7.6); at 12 weeks: 57.9 (7.2); p<0.001 at all timepoints compared to baseline (assumed data in mm) Revised Leeds Disability Questionnaire (RLDQ; 0-3; higher values indicate worse outcomes) · n=52; mean (SD): at baseline: 1.8 (0.5); at 3 weeks: 1.3 (0.5); at 6 weeks: 1.4 (0.4); at 12 weeks: 1.5 (0.5); p<0.001 at all timepoints compared to baseline ASAS 20 · Number of responders at 3 weeks: n=46 (88.5%) · Number of responders at 6 weeks: n=31 (59.6%) · Number of responders at 12 weeks: n=17 (32.7%) · ASAS 40 was achieved by 2 patients at the end of rehabilitation
Overall Risk of Bias	This was a small prospective case series of patients with active ankylosing spondylitis. Limited detail of the manual therapy component was provided i.e. neuromotor facilitation. No details were provided of the methods of outcome assessments. There was no comparative group
Other information	Not relevant

Table 118: Escalas et al., 2016

Bibliographic reference	Escalas, C., Dalichampt, M., Dougados, M., Poiraudeau, S., Evaluation of physiotherapy in a prospective cohort of early axial spondyloarthritis. Data from the DESIR cohort., Joint Bone Spine, 83, 185-190, 2016
Country/ies where the study was carried out	France
Study type	Retrospective analysis of a prospective cohort, evaluated with propensity score methods
Aim of the study	To assess whether physiotherapy delivered in a primary care setting improves function in patients with early inflammatory back pain suggesting a diagnosis of SpA
Study dates	Cohort recruitment between October 2007 and April 2010
Source of funding	Cohort study sponsored by the Département de la Recherche Clinique et du Développement de l'Assistance Publique–Hôpitaux de Paris. An unrestricted grant from Pfizer was allocated for the 10 years of the follow-up of the recruited patients.
Sample size	Cohort included 708 people with early axial SpA. 689 patients included in the analysis: 166 people had physiotherapy in the first 6 months, 523 people did not have physiotherapy in the first 6 months
Diagnostic criteria	Rheumatologist-diagnosis. Participants had to fulfil either Berlin or Calin criteria.
Inclusion criteria	18-50 years old Inflammatory back pain from 3 months – 3 years Symptoms suggestive of SpA
Exclusion criteria	History of anti-TNF use
Interventions	Physical therapy sessions delivered in primary care. The content of these sessions was not described.
Randomisation, allocation, blinding	Not applicable
Details	Statistical analysis: Analysed using propensity matching models, containing: • Demographics (sex, change, sick leave) • Clinical data (BMI, cervical spine rotation, intermalleolar distance, presence of thoracic pain) • Biological data (C-reactive protein)
Missing data handling/loss to follow up	Authors noted that where data were missing in patient records regarding the reason for prescribing physical therapy
Results	Between inclusion and 6 months, the mean number of physiotherapy sessions in the whole group was 7.4. Mean for people who had physiotherapy was 23.1. • Improvement of 20% in BASFI at 6 months (unadjusted): RR: 0.96 (95% CI 0.77 to 1.18) • Improvement of 20% in BASFI at 6 months (propensity matched): 1.15 (95% CI 0.91 to 1.45) • Improvement of 20% in BASFI at 12 months (propensity matched): 0.94 (95% CI 0.80 to 1.11) • Improvement of 20% in BASFI at 24 months (propensity matched): 1.09 (95% CI 0.90 to 1.33)

Bibliographic reference	Escalas, C., Dalichampt, M., Dougados, M., Poiraudeau, S., Evaluation of physiotherapy in a prospective cohort of early axial spondyloarthritis. Data from the DESIR cohort., Joint Bone Spine, 83, 185-190, 2016
Overall Risk of Bias	Serious, due to observational study design
Other information	Study is classified as indirectly related to question in the GRADE framework, due to lack of detail as to the nature of the physiotherapy.

E.3.2 Exercise for spondyloarthritis

Review Question 15

- What is the effectiveness of structured exercise compared with standard care for managing spondyloarthritis?

Table 119: Altan et al., 2012

Bibliographic reference	Altan,L., Korkmaz,N., Dizdar,M., Yurtkuran,M., Effect of Pilates training on people with ankylosing spondylitis, Rheumatology international, 32, 2093-2099, 2012
Country/ies where the study was carried out	Turkey
Study type	Randomised controlled trial, prospective, single blinded
Aim of the study	To investigate the effects of Pilates on pain, functional status, and quality of life in patients with ankylosing spondylitis.
Study dates	Not reported. Study published 2012.
Source of funding	Not reported
Sample size	55 participants were recruited; 53 completed the study.
Characteristics	Characteristics of recruited patients: Overall 30 men, 25 women. Mean (sd) overall age: 45.23(10.73). In Pilates group: 46.5(11.2); in control 43.6(10.1) Mean duration of disease 8.84 years Participants were allowed to continue their previous medication, but were requested not to use supplementary drugs or change the usual dosages throughout the study period and were asked not to take any pain killers in the morning of the assessment day. Regular drug treatment: 31% received NSAID, 32% sulfasalazine, 21% biological agent. 17% of participants used no regular medication
Inclusion criteria	Not explicitly reported. However, all participants were under a regular follow-up protocol and had a diagnosis of ankylosing spondylitis according the modified New York criteria.

Bibliographic reference	Altan,L., Korkmaz,N., Dizdar,M., Yurtkuran,M., Effect of Pilates training on people with ankylosing spondylitis, Rheumatology international, 32, 2093-2099, 2012
Exclusion criteria	Patients who had active peripheral arthritis, total spinal ankylosis, ESR over 50 mm/h, or CRP more than 10 times the normal value were excluded. The patients whose treatment regimens were changed during the last 2 months prior to the study were not included.
Details	Participant evaluation Evaluations performed just before intervention (week 0), immediately after (week 12) and 12 weeks following treatment (week 24) by blinded assessor. Outcome measurement Functional capacity - BASFI Disease activity - BASDAI Spinal mobility - BASMI Chest expansion - measurement of increase in chest circumference at the level of the forth intercostal after maximum inspiration following previous forced expiration. Health quality - ASQoL Statistical analysis Parameter normality testing using Shapiro-Wilk test. Intra-group comparisons using Wilcoxen test. Between-group comparisons using T test and Mann-Whitney U test. Categorical variables compared with chi-squared test and Fischer's exact test. P value threshold specified as 0.05.
Interventions	Exercise group (30 participants): Pilates exercise program of 1 hour was given by a certified trainer to 30 participants 3 times a week for 12 weeks. Exercise program followed the basic principles of Pilates method but particularly movements with low and medium difficulty levels were chosen to adapt the program to the physical capacity of the patients. Protocol comprised 9 modules: postural education, search for neutral position, sitting exercise, antalgic exercises, stretching exercises, proprioceptivity improvement exercises, and breathing education. Resistance bands and 26 cm Pilates balls were used as supportive equipment. Control group (25 participants): Continuation of previous standard treatment programs. The patients in the control group received usual care and were instructed to continue participating in their usual physical activity.
Results	Changes in measurement scores (mean (SD)) from baseline (week 0) measurements Joint Mobility Spinal mobility (BASMI) Exercise: Week 12: -0.4(0.7); Week 24: -0.4(0.8)

<table>
<tr><th>Bibliographic reference</th><th>Altan,L., Korkmaz,N., Dizdar,M., Yurtkuran,M., Effect of Pilates training on people with ankylosing spondylitis, Rheumatology international, 32, 2093-2099, 2012</th></tr>
<tr><td></td><td>Control: Week 12:-0.2(0.8); Week 24: 0.2(1.1)

Chest expansion (cm)
Exercise: Week 12: 0.2(0.3); Week 24: 0.2(0.4)
Control: Week 12: 0.2(0.4); Week 24: 0.1(0.5)

Physical function
Functional capacity (BASFI)
Exercise: Week 12: -0.7(1.5); Week 24: -0.7(1.2)
Control: Week 12: 0.1(0.9); Week 24: 0.1(1.1)

Disease activity (BASDAI)
Exercise: Week 12: -0.7(1.8); Week 24: -0.4(2.1)
Control: Week 12: 0.5(1.1); Week 24: 0.4(0.9)

Quality of Life
Health quality (ASQoL)
Exercise: Week 12: 0.3(2.9) ; Week 24: 0.1(3.4)
Control: Week 12: -0.2(1.5); Week 24: -0.4(1.7)</td></tr>
<tr><td>BASDAI</td><td>BASDAI<table><tr><td></td><td>Mean</td><td>SD</td><td>Total</td></tr><tr><td>Experimental</td><td>-0.40</td><td>2.10</td><td>30</td></tr><tr><td>Control</td><td>0.40</td><td>0.90</td><td>25</td></tr></table></td></tr>
<tr><td>BASFI</td><td>BASFI<table><tr><td></td><td>Mean</td><td>SD</td><td>Total</td></tr><tr><td>Experimental</td><td>-0.70</td><td>1.20</td><td>30</td></tr><tr><td>Control</td><td>0.10</td><td>1.10</td><td>25</td></tr></table></td></tr>
<tr><td>BASMI</td><td>BASMI</td></tr>
</table>

Bibliographic reference	Altan,L., Korkmaz,N., Dizdar,M., Yurtkuran,M., Effect of Pilates training on people with ankylosing spondylitis, Rheumatology international, 32, 2093-2099, 2012
	<table><tr><td></td><td>Mean</td><td>SD</td><td>Total</td></tr><tr><td>Experimental</td><td>-0.40</td><td>0.80</td><td>30</td></tr><tr><td>Control</td><td>0.20</td><td>1.10</td><td>25</td></tr></table>
ASQoL	ASQoL <table><tr><td></td><td>Mean</td><td>SD</td><td>Total</td></tr><tr><td>Experimental</td><td>0.10</td><td>3.40</td><td>30</td></tr><tr><td>Control</td><td>-0.40</td><td>1.70</td><td>25</td></tr></table>
Chest expansion	Chest expansion <table><tr><td></td><td>Mean</td><td>SD</td><td>Total</td></tr><tr><td>Experimental</td><td>0.20</td><td>0.40</td><td>30</td></tr><tr><td>Control</td><td>0.10</td><td>0.50</td><td>25</td></tr></table>
Was the allocation sequence adequately generated?	YES
Was allocation adequately concealed?	YES
Was knowledge of the allocated intervention adequately prevented during the study?	NO
Were incomplete outcome data adequately addressed?	UNCLEAR
Are reports of the study free of suggestion of selective outcome reporting?	UNCLEAR
Was the study apparently free of other problems that could put it at a high risk of bias?	UNCLEAR

Bibliographic reference	Altan,L., Korkmaz,N., Dizdar,M., Yurtkuran,M., Effect of Pilates training on people with ankylosing spondylitis, Rheumatology international, 32, 2093-2099, 2012
Risk of Bias	Participants were not blinded to treatment allocation
Other information	

Table 120: Analay et al., 2003

Bibliographic reference	Analay,Yildiz, Ozcan,Emel, Karan,Ayse, Diracoglu,Demirhan, Aydin,Resa, The effectiveness of intensive group exercise on patients with ankylosing spondylitis, Clinical rehabilitation, 17, 631-636, 2003
Country/ies where the study was carried out	Turkey
Study type	Randomised controlled trial
Aim of the study	To compare the effectiveness of supervised group exercise with home physiotherapy in people with ankylosing spondylitis.
Study dates	Not reported. Submitted 2002, published 2003
Source of funding	Not reported
Sample size	51 patients recruited, 45 remaining at follow up
Characteristics	Intervention (group therapy) age (mean(sd)): 36.7 (11.3) gender:3 female, 20 male weight (mean(sd)): 69.8(9.6) kg height (mean(sd)): 170.8(5.8) cam Control (home exercise) age (mean(sd)): 34.3(7.9) gender: 4 female, 18 male weight (mean(sd)): 71.1(10.4)kg height (mean(sd)): 169.3(7.0) cm
Inclusion criteria	Diagnosed according to Amor criteria

Bibliographic reference	Analay,Yildiz, Ozcan,Emel, Karan,Ayse, Diracoglu,Demirhan, Aydin,Resa, The effectiveness of intensive group exercise on patients with ankylosing spondylitis, Clinical rehabilitation, 17, 631-636, 2003
	Aged 18-55 Able to participate in the proposed exercise
Exclusion criteria	People with systemic organ involvement, severe deformities of limited hip and knee joint motion preventing regular cycling Those treated with physiotherapy in the last three months People receiving DMARDs People already practicing regular exercise
Details	Diagnostic criteria Amor criteria Randomisation, allocation, blinding Randomisation by sealed envelopes on 1:1 basis to control or exercise group. Diagnosing physician and the physician making the pre- and post-intervention assessments were different people. a different physiotherapist gave the exercises. Assessing doctor was blinded to treatment allocation. Therapist was blinded to patients' clinical evaluations Measurements Pain measured on VAS, morning stiffness by questionnaire. No detail was given about how flexibility tests were performed. General physical condition was evaluated with Astrand test. BASFI used to measure functional status. Statistical analysis Methods not stated
Interventions	All patients had a 1 hour training programme at entry, containing information about spondyloarthropathies and the purpose of physical exercise. Intervention: physical therapy programme Delivered to 4-5 subjects for 6 weeks (3 days a week, 50 minutes per day) Supervised by physiotherapist stretching, mobilisation and strengthening exercises for lower, upper extremities and back muscles Aerobic exercise on static bicycle Postural and respiratory exercises Exercises performed without resistance then, according to individual tolerance, according to the De Lateur method

Bibliographic reference	Analay,Yildiz, Ozcan,Emel, Karan,Ayse, Diracoglu,Demirhan, Aydin,Resa, The effectiveness of intensive group exercise on patients with ankylosing spondylitis, Clinical rehabilitation, 17, 631-636, 2003
	Control (home exercise) Patients were taught the same exercises taught to the intervention group but asked to perform these at home individually for six weeks (3 days a week) Called by phone every week
Results	Note: in the hospital exercise group there were 27 patients at baseline and 23 remaining at follow-up; in control group there were 24 at baseline and 22 at follow-up Pain Pain at rest, visual analogue scale (mean (sd)) Exercise (hospital): baseline: 3.82(3.4); post-treatment: 3.3(2.3); 3-months: 3.43(2.5) Control: baseline: 3.13(2.6); post-treatment: 3.09(3.6); 3-months: 3.18(3.1) Pain during activity, visual analogue scale Exercise (hospital): baseline: 4.47(3.2); post-treatment: 4.21(2.8); 3-months: 4.65(2.6) Control: baseline: 4.59(3.3); post-treatment: 4.31(3.3); 3-months: 5.31(3.2) Morning stiffness Exercise (hospital): baseline: 38.65(60.32); post-treatment: 20.87(32.34); 3-months: 24.04(36.24) Control: baseline: 36.59(51.44); post-treatment: 37(62.01); 3-months: 35.54(36.77) Adverse events None reported Joint mobility Fingertip to floor distance (cm) (mean (sd)) Exercise (hospital): baseline: 20.77(14.03); post-treatment: 15.5(12.97); 3-months: 17.13(13.63) Control: baseline: 19.09(17.95); post-treatment: 18.13(17.92); 3-months: 18.98(17.64) Chest expansion (cm) (mean (sd)) Exercise (hospital): baseline: 3.97(2.09); post-treatment: 4.73(1.94); 3-months: 4.28(2.14) Control: baseline: 4.13(2.31); post-treatment: 4.22(2.13); 3-months: 4.0(2.39) Modified lumbar Schober test (cm) (mean (sd))

<table>
<tr><th>Bibliographic reference</th><th>Analay,Yildiz, Ozcan,Emel, Karan,Ayse, Diracoglu,Demirhan, Aydin,Resa, The effectiveness of intensive group exercise on patients with ankylosing spondylitis, Clinical rehabilitation, 17, 631-636, 2003</th></tr>
<tr><td></td><td>Exercise (hospital): baseline: 4.38(2.82); post-treatment: 5.26(3.16); 3-months: 5.13(3.16)
Control: baseline: 3.28(2.82); post-treatment: 3.96(3.16); 3-months:3.13(3.16)

Tragus-to-wall distance (cm)
Exercise (hospital): baseline: 16.97(5.63); post-treatment: 14.02(5.18); 3-months: 14.71(5.22)
Control: baseline: 15.54(3.32); post-treatment: 14.81(3.42); 3-months: 14.95(3.87)

Intermalleolar distance (cm)
Exercise (hospital): baseline: 90.95(21.68); post-treatment: 100.40(22.0); 3-months: 97.90(19.71)
Control: baseline: 92.95(21.24); post-treatment: 94.95(21.69); 3-months: 96.04(24.29)

Physical function
BASFI (mean (sd))
Exercise (hospital): baseline: 26.34(20.10); post-treatment: 20.0(16.76); 3-months:22.0(17.15)
Control: baseline: 27.59(17.82); post-treatment: 27.31(20.42); 3-months: 26.13(17.20)

Other measurements in study not reported here: VO2max

Quality of life
Not reported

Imaging
Not reported

Composite measures
Beck score - not reported here</td></tr>
<tr><td>Pain</td><td>Pain<table><tr><td></td><td>Mean</td><td>SD</td><td>Total</td></tr><tr><td>Experimental</td><td>-0.39</td><td>3.40</td><td>23</td></tr></table></td></tr>
</table>

Bibliographic reference	Analay,Yildiz, Ozcan,Emel, Karan,Ayse, Diracoglu,Demirhan, Aydin,Resa, The effectiveness of intensive group exercise on patients with ankylosing spondylitis, Clinical rehabilitation, 17, 631-636, 2003
	Control 0.05 3.40 22
BASFI	BASFI Mean SD Total Experimental -4.34 20.10 23 Control -1.46 20.10 22
Finger-floor distance	Finger-floor distance Mean SD Total Experimental -3.64 17.95 23 Control -0.11 17.95 22
Schober test	Schober test Mean SD Total Experimental 0.75 3.16 23 Control -0.15 3.16 22
Chest expansion	Chest expansion

Bibliographic reference	Analay,Yildiz, Ozcan,Emel, Karan,Ayse, Diracoglu,Demirhan, Aydin,Resa, The effectiveness of intensive group exercise on patients with ankylosing spondylitis, Clinical rehabilitation, 17, 631-636, 2003
	<table><tr><td></td><td>Mean</td><td>SD</td><td>Total</td></tr><tr><td>Experimental</td><td>0.31</td><td>2.39</td><td>23</td></tr><tr><td>Control</td><td>-0.13</td><td>2.39</td><td>22</td></tr></table>
Stiffness	Stiffness <table><tr><td></td><td>Mean</td><td>SD</td><td>Total</td></tr><tr><td>Experimental</td><td>-14.61</td><td>60.32</td><td>23</td></tr><tr><td>Control</td><td>-1.05</td><td>60.32</td><td>22</td></tr></table>
Cervical flexion (occiput- and tragus-wall tests)	Cervical flexion (occiput- and tragus-wall tests) <table><tr><td></td><td>Mean</td><td>SD</td><td>Total</td></tr><tr><td>Experimental</td><td>-2.26</td><td>5.63</td><td>23</td></tr><tr><td>Control</td><td>-0.73</td><td>5.63</td><td>22</td></tr></table>
Intermalleolar distance	Intermalleolar distance <table><tr><td></td><td>Mean</td><td>SD</td><td>Total</td></tr><tr><td>Experimental</td><td>6.14</td><td>24.29</td><td>23</td></tr><tr><td>Control</td><td>3.09</td><td>24.29</td><td>22</td></tr></table>

Bibliographic reference	Analay,Yildiz, Ozcan,Emel, Karan,Ayse, Diracoglu,Demirhan, Aydin,Resa, The effectiveness of intensive group exercise on patients with ankylosing spondylitis, Clinical rehabilitation, 17, 631-636, 2003
Was the allocation sequence adequately generated?	YES
Was allocation adequately concealed?	YES
Was knowledge of the allocated intervention adequately prevented during the study?	NO
Were incomplete outcome data adequately addressed?	YES
Are reports of the study free of suggestion of selective outcome reporting?	YES
Was the study apparently free of other problems that could put it at a high risk of bias?	YES
Risk of Bias	For this intervention, participant blinding to allocation is not feasible. However, attempts were made to achieve good assessor blinding.
Other information	Mean differences and SDs calculated manually according to Cochrane Handbook guidelines

Table 121: Bulstrode et al., 1987

Bibliographic reference	Bulstrode,S.J., Barefoot,J., Harrison,R.A., Clarke,A.K., The role of passive stretching in the treatment of ankylosing spondylitis, British journal of rheumatology, 26, 40-42, 1987
Country/ies where the study was carried out	UK
Study type	Randomised controlled trial
Aim of the study	To establish whether daily passive stretching of soft tissues around the hip joint in people with ankylosing spondylitis could increase the range of movement and whether any improvement could be maintained in the long term.

Bibliographic reference	Bulstrode,S.J., Barefoot,J., Harrison,R.A., Clarke,A.K., The role of passive stretching in the treatment of ankylosing spondylitis, British journal of rheumatology, 26, 40-42, 1987
Study dates	Not reported. Submitted 1985, published 1987.
Source of funding	Not reported
Sample size	39 people with ankylosing spondylitis: 27 in the intervention group and 12 in the control
Characteristics	No baseline demographic or disease state/duration characteristics were reported
Inclusion criteria	Patients admitted to Royal National Hospital for Rheumatic Diseases for a 15 day rehabilitation programme
Exclusion criteria	None reported
Details	Recruitment and randomisation 39 consecutively admitted patients were recruited and allocated in blocks of 9 with the aim of having two intervention group participants for every one control. No information on blinding or allocation concealment Measurements Measurements were recorded by an independent assessor blinded to treatment allocation. The following were measured at admission, discharge and at six months: flexion extension (knee in extension) extension (knee in flexion) single abduction bilateral abduction (intermalleolar distance) medial rotation lateral rotation Statistical analysis Two-tailed Student's two-sample T-test was used to analyse between-group differences

Bibliographic reference	Bulstrode,S.J., Barefoot,J., Harrison,R.A., Clarke,A.K., The role of passive stretching in the treatment of ankylosing spondylitis, British journal of rheumatology, 26, 40-42, 1987
Interventions	Intervention A 'contract and relax' technique followed by a passive stretch of the muscle groups, repeated three times. Group participants were taught how to perform the stretching techniques on themselves and with the assistance of a helper. The control group received no intervention.
Results	Results reported as change at three weeks (mean (sd)) Pain Not reported Adverse events Joint mobility Flexion Exercise: 7.5(9.9) Control: 3.8(6.9) Extension (knee in extension) Exercise: 2.4(4.4) Control: -0.4(4.3) Extension (knee in flexion) Exercise: 3.2(4.1) Control: -0.1(4.3) Single abduction Exercise: 3.5(4.4) Control: 0.08(5.6) Bilateral abduction (intermalleolar distance) Exercise: 10.0(7.2) Control: 3.8(6.4)

<table>
<tr><th>Bibliographic reference</th><th>Bulstrode,S.J., Barefoot,J., Harrison,R.A., Clarke,A.K., The role of passive stretching in the treatment of ankylosing spondylitis, British journal of rheumatology, 26, 40-42, 1987</th></tr>
<tr><td></td><td>Medial rotation
Exercise: 4.7(5.3)
Control: 0.9(5.2)

Lateral rotation
Exercise: 6.6(6.3)
Control: 1.0(5.1)

Physical function
Not reported

Quality of life
Not reported

Imaging
Not reported

Composite measures
Not reported</td></tr>
<tr><td>Intermalleolar distance</td><td>Intermalleolar distance<table><tr><td></td><td>Mean</td><td>SD</td><td>Total</td></tr><tr><td>Experimental</td><td>10.00</td><td>7.20</td><td>27</td></tr><tr><td>Control</td><td>3.80</td><td>6.40</td><td>12</td></tr></table></td></tr>
<tr><td>Was the allocation sequence adequately generated?</td><td>UNCLEAR</td></tr>
<tr><td>Was allocation adequately concealed?</td><td>UNCLEAR</td></tr>
<tr><td>Was knowledge of the allocated intervention adequately prevented during the study?</td><td>UNCLEAR</td></tr>
</table>

Bibliographic reference	Bulstrode,S.J., Barefoot,J., Harrison,R.A., Clarke,A.K., The role of passive stretching in the treatment of ankylosing spondylitis, British journal of rheumatology, 26, 40-42, 1987
Were incomplete outcome data adequately addressed?	UNCLEAR
Are reports of the study free of suggestion of selective outcome reporting?	UNCLEAR
Was the study apparently free of other problems that could put it at a high risk of bias?	NO
Risk of Bias	Limited baseline data (no report on age, gender, duration/stage of disease) reported, making it difficult to determine whether randomisation was successful or whether there may be selection bias. No detail given on randomisation, allocation concealment or blinding.
Other information	n/a

Table 122: Cagliyan et al., 2007

Bibliographic reference	Cagliyan,A., Kotevoglu,N., Onal,T., Tekkus,B., Kuran,B., Does group exercise program add anything more to patients with ankylosing spondylitis?, Journal of back and musculoskeletal rehabilitation, 20, 79-85, 2007
Country/ies where the study was carried out	Turkey
Study type	Randomised controlled trial
Aim of the study	To compare a group exercise programme performed at hospital with a home exercise programme in patients with ankylosing spondylitis.
Study dates	Not reported. Published 2007
Source of funding	Not reported
Sample size	46 participants randomised into two groups of 23
Characteristics	Patient characteristics

Bibliographic reference	Cagliyan,A., Kotevoglu,N., Onal,T., Tekkus,B., Kuran,B., Does group exercise program add anything more to patients with ankylosing spondylitis?, Journal of back and musculoskeletal rehabilitation, 20, 79-85, 2007
	Exercise (n=23): 3 female, mean age 36.8(9.4) mean BMI 24.2(3.6) Home (n=23): 5 female, mean age 35.2, mean BMI 25.6(4.6) Diagnostic criteria Diagnosed according to modified New York criteria
Inclusion criteria	Able to tolerate cardiovascular exercises Able to come to attend the hospital for the exercise programme
Exclusion criteria	Participants were excluded if one of the following applied: Juvenile patients Presence of comorbidities or another systemic disease Infection Lower back pain due to lumbar disc herniation
Details	Randomisation Patients divided randomly into two groups. No details of sequence method or allocation concealment Measurements Patients were evaluated at baseline, 3 months and 6 months by the same observer. Measurements included a number of standardised scales (BASFI, BASDAI, SF-36, Beck depression scale) as well as a number of physical and self-reported measures. Analysis One way Anova, Students t test, Mann Whitney U test and Wilcoxen test were used fir quantitative data. Chi squared test and Fischer Exact Ki-square test used for qualitative data.
Interventions	Both groups attended an educational programme of one hour covering clinical aspects (disease course, signs and symptoms) of the disease. Handouts given prior to the session. Intervention Exercise under supervision of physiotherapist at the hospital, 2 sessions of 1 hour per week for 3 months.

Bibliographic reference	Cagliyan,A., Kotevoglu,N., Onal,T., Tekkus,B., Kuran,B., Does group exercise program add anything more to patients with ankylosing spondylitis?, Journal of back and musculoskeletal rehabilitation, 20, 79-85, 2007
	Exercise programme included joint range of motion, flexibility of the cervical, thoracic and lumbar spine, stretching of the shortened muscles, and respiration and posture exercises. Control Exercise at home. Exercises taught to group and advised to do them for 3 months at home. Checked via telephone and motivated as needed.
Results	Pain Pain at rest, visual analogue scale (mean (sd)) Exercise (supervised): baseline: 4.1(2.9); 3 months: 1.9(1.9); 6 months: 2.7(2.7) Control (home exercise): baseline: 2.2(2.7); 3 months: 2.5(2.4); 6 months: 3.5(3.1) Pain during activity, visual analogue scale Exercise (supervised): baseline: 4.6(2.8); 3 months: 2.2(1.9); 6 months: 2.7(2.7) Control (home exercise): baseline: 4.3(3.2); 3 months: 2.5(2.4); 6 months: 3.5(3.1) Morning stiffness: Not fully reported Adverse events Not reported Joint mobility Fingertip to floor distance (cm) (mean (sd)) Exercise (supervised): baseline: 20.8(12.5); 3 months: 12.4(10.7); 6 months: 14.3(12.1) Control (home exercise): baseline: 21.0(15.2); 3 months: 21.4(16.3); 6 months: 19.6(17.5) Modified lumbar Schober test (cm) (mean (sd)) Exercise (supervised): baseline: 4.2(1.9); 3 months: 5.3(2.8); 6 months: 4.4(1.8) Control (home exercise): baseline: 4.2(2.4); 3 months: 4.0(2.3); 6 months: 3.9(2.1) Occiput-to-wall distance (cm) Exercise (supervised): baseline: 9.1(4.2); 3 months: 7.1(4.5); 6 months: 5.1(4.9)

Bibliographic reference	Cagliyan,A., Kotevoglu,N., Onal,T., Tekkus,B., Kuran,B., Does group exercise program add anything more to patients with ankylosing spondylitis?, Journal of back and musculoskeletal rehabilitation, 20, 79-85, 2007
	Control (home exercise): baseline: 9.0(5.9); 3 months: 7.8(6.4); 6 months: 6.3(6.6) Intermalleolar-distance Exercise (supervised): baseline: 97.7(23.9); 3 months: 111.0(20.7); 6 months: 110.9(23.4) Control (home exercise): baseline: 86.2(30.6); 3 months: 94.2(31.8); 6 months: 96.3(33.9) Cervical rotation Exercise (supervised): baseline: 59(21); 3 months: 70(20); 6 months: 71(21) Control (home exercise): baseline: 70(21); 3 months: 73(22); 6 months: 73(23) Other outcomes reported in article, not reported here: Dorsal Schober Physical function BASFI (mean (sd)) Exercise (supervised): baseline: 3.3(1.8); 3 months: 1.6(1.4); 6 months: 1.9(1.4) Control (home exercise): baseline: 2.3(2.3); 3 months: 2.8(2.3); 6 months: 3.4(3.0) BASDAI (mean (sd)) Exercise (supervised): baseline: 4.3(1.9); 3 months: 2.4(1.0); 6 months: 2.7(1.5) Control (home exercise): baseline: 1.9(1.7); 3 months: 3.4(1.8); 6 months: 3.8(2.3) Quality of life SF-36 Physical function Exercise (supervised): baseline: 73.4(14.1); 3 months: 87.8(9.7); 6 months: 80.6(30.6) Control (home exercise): baseline: 67.3(21.2); 3 months: 72.8(22.5); 6 months: 74.1(24.9) SF-36 Physical role difficulty Exercise (supervised): baseline: -58.6(41.0); 3 months: -23.9(29.6); 6 months: -29.3(34.2) Control (home exercise): baseline: -60.8(33.5); 3 months: -48.9(39.5); 6 months: -52.1(39.1) SF-36 Mental Health Exercise (supervised): baseline: 57.0(17.9); 3 months: 75.1(15.0); 6 months: 66.0(27.1)

<table>
<tr><th>Bibliographic reference</th><th>Cagliyan,A., Kotevoglu,N., Onal,T., Tekkus,B., Kuran,B., Does group exercise program add anything more to patients with ankylosing spondylitis?, Journal of back and musculoskeletal rehabilitation, 20, 79-85, 2007</th></tr>
<tr><td></td><td>Control (home exercise): baseline: 57.7(22.4); 3 months: 64.3(20.2); 6 months: 60.0(29.9)

Imaging
Not reported

Composite measures</td></tr>
<tr><td>Pain</td><td>Pain<table><tr><td></td><td>Mean</td><td>SD</td><td>Total</td></tr><tr><td>Experimental</td><td>1.40</td><td>2.90</td><td>23</td></tr><tr><td>Control</td><td>1.30</td><td>2.90</td><td>23</td></tr></table></td></tr>
<tr><td>BASDAI</td><td>BASDAI<table><tr><td></td><td>Mean</td><td>SD</td><td>Total</td></tr><tr><td>Experimental</td><td>-1.60</td><td>2.30</td><td>23</td></tr><tr><td>Control</td><td>1.90</td><td>2.30</td><td>23</td></tr></table></td></tr>
<tr><td>BASFI</td><td>BASFI<table><tr><td></td><td>Mean</td><td>SD</td><td>Total</td></tr><tr><td>Experimental</td><td>-1.40</td><td>3.00</td><td>23</td></tr><tr><td>Control</td><td>1.10</td><td>3.00</td><td>23</td></tr></table></td></tr>
<tr><td>Finger-floor distance</td><td>Finger-floor distance<table><tr><td></td><td>Mean</td><td>SD</td><td>Total</td></tr><tr><td>Experimental</td><td>-6.50</td><td>17.50</td><td>23</td></tr><tr><td>Control</td><td>-1.40</td><td>17.50</td><td>23</td></tr></table></td></tr>
<tr><td>Schober test</td><td>Schober test</td></tr>
</table>

Bibliographic reference	Cagliyan,A., Kotevoglu,N., Onal,T., Tekkus,B., Kuran,B., Does group exercise program add anything more to patients with ankylosing spondylitis?, Journal of back and musculoskeletal rehabilitation, 20, 79-85, 2007
	<table><tr><td></td><td>Mean</td><td>SD</td><td>Total</td></tr><tr><td>Experimental</td><td>0.20</td><td>2.40</td><td>23</td></tr><tr><td>Control</td><td>-0.30</td><td>2.40</td><td>23</td></tr></table>
Cervical flexion (occiput- and tragus-wall tests)	Cervical flexion (occiput- and tragus-wall tests)<table><tr><td></td><td>Mean</td><td>SD</td><td>Total</td></tr><tr><td>Experimental</td><td>-4.00</td><td>6.60</td><td>23</td></tr><tr><td>Control</td><td>-2.70</td><td>6.60</td><td>23</td></tr></table>
Cervical rotation	Cervical rotation<table><tr><td></td><td>Mean</td><td>SD</td><td>Total</td></tr><tr><td>Experimental</td><td>12.00</td><td>23.00</td><td>23</td></tr><tr><td>Control</td><td>3.00</td><td>23.00</td><td>23</td></tr></table>
Intermalleolar distance	Intermalleolar distance<table><tr><td></td><td>Mean</td><td>SD</td><td>Total</td></tr><tr><td>Experimental</td><td>13.20</td><td>33.90</td><td>23</td></tr><tr><td>Control</td><td>10.10</td><td>33.90</td><td>23</td></tr></table>
Was the allocation sequence adequately generated?	UNCLEAR
Was allocation adequately concealed?	UNCLEAR
Was knowledge of the allocated intervention adequately prevented during the study?	UNCLEAR
Were incomplete outcome data adequately addressed?	UNCLEAR

Bibliographic reference	Cagliyan,A., Kotevoglu,N., Onal,T., Tekkus,B., Kuran,B., Does group exercise program add anything more to patients with ankylosing spondylitis?, Journal of back and musculoskeletal rehabilitation, 20, 79-85, 2007
Are reports of the study free of suggestion of selective outcome reporting?	NO
Was the study apparently free of other problems that could put it at a high risk of bias?	NO
Risk of Bias	No description of treatment allocation method, or blinding of staff assessing patients or carrying out the intervention. Reporting of outcomes inconsistent - most appear in detail in tables, but two (chest expansion, morning stiffness) only partially reported in text, and one (number of swollen joints) specified in methods but not reported in results.
Other information	Detail about number of participants per treatment group not clearly reported - from baseline characteristics table it was inferred that there were 23 per group. Mean difference after 6 months manually calculated, with SDs imputed following guidance in Cochrane handbook

Table 123: Chimenti et al., 2014

Bibliographic reference	Chimenti, M.S., Triggianese, P.C., Santoro, M., Lucchetti, R., Perricone, R.Self-reported adherence to a home-based exercise program among patients affected by psoriatic arthritis with minimal disease activity, Drug Development Research, 75, S57-59, 2014
Population	People with minimal disease activity' psoriatic arthritis
Setting	Italy
Study type	single arm intervention
Aim of the study	To evaluate the benefits of a home—based exercises programme on disease activity and quality of life in 'minimal disease activity' people with psoriatic arthritis
Study dates	Not reported
Source of funding	Pfizer Italia
Sample size	30 participants of whom 23 completed the exercise program.
Characteristics	12 women, 18 men. Mean age 50.8 years (SD 9.5 years). All participants were receiving combination therapy of an anti-TNF and at least one DMARD.
Inclusion Criteria	People with minimal disease activity PsA on stable drug therapy for at least 3 months
Exclusion Criteria	Not reported
Methods	Exercise programme delivered by a single physiotherapist. It comprised:

Bibliographic reference	Chimenti, M.S., Triggianese, P.C., Santoro, M., Lucchetti, R., Perricone, R.Self-reported adherence to a home-based exercise program among patients affected by psoriatic arthritis with minimal disease activity, Drug Development Research, 75, S57-59, 2014
	Three circuits of aerobic exercises performed in intervals of 3-4 mins for 40 mins. Exercises performed at least 10 times, once a day, twice a week at home
Results	Pain VAS (mean (SD)): Baseline: 43.7 (23.1); 12 weeks: 48.6 (24.8) Patient global VAS (mean (SD)): Baseline: 46.9 (18.7); 12 weeks: 42.9 (27.01) SpA-HAQ (mean (SD)): Baseline: 0.58 (0.4):12 weeks: 0.56 (0.51)
Limitations	Very limited reporting of study methods and population characteristics. No comparison group.
Other information	Risk of bias assessment Was the allocation sequence adequately generated? No Was allocation adequately concealed? No Was knowledge of the allocated intervention adequately prevented during the study? No Were incomplete outcome data adequately addressed? Unclear Are reports of the study free of suggestion of selective outcome reporting? Yes Was the study apparently free of other problems that could put it at a high risk of bias? no Risk of bias: Very serious risk of bias due to lack of randomised control group

Table 124: Fang 2016

Bibliographic reference	Fang, H., Cai, W., Pan, Y, Wu, D., Liang, L, Six month home-based exercise and supervised training in patients with ankylosing spondylitis, Inter J Clin Exp Med, 9 (3): 6635-41, 2016
Population	People with ankylosing spondylitis
Setting	Recruitment from hospital settings in Guanghou, China
Study type	Randomised controlled trial
Aim of the study	To investigate the effects on mobility, physical function and quality of life of combined home-based exercise and supervised training for people with AS.
Study dates	November 2012 – October 2014

Bibliographic reference	Fang, H., Cai, W., Pan, Y, Wu, D., Liang, L, Six month home-based exercise and supervised training in patients with ankylosing spondylitis, Inter J Clin Exp Med, 9 (3): 6635-41, 2016
Source of funding	Not reported
Sample size	65 assessed for eligibility, 21 excluded, 41 randomised. Intervention group: 24 of whom 3 were lost to follow up. Control group: 20 of whom 7 were lost to follow up.
Characteristics	Intervention group (n=21): age (mean (SD): 26.62 (4.72) male, n (%): 17 (81) disease duration, years (mean (SD)): 4.56 (3.92) drug use: NSAIDS, n (%): 20 (95.2) Biologics, n (%): 12 (57.1) Others, n (%): 12 (57.1) Control group (n= 13): age (mean (SD): 26.46 (6.78) male, n (%): 13 (100) disease duration, years (mean (SD)): 4.88 (3.50) drug use: NSAIDS, n (%): 13 (100) Biologics n (%): 10 76.9) Others n (%): 9 (69.2)
Inclusion Criteria	AS confirmed with modified NY criteria 16-60 years old Female patients of childbearing age agreed to used contraception till the end of the study sufficient literacy to complete study programme disease of at least 6 months duration, in well-controlled state
Exclusion Criteria	pregnant/lactating women affected joints have experienced trauma or surgery in the last year fibromyalgia heart failure, multiple sclerosis, severe COPD, recurrent infection, lymphoma or other malignancies, history of TB people with mental illnesses people who cannot regularly attend the clinic

Bibliographic reference	Fang, H., Cai, W., Pan, Y, Wu, D., Liang, L, Six month home-based exercise and supervised training in patients with ankylosing spondylitis, Inter J Clin Exp Med, 9 (3): 6635-41, 2016
Methods	Randomisation sequence was computer generated Exercise intervention : Flexibility home based exercises at least 3 times a week for 6 months Each exercise [session] lasted 60 minutes Based on American College of Sports Medicine recommendations. Comprised warm up exercises, chest exercises, muscle exercises of lumbar spine, abdominal exercise, waist muscle group exercise People in this group attended hospital once a month for one-to-one exercise training under the guidance of the physiotherapist Followed up by research nurse by telephone every 2 weeks to check in participants were completing exercises, had adverse events, or needed any questions answered Control group: Doctor guidance on conventional drugs and disease education including home based exercise training, but not one to one exercise therapy Measures: Participants were evaluated at baseline and six months, with measures including BASMI, BASDAI, BASFI and the Chinese version of SF-36v2 (quality of life measure)
Results	BASMI (mean (SD)) Intervention group: Baseline: 1.62 (1.94); 6 months: 1.19 (1.66) Control group Baseline: 2.31 (2.06);6 months: 2.00 (1.87) BASDAI (mean (SD)): Intervention group Baseline: 2.66 (1.69); 6 months: 1.21 (1.54) Control group Baseline: 3.19 (1.29); 6 months: 2.0 (1.64) BASFI (mean (SD)): Intervention group Baseline: 1.35 (1.74);6 months: 0.24 (0.75)

Bibliographic reference	Fang, H., Cai, W., Pan, Y, Wu, D., Liang, L, Six month home-based exercise and supervised training in patients with ankylosing spondylitis, Inter J Clin Exp Med, 9 (3): 6635-41, 2016
	Control group Baseline: 2.05 (2.26); 6 months: 1.63 (2.24) SF36v2 (mean (SD)) Composite score not reported; reported results were stratified by survey domain
Limitations	Authors highlight the number of non-completing participants which lead to an imbalance in numbers across the two groups
Other information	Risk of bias assessment Was the allocation sequence adequately generated? Yes Was allocation adequately concealed? Unclear Was knowledge of the allocated intervention adequately prevented during the study? Yes Were incomplete outcome data adequately addressed? unclear Are reports of the study free of suggestion of selective outcome reporting? Yes Was the study apparently free of other problems that could put it at a high risk of bias? Yes Risk of bias: Moderate risk of bias due to high drop-out rate

Table 125: Hseih 2014

Bibliographic reference	Hseih, L.F., Chuang, C.C., Tseng, C.S., Wei, J.C.C., Hsu, W.C, Lin, Y.J. Combined home exercise is more effective than range of motion home exercise in patients with ankylosing spondylitis: a randomised controlled trial. BioMed Research International, 2014
Population	People with ankylosing spondylitis
Setting	Recruitment from outpatient clinics of allergy-immunology-rheumatology in a private teaching hospital and an AS care group (Taiwan)
Study type	Randomised controlled trial
Aim of the study	To compare the effectiveness of combined home exercise and range of motion home exercise in people with ankylosing spondylitis.
Study dates	Not reported
Source of funding	Grants from the Taiwan National Science Council
Sample size	44 people assessed for eligibility, of whom 22 were randomised (11 per group), and 3 were lost to follow up. 9 were available for the final analysis

Bibliographic reference	Hseih, L.F., Chuang, C.C., Tseng, C.S., Wei, J.C.C., Hsu, W.C, Lin, Y.J. Combined home exercise is more effective than range of motion home exercise in patients with ankylosing spondylitis: a randomised controlled trial. BioMed Research International, 2014
Characteristics	Intervention group (n=9): Age, yrs (mean (SD)): 36.2 (11.7) Male (n): 6 Disease duration, years (mean (SD)): 11.1 (6.8) Medication NSAID (n yes): 9 DMARD (n yes): 6 Control group (n=10): Age, yrs (mean (SD)): 42.1 (8.8) Male (n): 7 Disease duration, years (mean (SD)): 17.3 (10.7) Medication NSAID (n yes): 10 DMARD (n yes): 7
Inclusion Criteria	Modified NY criteria met Aged 20-65 Disease well-controlled Disease of at least 6 months' duration
Exclusion Criteria	Presences of serious medical conditions or acute febrile disorders History of arthroplasties or major operations of the knee or hip joints Severe arthritis or contracture of knee or hip joints which preclude exercise testing with a bicycle
Methods	Interventions (Combined Home Exercise (COMB)): Range of motion exercises (spine and major joints) provided by a senior physiotherapist. Also chest expansion and breathing exercises. Participants received an exercise booklet. Following instruction on how to carry out the exercises, participants were to perform them at home daily for 3 months. Each to be repeated 5 times. Strengthening exercises of the spine and major joints. 10 repetitions of each, two sets of strengthening exercises at a time, twice a week, with rests of 2-3 minutes between repetitions. Aerobic exercises (fast walking, cycling, swimming) consisting of 5 minutes of stretching, 5 minute warm up, 20-30 minutes aerobic exercise and 5 minute cool down Control (Range of motion exercise only (ROM)):

Bibliographic reference	**Hseih, L.F., Chuang, C.C., Tseng, C.S., Wei, J.C.C., Hsu, W.C, Lin, Y.J. Combined home exercise is more effective than range of motion home exercise in patients with ankylosing spondylitis: a randomised controlled trial. BioMed Research International, 2014**
	Range of motion exercises described above
Results	Intervention group (n=9) BAS-G (mean (SD)): Baseline: 5.6 (2.7); 3 months: 3.6 (2.0) BASFI (mean (SD)): Baseline: 3.7 (3.3);3 months: 1.9 (2.3) BASDAI (mean (SD)): Baseline: 4.2 (1.9); 3 months: 3.7 (1.8) Control group (n=10) BAS-G (mean (SD)): Baseline: 5.0 (2.8); 3 months: 4.1 (3.5) BASFI (mean (SD)) Baseline: 3.5 (2.9); 3 months: 3.5 (3.1) BASDAI (mean (SD)): Baseline: 4.5 (2.1); 3 months: 4.5 (3.0)
Limitations	Authors highlight that duration of disease was on average long, leading to advanced disease in some people, and the short period over which outcomes were measured.
Other information	Risk of bias assessment Was the allocation sequence adequately generated? Yes Was allocation adequately concealed? Yes Was knowledge of the allocated intervention adequately prevented during the study? Yes Were incomplete outcome data adequately addressed? Unclear Are reports of the study free of suggestion of selective outcome reporting? No Was the study apparently free of other problems that could put it at a high risk of bias? Yes Risk of Bias:

Bibliographic reference	Hseih, L.F., Chuang, C.C., Tseng, C.S., Wei, J.C.C., Hsu, W.C, Lin, Y.J. Combined home exercise is more effective than range of motion home exercise in patients with ankylosing spondylitis: a randomised controlled trial. BioMed Research International, 2014
	Low risk of bias

Table 126: Ince et al., 2006

Bibliographic reference	Ince,Gonca, Sarpel,Tunay, Durgun,Behice, Erdogan,Seref, Effects of a multimodal exercise program for people with ankylosing spondylitis, Physical therapy, 86, 924-935, 2006
Country/ies where the study was carried out	Turkey
Study type	Randomised controlled trial
Aim of the study	To examine the effects of a multimodal exercise program (including aerobic, stretching, and pulmonary exercises) on ankylosing spondylitis-associated restrictions.
Study dates	Not reported. Published 2006
Source of funding	Unclear. Possibly Cukurova University, Adana, Turkey
Sample size	Convenience sample of 35 patients referred, of which 30 were recruited.
Characteristics	All diagnosed according to modified New York criteria, and classified as stage I ("patient performs all usual activities without handicaps") or stage II ("functional capacity adequate to conduct normal activities despite handicap or discomfort or limited mobility of 1 or more joints") based on Steinbrocker Function Criteria. All were taking nonsteroidal anti-inflammatory drugs and sulfasalazine (2g daily). Exercise group (mean (sd)) 15 participants: 6 female, 9 male; 13 with stage I, 2 with stage II Age: 33.37(5.15); height (cm): 167.73(7.91); body weight(kg): 70.27(12.70); disease duration(years): 8.27(5.71) Control group (mean (sd)) 15 participants: 6 female, 9 male; 13 with stage I, 2 with stage II Age: 36.13(7.20); height (cm): 166.87(7.84); body weight(kg): 68.50(9.22); disease duration(years): 9.79(6.46)
Inclusion criteria	Not reported
Exclusion criteria	Referred patients were excluded if communication with them could not be established following referral. Implicit exclusion of patients not in contact with referral source.
Details	All patients assessed at baseline and 3 months. Physical measurements:

Bibliographic reference	Ince,Gonca, Sarpel,Tunay, Durgun,Behice, Erdogan,Seref, Effects of a multimodal exercise program for people with ankylosing spondylitis, Physical therapy, 86, 924-935, 2006
	Maximal oxygen intake measured during PWC170 bicycle test. Heart rate measured with chronometer Spinal mobility measured by inclinometer, using curve angle method Chest expansion measured as difference in chest circumference at maximal inspiration and expiration at the level of the fourth intercostal space Occiput-wall distance Finger-floor distance Chin to chest distance Modified Schober Flexion Test Vital capacity measured using computerised spirometer Statistical analysis Student T test (2-tailed) and paired-samples T tests used for comparison of groups, with significance level specified as 0.05.
Interventions	Exercise group: Informed about exercises that would be helpful for their illness. Additionally received supervised exercise training: Multimodal exercise programme lasting 3 months (3 days/week, 50 mins per session) Sessions led by exercise instructor, supervised by physician. Programme comprised warm up (10 mins), main period (20 mins), cool down (10 mins) and featured aerobic exercises, stretching exercises and pulmonary exercises Control group: Informed about exercises that would be helpful for their illness only Participants in both groups were examined monthly by the same physician, all received NSAIDs and sulfasalazine (2g daily)
Results	All measurements reported at baseline and 3 months Pain Not reported Adverse events Not reported Joint mobility Chest expansion (cm, mean(sd)): Exercise: baseline: 2.40(1.38); 3 months: 3.23(1.60)

Bibliographic reference	Ince,Gonca, Sarpel,Tunay, Durgun,Behice, Erdogan,Seref, Effects of a multimodal exercise program for people with ankylosing spondylitis, Physical therapy, 86, 924-935, 2006
	Control: baseline: 1.87(0.94); 3 months: 1.77(1.67) Chin to chest distance (cm, mean(sd)): Exercise: baseline: 2.97(1.51); 3 months: 2.50(1.73) Control: baseline: 3.68(1.39); 3 months: 4.38(1.63) Finger to floor distance (cm, mean(sd)): Exercise: baseline: 18.13(16.16); 3 months: 14.67(16.55) Control: baseline: 18.70(14.46); 3 months: 18.07(14.74) Occiput to wall distance (cm, mean(sd)): Exercise: baseline: 4.48(3.21); 3 months: 4.23(3.27) Control: baseline: 5.83(3.48); 3 months: 6.79(3.27) Modified Schober Flexion test (cm, mean(sd)): Exercise: baseline: 13.63(1.74); 3 months: 13.83(1.62) Control: baseline: 12.91(1.81); 3 months: 12.48(1.77) Physical function PWC170Test (W/kg, mean(sd)): Exercise: baseline: 1.57(0.31); 3 months: 2.25(0.61) Control: baseline: 1.78(0.62); 3 months: 1.56(0.60) Predicted vital capacity (% predicted, mean(sd)): Exercise: baseline: 88.53(11.94); 3 months: 89.29(14.96) Control: baseline: 81.77(11.30); 3 months: 76.05(14.60) Quality of life Not reported Imaging Not reported Composite measures Not reported
Finger-floor distance	Finger-floor distance

Bibliographic reference	Ince,Gonca, Sarpel,Tunay, Durgun,Behice, Erdogan,Seref, Effects of a multimodal exercise program for people with ankylosing spondylitis, Physical therapy, 86, 924-935, 2006
	<table><tr><td></td><td>Mean</td><td>SD</td><td>Total</td></tr><tr><td>Experimental</td><td>-3.46</td><td>16.55</td><td>15</td></tr><tr><td>Control</td><td>-0.63</td><td>16.55</td><td>15</td></tr></table>
Schober test	Schober test <table><tr><td></td><td>Mean</td><td>SD</td><td>Total</td></tr><tr><td>Experimental</td><td>0.20</td><td>1.81</td><td>15</td></tr><tr><td>Control</td><td>-0.43</td><td>1.81</td><td>15</td></tr></table>
Chest expansion	Chest expansion <table><tr><td></td><td>Mean</td><td>SD</td><td>Total</td></tr><tr><td>Experimental</td><td>0.83</td><td>1.67</td><td>15</td></tr><tr><td>Control</td><td>-0.10</td><td>1.67</td><td>15</td></tr></table>
Cervical flexion (occiput- and tragus-wall tests)	Cervical flexion (occiput- and tragus-wall tests) <table><tr><td></td><td>Mean</td><td>SD</td><td>Total</td></tr><tr><td>Experimental</td><td>-0.25</td><td>3.48</td><td>15</td></tr><tr><td>Control</td><td>0.96</td><td>3.48</td><td>15</td></tr></table>
Was the allocation sequence adequately generated?	UNCLEAR
Was allocation adequately concealed?	UNCLEAR
Was knowledge of the allocated intervention adequately prevented during the study?	NO
Were incomplete outcome data adequately addressed?	UNCLEAR

Bibliographic reference	Ince,Gonca, Sarpel,Tunay, Durgun,Behice, Erdogan,Seref, Effects of a multimodal exercise program for people with ankylosing spondylitis, Physical therapy, 86, 924-935, 2006
Are reports of the study free of suggestion of selective outcome reporting?	YES
Was the study apparently free of other problems that could put it at a high risk of bias?	UNCLEAR
Risk of Bias	Exercise instructor blinded to physiological measurements. Participants likely unblinded, unclear if physician undertaking measurements was blinded.
Other information	Mean differences and SD manually calculated in accordance with Cochrane Handbook guidelines

Table 127: Jennings 2015

Bibliographic reference	Jennings, F., Olivera, H.A., de Souza M.C., da Graca Cruz, V., Effects of aerobic training in patients with ankylosing spondylitis, The Journal of Rheumatology, 42(12): 2347- 2353, 2015
Setting	Recruitment from outpatient clinics in Sao Paulo, Brazil
Study type	Randomised controlled trial with blinded evaluator
Aim of the study	To assess the effectiveness of aerobic training in the improvement of functional capacity spinal mobility, disease activity, and quality of life in patients with AS.
Study dates	Not reported
Source of funding	Supported by Fundacao de Amparo a Pesquisa do Estado de Sao Paulo (FAPESP) grant #2009/51397-2
Sample size	136 people approached, 56 not selected (ineligible, unable/unwilling to participate). 3 were excluded during early study stage. 77 patients complete baseline assessment, 7 withdrew consent before randomisation. Of the 70 remaining, 35 were randomised to each arm of the trial.
Characteristics	Intervention group (n=35): age (mean (SD)): 42.9 (9.9) male, n: 26 disease duration, yrs (mean (SD)): 16.0 (8.9) time of diagnosis, yrs (mean (SD)): 7.4 (6.3) medications, n(%) none: 5 (14.3) NSAID continuous:15 (42.9)

Bibliographic reference	Jennings, F., Olivera, H.A., de Souza M.C., da Graca Cruz, V., Effects of aerobic training in patients with ankylosing spondylitis, The Journal of Rheumatology, 42(12): 2347- 2353, 2015
	Corticosteroid: 0 (0) Methotrexate: 7 (20) Sulfasalazine: 4 (11.4) Anti-TNF therapy: 14 (40) Control group (n=35): age (mean (SD)): 40.2 (9.3) male, n: 23 disease duration, yrs (mean (SD)): 13.4 (7.8) time of diagnosis, yrs (mean (SD)): 7.5 (6.5) medications, n(%) none: 5 (14.3) NSAID continuous: 11. (31.4) Corticosteroid: 4 (11.4) Methotrexate: 8 (22.9) Sulfasalazine:6 (17.1) Anti-TNF therapy: 17 (48.5)
Inclusion Criteria	Patients classified as having AS by modified NY criteria with Steinbroker class 1=I-II Stable doses of DMARDs/anti-TNF biological therapies for at least 3 months Stable doses of NSAIDs/corticosteroids for at least 4 weeks Maximum dose of 10mg/day corticosteroid (prednisone or equivalent) was permitted
Exclusion Criteria	Uncontrolled hypertension History of heart failure and/or coronary revascularisation History of syncope or exercise induced arrhythmias Decompensated Type I diabetes mellitus Sever psychiatric diseases Fibromyalgia Other medical conditions more incapacitating than AS Hip arthroplasty in the last year Conditions that prevented walking History of regular physical exercise in last 6 months (at least 30 minutes 3 times a week)

Bibliographic reference	Jennings, F., Olivera, H.A., de Souza M.C., da Graca Cruz, V., Effects of aerobic training in patients with ankylosing spondylitis, The Journal of Rheumatology, 42(12): 2347- 2353, 2015
Methods	Blinding: Treatment allocation: Randomisation by computer-generated list. Allocation of patients was concealed in sealed envelopes and retained by an independent person not involved in the study. Intervention group: aerobic exercise (walking)and stretching exercises. Sessions of around 80 minutes, 3 times a week for 12 weeks. Aerobic training involved 5 minute warm up, 40 minutes of walking at anaerobic threshold heartrate, 5 minute cool down. Stretching exercises: directed to the segments and muscle groups for the trunk and lower limbs. 3 repetitions of 30 minutes each. Control group: stretching exercises for about 30 minutes 3 times a week for 12 weeks
Results	Intervention group (n=35) BASFI (mean (SD)): Baseline: 4.28 (2.78); 24 weeks: 3.47 (2.48) HAQ-S (mean (SD)): Baseline: 1.04 (0.59); 24 weeks: 1.01 (0.55) BASMI (mean (SD)): Baseline: 5.15 (1.95); 24 weeks: 4.95 (2.03) BASDAI (mean (SD)): Baseline: 3.46 (2.39); 24 weeks: 2.87 (1.97) Control group (n=35) BASFI (mean (SD)): Baseline: 4.27 (2.32); 24 weeks: 3.73 (2.19) HAQ-S (mean (SD)): Baseline: 1.01 (0.55); 24 weeks: 0.97 (0.59) BASMI (mean (SD)):

Bibliographic reference	Jennings, F., Olivera, H.A., de Souza M.C., da Graca Cruz, V., Effects of aerobic training in patients with ankylosing spondylitis, The Journal of Rheumatology, 42(12): 2347- 2353, 2015
	Baseline: 4.79 (2.22); 24 weeks: 4.61 (2.24) BASDAI (mean (SD)): Baseline: 3.62 (2.06); 24 weeks: 3.27 (2.07)
Limitations	
Other information	Risk of bias assessment Was the allocation sequence adequately generated? Yes Was allocation adequately concealed? Yes Was knowledge of the allocated intervention adequately prevented during the study? Unclear Were incomplete outcome data adequately addressed? Yes Are reports of the study free of suggestion of selective outcome reporting? Yes Was the study apparently free of other problems that could put it at a high risk of bias? Yes Risk of Bias: Low risk of bias

Table 128: Karapolat et al., 2009

Bibliographic reference	Karapolat,H., Eyigor,S., Zoghi,M., Akkoc,Y., Kirazli,Y., Keser,G., Are swimming or aerobic exercise better than conventional exercise in ankylosing spondylitis patients? A randomized controlled study, European journal of physical and rehabilitation medicine, 45, 449-457, 2009
Country/ies where the study was carried out	Turkey
Study type	Randomised controlled trial
Aim of the study	To compare the effects of conventional exercise, swimming and walking on the pulmonary functions, aerobic capacity, quality of life, Bath indexes and psychological symptoms in patients with ankylosing spondylitis
Study dates	2006 to 2008
Source of funding	None

Bibliographic reference	**Karapolat,H., Eyigor,S., Zoghi,M., Akkoc,Y., Kirazli,Y., Keser,G., Are swimming or aerobic exercise better than conventional exercise in ankylosing spondylitis patients? A randomized controlled study, European journal of physical and rehabilitation medicine, 45, 449-457, 2009**
Sample size	45 participants registered, 15 randomised to each of 3 arms. Following dropouts there were 13 in swimming + conventional exercise group, 12 in walking + conventional exercise group and 12 in conventional exercise only group.
Characteristics	Baseline characteristics of completers in each group: Swimming + conventional exercise (n=13) Age (mean (sd)): 50.15 (12.40); sex (male, n): 10; duration of disease in years (mean (sd)): 20.62 (10.10) ; salazopirin (n): 2; methotrexate (n): 1; salazopirin + methotrexate (n): 0 Walking + conventional exercise Age (mean (sd)): 46.92 (13.40); sex (male, n): 8; duration of disease in years (mean (sd)): 17.42(12.43); salazopirin (n): 3; methotrexate (n): 2; salazopirin + methotrexate (n): 1 Conventional exercise (control) Age (mean (sd)): 48.42 (9.47); sex (male, n): 9; duration of disease in years (mean (sd)): 18.63(7.52); salazopirin (n): 1; methotrexate (n): 3; salazopirin + methotrexate (n): 2
Inclusion criteria	Able to swim Outpatients without complications Able to understand questionnaire content and exercise programme
Exclusion criteria	Inability or unwillingness to participate in physiotherapy Systemic organic involvement Active peripheral joint inflammation Severe comorbidities affecting heart, lung, liver or kidneys Receiving disease modifying drugs other than sulfasalazine or methotrexate within the four weeks of enrolment Previous use of TNF alpha blockers Performing regular exercise during preceding 6 months
Details	Additionally, all subjects had a pulmonary function test and had their functional capacity assessed by cardiopulmonary exercise test and a 6 minute walking test. During testing, 12-lead electrocardiogram was continuously monitored for rhythm, rate and ST-T changes. Blood pressure readings were taken at baseline and post-exercise. pVO2 and VCO2 were also monitored. Participants underwent echocardiography to exclude any possible cardiovascular pathology.

Bibliographic reference	**Karapolat,H., Eyigor,S., Zoghi,M., Akkoc,Y., Kirazli,Y., Keser,G., Are swimming or aerobic exercise better than conventional exercise in ankylosing spondylitis patients? A randomized controlled study, European journal of physical and rehabilitation medicine, 45, 449-457, 2009**
	Outcomes were measured by administering the BASFI, BASDAI and BASMI questionnaires, along with the Beck Depression Inventory and the Nottingham Health profile. No description of the flexibility measurement methods was reported.
Interventions	All participants were asked to carry out 'conventional exercise' (CE) Group 1: swimming+CE Freestyle swimming in community swimming pool, 30 mins per day, three times a week for six weeks 10 minute warm up, 5 minute stretching, followed by 30 minutes of moderate intensity swimming (60-70% heart rate reserve - 12 beats/minute), concluding with 10 minute cooling down and 5 minute stretch Mean heart rate measured by heart rate monitor (Polar Edge) Pool was a physiotherapeutic pool heated to 32°C Additionally, CE as described below Group 2: walking+CE 30 mins of walking per day, three times a week for six weeks Performed at 60-70% of pVO2, at level of 13-15 on the Borg scale and 60-70% heart rate reserve Heart rate monitored throughout using Polar Beat watch Additionally, CE as described below Group 3: CE only Flexibility exercises for cervical, thoracic and lumbar spine Stretching exercises for major muscle groups (erector spine, shoulder muscles, hip flexors, hamstrings, quadriceps stretch) Respiratory exercises (pursed-lip breathing, expiratory abdominal augmentation, synchronisation of thoracic and abdominal movement) Total time: 30 mins, once a day for 6 days
Results	Pain Pain domain of the Nottingham Health Profile (mean (SD)) Swimming+CE: pre: 27.89 (32.74); post: 25.00 (28.41) Walking +CE: pre: 25.00 (25.62); post: 19.79 (26.89) CE (control): pre: 25.75 (25.28); post: 21.04 (34.32) Adverse events None

Bibliographic reference	Karapolat,H., Eyigor,S., Zoghi,M., Akkoc,Y., Kirazli,Y., Keser,G., Are swimming or aerobic exercise better than conventional exercise in ankylosing spondylitis patients? A randomized controlled study, European journal of physical and rehabilitation medicine, 45, 449-457, 2009
	Joint mobility BASMI Swimming+CE: pre: 5.15 (2.27); post: 4.54 (2.07) Walking +CE: pre: 4.54 (2.58); post: 4.18 (2.99) CE (control): pre: 3.83 (3.75); post: 3.75 (2.67) Modified Schober's distance Swimming+CE: pre: 2.39 (1.30); post: 2.27 (1.05) Walking +CE: pre: 3.00 (1.72); post: 2.77 (1.66) CE (control): pre: 3.25 (1.53); post: 3.25 (2.13) Chest expansion Swimming+CE: pre: 3.38 (1.09); post: 4.67 (2.27) Walking +CE: pre: 3.40 (1.24); post: 3.85 (1.70) CE (control): pre: 4.08 (2.24); post: 4.13 (2.15) Tragus-wall distance Swimming+CE: pre: 19.00(8.23); post: 15.54(4.54) Walking +CE: pre: 18.54(9.62); post: 17.82(9.18) CE (control): pre: 15.63(4.67); post: 15.63(4.93) Intermalleolar distance Swimming+CE: pre: 89.35(23.77); post: 91.46(22.01) Walking +CE: pre: 92.09(18.16); post: 91.41(23.36) CE (control): pre: 94.88(19.80); post: 97.00(25.11) Hand to floor distance

Bibliographic reference	Karapolat,H., Eyigor,S., Zoghi,M., Akkoc,Y., Kirazli,Y., Keser,G., Are swimming or aerobic exercise better than conventional exercise in ankylosing spondylitis patients? A randomized controlled study, European journal of physical and rehabilitation medicine, 45, 449-457, 2009
	Swimming+CE: pre: 20.53(13.97); post: 19.04(12.36) Walking +CE: pre: 22.27(7.88); post: 20.32(8.76) CE (control): pre: 24.79(10.59); post: 25.25(10.66) Also measured in study but not reported here: Cervical rotation, lumbar lateral flexion Physical function BASFI Swimming+CE: pre: 2.34 (1.70); post: 1.97 (1.24) Walking +CE: pre: 2.25 (1.81); post: 2.25 (2.30) CE (control): pre: 2.70 (2.52); post: 3.13 (2.65) BASDAI Swimming+CE: pre: 2.73 (1.93); post: 1.90 (1.61) Walking +CE: pre: 2.49 (1.68); post: 2.68 (2.19) CE (control): pre: 2.65 (2.13); post: 2.03 (1.86) Also measured in study but not reported here: 6 minute walking test, maximal O2 consumption, respiratory exchange ratio, anaerobic threshold, forced vital capacity, forced expiratory volume in one second, vital capacity Quality of life Nottingham Health Profile used as a measure of quality of life, and reported separately across the following domains: energy level, pain, emotional reaction, sleep, social isolation, physical mobility Imaging Not reported Composite measures Beck depression inventory
Pain	Pain

Bibliographic reference	Karapolat,H., Eyigor,S., Zoghi,M., Akkoc,Y., Kirazli,Y., Keser,G., Are swimming or aerobic exercise better than conventional exercise in ankylosing spondylitis patients? A randomized controlled study, European journal of physical and rehabilitation medicine, 45, 449-457, 2009
	<table><tr><th></th><th>Mean</th><th>SD</th><th>Total</th></tr><tr><td>Experimental</td><td>-2.89</td><td>34.32</td><td>13</td></tr><tr><td>Control</td><td>-4.71</td><td>34.32</td><td>12</td></tr></table>
BASMI	BASMI <table><tr><th></th><th>Mean</th><th>SD</th><th>Total</th></tr><tr><td>Experimental</td><td>-0.61</td><td>3.75</td><td>13</td></tr><tr><td>Control</td><td>-0.08</td><td>3.75</td><td>12</td></tr></table>
Finger-floor distance	Finger-floor distance <table><tr><th></th><th>Mean</th><th>SD</th><th>Total</th></tr><tr><td>Experimental</td><td>-1.49</td><td>13.97</td><td>13</td></tr><tr><td>Control</td><td>0.46</td><td>13.97</td><td>12</td></tr></table>
Schober test	Schober test <table><tr><th></th><th>Mean</th><th>SD</th><th>Total</th></tr><tr><td>Experimental</td><td>-0.12</td><td>2.13</td><td>13</td></tr><tr><td>Control</td><td>0.00</td><td>2.13</td><td>12</td></tr></table>

Bibliographic reference	Karapolat,H., Eyigor,S., Zoghi,M., Akkoc,Y., Kirazli,Y., Keser,G., Are swimming or aerobic exercise better than conventional exercise in ankylosing spondylitis patients? A randomized controlled study, European journal of physical and rehabilitation medicine, 45, 449-457, 2009
Chest expansion	Chest expansion Mean: Experimental 1.29, Control 0.05 SD: Experimental 2.27, Control 2.27 Total: Experimental 13, Control 12
Cervical flexion (occiput- and tragus-wall tests)	Cervical flexion (occiput- and tragus-wall tests) Mean: Experimental -3.46, Control 0.00 SD: Experimental 8.23, Control 8.23 Total: Experimental 13, Control 12
Cervical rotation	Cervical rotation Mean: Experimental 2.96, Control 0.00 SD: Experimental 21.59, Control 21.59 Total: Experimental 13, Control 12
Intermalleolar distance	Intermalleolar distance Mean: Experimental 2.11 SD: Experimental 25.11 Total: Experimental 13

Bibliographic reference	**Karapolat,H., Eyigor,S., Zoghi,M., Akkoc,Y., Kirazli,Y., Keser,G., Are swimming or aerobic exercise better than conventional exercise in ankylosing spondylitis patients? A randomized controlled study, European journal of physical and rehabilitation medicine, 45, 449-457, 2009**
	Control | 2.12 | 25.11 | 12
Dichotomous adverse events	Dichotomous adverse events | | Events | Total | | Experimental | 0 | 13 | | Control | 0 | 12 |
Was the allocation sequence adequately generated?	YES
Was allocation adequately concealed?	YES
Was knowledge of the allocated intervention adequately prevented during the study?	UNCLEAR
Were incomplete outcome data adequately addressed?	YES
Are reports of the study free of suggestion of selective outcome reporting?	YES
Was the study apparently free of other problems that could put it at a high risk of bias?	YES
Risk of Bias	In common with others exploring this question, it is unlikely that participants were blind to allocation. It is not reported whether assessors were blinded to allocation.
Other information	Error in flow chart of participants - swimming group should possibly be n=13, control group n=12?

Bibliographic reference	**Karapolat,H., Eyigor,S., Zoghi,M., Akkoc,Y., Kirazli,Y., Keser,G., Are swimming or aerobic exercise better than conventional exercise in ankylosing spondylitis patients? A randomized controlled study, European journal of physical and rehabilitation medicine, 45, 449-457, 2009**
	Some values within the results table suggestive of possible errors - may be worth contacting authors for clarification Mean differences and SD manually calculated in accordance with Cochrane Handbook guidelines

Table 129: Kjeken et al., 2013

Bibliographic reference	**Kjeken,Ingvild, Bo,Ingvild, Ronningen,Aud, Spada,Cristina, Mowinckel,Petter, Hagen,Kare Birger, Dagfinrud,Hanne, A three-week multidisciplinary in-patient rehabilitation programme had positive long-term effects in patients with ankylosing spondylitis: randomized controlled trial, Journal of rehabilitation medicine : official journal of the UEMS European Board of Physical and Rehabilitation Medicine, 45, 260-267, 2013**
Country/ies where the study was carried out	Norway
Study type	Randomised controlled trial
Aim of the study	To evaluate the mean overall effects over a 1-year period of a multidisciplinary in-patient rehabilitation programme for patients with ankylosing spondylitis.
Study dates	February 2006 to April 2010
Source of funding	Health South-East, Norway, grant number 2006077
Sample size	One hundred participants were recruited and randomised. One was excluded from intervention group and four were excluded or dropped out of control group at 4 months, leaving 95 participants (46 in rehabilitation group, 49 in control).
Characteristics	Rehabilitation group (n=46): age (mean (sd)): 49.4(10.3); female: 21.7%; disease duration in years (mean (sd)): 14.9(9.6); symptom duration in years (mean (sd)): 23.8(11.3) Medications: analgesics (%): 28.3; NSAIDs (%): 73.9; DMARDs (%): 6.5; biological therapy (%): 2.2 Control group (n=49): age (mean (sd)): 48.6(9.4); female: 46.9%; disease duration in years (mean (sd)): 16.1(12.0); symptom duration in years (mean (sd)): 23.5(11.1) Medications: analgesics (%): 32.7; NSAIDs (%): 77.6; DMARDs (%): 2.0; biological therapy (%): 6
Inclusion criteria	Previous diagnosis of AS by Rheumatologist based on modified New York criteria

Bibliographic reference	**Kjeken,Ingvild, Bo,Ingvild, Ronningen,Aud, Spada,Cristina, Mowinckel,Petter, Hagen,Kare Birger, Dagfinrud,Hanne, A three-week multidisciplinary in-patient rehabilitation programme had positive long-term effects in patients with ankylosing spondylitis: randomized controlled trial, Journal of rehabilitation medicine : official journal of the UEMS European Board of Physical and Rehabilitation Medicine, 45, 260-267, 2013**
	18 to 65 years old BASDAI scale score of >=40mm Ability to communicate in Norwegian
Exclusion criteria	Coronary heart disease Pregnancy Impaired function e.g. due to other significant medical problems Surgery or rehabilitation within the last 6 months Participants in control group excluded at 4 month control if they reported participation in multidisciplinary rehabilitation after baseline assessment Both groups: excluded at 12 month control if they had started biological therapy during trial period or reported multidisciplinary rehabilitation after the 4 month assessment
Details	Randomisation Patients were randomly allocated using concealed opaque envelopes, using a computer-generated randomisation sequence produced by a statistician not involved in the study. Patients and therapists delivering the intervention were aware of the treatment allocation, but observer blinding was attempted by using a second blinded assessor at the 12 month assessment. Patients were asked not to inform the assessors about their group allocation. Measurements Baseline and 12 month measurements were performed face to face at the hospital. 4 month measures were limited to patient-reported outcomes collected via postal questionnaires. Primary outcomes were specified as the BASDAI and BASFI scores. Secondary outcomes were spinal and hip mobility measured by BASMI, and wellbeing measured by BASG. The SF-36 questionnaire was also used as a generic health measure. The COPM instrument was also used to describe and measure patient's perception of activity performance and satisfaction with performance over time. Statistical analyses Differences at baseline between the two groups were measured using t-tests, Mann-Whitney tests and chi squared tests. Within-group differences were examined by paired t-tests. Treatment effects were also assessed using mixed models for repeated measures analysis, adjusting for gender and individual baseline characteristics.
Interventions	Both groups received relevant medication Exercise intervention: Weekly exercise programme (combination of exercises in the gym, in a hot water pool, and outdoor physical activities)

Bibliographic reference	**Kjeken,Ingvild, Bo,Ingvild, Ronningen,Aud, Spada,Cristina, Mowinckel,Petter, Hagen,Kare Birger, Dagfinrud,Hanne, A three-week multidisciplinary in-patient rehabilitation programme had positive long-term effects in patients with ankylosing spondylitis: randomized controlled trial, Journal of rehabilitation medicine : official journal of the UEMS European Board of Physical and Rehabilitation Medicine, 45, 260-267, 2013**
	Dose, intensity and frequency of different elements of the package was individually adopted to ensure an optimal starting level and progression for each patient Individual physiotherapy when needed, including manual therapies Control: Treatment as usual, which could include consultations with rheumatologist or physician, community based physiotherapy and/or self-management in terms of physical activity and exercises. Control group offered rehabilitation stay after study completion.
Results	Pain: Not reported Adverse events: Not reported Joint mobility: BASMI (mean (95%CI)) Rehabilitation: baseline: 3.0 (2.3, 3.6); 4 months: n/a; 12 months: 2.8 (2.4, 3.3) Control: baseline: 2.6 (2.1, 3.1); 4 months: n/a; 12 months: 2.8 (2.4, 3.2) Physical function: BASDAI (mean (95%CI)) Rehabilitation: baseline: 57.8 (54.4, 60.8); 4 months: 43.2 (37.3, 49.2); 12 months: 49.6 (43.0, 56.2) Control: baseline: 56.9 (53.4, 60.4); 4 months: 57.5 (51.3, 63.6); 12 months: 54.5 (48.1, 60.9) BASFI (mean (95%CI)) Rehabilitation: baseline: 38.6 (33.5, 43.6); 4 months: 33.6 (28.7, 38.6); 12 months: 38.0 (32.5, 43.5) Control: baseline: 42.4 (36.8, 48.0); 4 months: 39.6 (34.6, 44.7); 12 months: 38.6 (33.6, 43.8) Quality of life: Assorted domains of SF-36 were reported (physical function, social functioning, role physical, role mental, mental health, vitality, bodily pain, general health)

<table>
<tr><th>Bibliographic reference</th><th>Kjeken,Ingvild, Bo,Ingvild, Ronningen,Aud, Spada,Cristina, Mowinckel,Petter, Hagen,Kare Birger, Dagfinrud,Hanne, A three-week multidisciplinary in-patient rehabilitation programme had positive long-term effects in patients with ankylosing spondylitis: randomized controlled trial, Journal of rehabilitation medicine : official journal of the UEMS European Board of Physical and Rehabilitation Medicine, 45, 260-267, 2013</th></tr>
<tr><td></td><td>Imaging:

Composite measures:
BAS-G (mean (95%CI))
Rehabilitation: baseline: 56.2 (51.0, 61.3); 4 months: 46.1 (40.1, 52.1); 12 months: 41.7 (34.9, 48.5)
Control: baseline: 57.5 (52.2, 62.7); 4 months: 52.5 (46.3, 48.7); 12 months: 50.5 (44.1, 56.8)</td></tr>
<tr><td>BASDAI</td><td>BASDAI<table><tr><td></td><td>Mean</td><td>SD</td><td>Total</td></tr><tr><td>Experimental</td><td>-8.20</td><td>22.90</td><td>46</td></tr><tr><td>Control</td><td>-2.40</td><td>22.90</td><td>49</td></tr></table></td></tr>
<tr><td>BASFI</td><td>BASFI<table><tr><td></td><td>Mean</td><td>SD</td><td>Total</td></tr><tr><td>Experimental</td><td>-0.60</td><td>20.00</td><td>46</td></tr><tr><td>Control</td><td>-3.80</td><td>20.00</td><td>49</td></tr></table></td></tr>
<tr><td>BASMI</td><td>BASMI<table><tr><td></td><td>Mean</td><td>SD</td><td>Total</td></tr><tr><td>Experimental</td><td>-0.20</td><td>2.20</td><td>46</td></tr><tr><td>Control</td><td>0.20</td><td>2.20</td><td>49</td></tr></table></td></tr>
<tr><td>BASG</td><td>BASG<table><tr><td></td><td>Mean</td><td>SD</td><td>Total</td></tr><tr><td>Experimental</td><td>-14.50</td><td>22.70</td><td>46</td></tr><tr><td>Control</td><td>-7.00</td><td>22.70</td><td>49</td></tr></table></td></tr>
</table>

Bibliographic reference	Kjeken,Ingvild, Bo,Ingvild, Ronningen,Aud, Spada,Cristina, Mowinckel,Petter, Hagen,Kare Birger, Dagfinrud,Hanne, A three-week multidisciplinary in-patient rehabilitation programme had positive long-term effects in patients with ankylosing spondylitis: randomized controlled trial, Journal of rehabilitation medicine : official journal of the UEMS European Board of Physical and Rehabilitation Medicine, 45, 260-267, 2013
Was the allocation sequence adequately generated?	YES
Was allocation adequately concealed?	YES
Was knowledge of the allocated intervention adequately prevented during the study?	YES
Were incomplete outcome data adequately addressed?	UNCLEAR
Are reports of the study free of suggestion of selective outcome reporting?	YES
Was the study apparently free of other problems that could put it at a high risk of bias?	YES
Risk of Bias	Follow up assessing observer blinded to treatment allocation, participants and therapists were not. Clear reporting on loss to follow up, though quite large numbers did not finish the study.
Other information	Mean differences and SD manually calculated in accordance with Cochrane Handbook guidelines

Table 130: Kraag et al., 1990

Bibliographic reference	Kraag,G., Stokes,B., Groh,J., Helewa,A., Goldsmith,C., The effects of comprehensive home physiotherapy and supervision on patients with ankylosing spondylitis--a randomized controlled trial, The Journal of rheumatology, 17, 228-233, 1990
Country/ies where the study was carried out	Canada
Study type	Randomised controlled trial

Bibliographic reference	**Kraag,G., Stokes,B., Groh,J., Helewa,A., Goldsmith,C., The effects of comprehensive home physiotherapy and supervision on patients with ankylosing spondylitis--a randomized controlled trial, The Journal of rheumatology, 17, 228-233, 1990**
Aim of the study	To determine whether a home programme of therapeutic exercise with disease education is effective in patients with ankylosing spondylitis with reduced spinal mobility and function.
Study dates	Not reported. Article submitted 1989, published 1990
Source of funding	National Health and Research Development Program, Health and Welfare Canada, grant number 6606-2385-43
Sample size	53 patients (26 exercise group, 27 control). At follow up there were 22 in exercise group and 26: results on these were used in this review question.
Characteristics	Overall mean age was 37.8 years, with a range of 19 to 73 years. All patients satisfied New York criteria for AS. An inclusion criteria score was generated by assessing and scoring lower back pain, rib cage pain and stiffness, limited chest expansion, limited motion in lumbar spine, past or present evidence of iritis, bilateral radiological sacroiliitis and radiographic syndesmophytosis. In both groups the disease was described as 'not mild' and many patients had symptoms not limited to the sacroiliac joint (e.g. thoracic involvement). Exercise group male (%): 76.9 continuous pain (years, mean (sd)): 15.8 (27.6) function score: 0.50 (3.51) morning stiffness in last week (%): 85.2 inclusion criteria score mean(sd): 7.2(1.4) Control group male (%): 81.5 continuous pain (years, mean (sd)): 16.9 (28.0) function score: 0.33 (3.6) morning stiffness in last week (%): 85.2 inclusion criteria score mean(sd): 7.6(0.9)
Inclusion criteria	Confirmed diagnosis of AS based on New York Criteria

Bibliographic reference	**Kraag,G., Stokes,B., Groh,J., Helewa,A., Goldsmith,C., The effects of comprehensive home physiotherapy and supervision on patients with ankylosing spondylitis--a randomized controlled trial, The Journal of rheumatology, 17, 228-233, 1990**
	Stable clinical status and drug therapy ARA functional class 1, 2 or 3 English comprehension Absence of corticosteroid therapy for at least 3 months and immunosuppresive therapy for at least 6 months pre-study No surgery anticipated in next 4 months Female participants: practicing reliable contraception and not pregnant
Exclusion criteria	Patients with more than 10% loss of flexion in either hip joint Those receiving any contravening treatment
Details	Randomisation Randomisation was age stratified (18-35 years, 36 years and over). Within each stratum, block randomisation was carried out (blocks of 4) Measurements Measurements were taken by blinded assessors; the same assessor was used at baseline and 4 months to avoid inter-observer variation. A range of measurements of spinal mobility were taken at baseline and follow up. In addition a modified version of the Toronto Activities of Daily Living Questionnaire was used to identify changes in participant daily function over the study period Statistical analysis Standard summary statistics for descriptive analysis. Chi squared statistics and unpaired t-tests were used to compare the intervention and control groups.
Interventions	Both groups were instructed to continue stable medical therapy, but not seek medical attention for their condition during the study period, except in case of medical emergency. Intervention group Physiotherapist-led exercises and a daily self-administered exercise programme. The study period was 14 weeks, with the physiotherapist-led component tapering off between 6-16 weeks.

Bibliographic reference	**Kraag,G., Stokes,B., Groh,J., Helewa,A., Goldsmith,C., The effects of comprehensive home physiotherapy and supervision on patients with ankylosing spondylitis--a randomized controlled trial, The Journal of rheumatology, 17, 228-233, 1990**
	Exercises included demonstration of correct posture in lying, sitting or standing, and therapeutic exercise to increase the mobility of the spine, rib cage and peripheral joints and increase muscle strength and resistance. An additional self-administered daily exercise programme tailored to the individual patient. Participants were treated in their homes or workplaces no fewer than 8 times and no more than 16 times during the study period. Control group Participants in the control group did not receive any intervention but were offered the programme at the end of the study period.
Results	Reported results are for patients who completed the study only. Results are mean (sd) changes from baseline at study completion Pain Pain scale (mm) Exercise: 7.2(25.9) Control: -3.4(25.4) Adverse events None reported as adverse events. However patients lost to follow up included 3 who experienced disease flare requiring medical intervention and 1 with a prescribed medication change due to drug side effects experienced after entering the study. Joint mobility Finger-floor distance (cm) Exercise: -8.0 (5.0) Control: 2.0 (9.3) Spinal alignment (cm) Exercise: -0.6 (1.9) Control: -0.2 (2.0) Schober test (cm)

<table>
<tr><th>Bibliographic reference</th><th>Kraag,G., Stokes,B., Groh,J., Helewa,A., Goldsmith,C., The effects of comprehensive home physiotherapy and supervision on patients with ankylosing spondylitis--a randomized controlled trial, The Journal of rheumatology, 17, 228-233, 1990</th></tr>
<tr><td></td><td>Exercise: -2.1 (6.5)
Control: -2.6 (10.1)

Physical function
Function score:
Exercise: 4.14 (2.92)
Control: 0.08 (1.39)

Quality of life
No outcomes reported

Imaging
No outcomes reported

Composite measures
No additional outcomes reported</td></tr>
<tr><td>Pain</td><td>Pain<table><tr><td></td><td>Mean</td><td>SD</td><td>Total</td></tr><tr><td>Experimental</td><td>7.20</td><td>25.90</td><td>22</td></tr><tr><td>Control</td><td>-3.40</td><td>25.40</td><td>26</td></tr></table></td></tr>
<tr><td>Finger-floor distance</td><td>Finger-floor distance<table><tr><td></td><td>Mean</td><td>SD</td><td>Total</td></tr><tr><td>Experimental</td><td>-8.00</td><td>5.00</td><td>22</td></tr></table></td></tr>
</table>

Bibliographic reference	**Kraag,G., Stokes,B., Groh,J., Helewa,A., Goldsmith,C., The effects of comprehensive home physiotherapy and supervision on patients with ankylosing spondylitis--a randomized controlled trial, The Journal of rheumatology, 17, 228-233, 1990**
	<table><tr><td>Control</td><td>2.00</td><td>9.30</td><td>26</td></tr></table>
Schober test	Schober test <table><tr><td></td><td>Mean</td><td>SD</td><td>Total</td></tr><tr><td>Experimental</td><td>-2.10</td><td>6.50</td><td>22</td></tr><tr><td>Control</td><td>-2.60</td><td>10.10</td><td>26</td></tr></table>
Cervical flexion (occiput- and tragus-wall tests)	Cervical flexion (occiput- and tragus-wall tests) <table><tr><td></td><td>Mean</td><td>SD</td><td>Total</td></tr><tr><td>Experimental</td><td>-0.60</td><td>1.90</td><td>22</td></tr><tr><td>Control</td><td>-0.20</td><td>2.00</td><td>26</td></tr></table>
Was the allocation sequence adequately generated?	YES
Was allocation adequately concealed?	UNCLEAR
Was knowledge of the allocated intervention adequately prevented during the study?	NO
Were incomplete outcome data adequately addressed?	YES
Are reports of the study free of suggestion of selective outcome reporting?	UNCLEAR

Bibliographic reference	Kraag,G., Stokes,B., Groh,J., Helewa,A., Goldsmith,C., The effects of comprehensive home physiotherapy and supervision on patients with ankylosing spondylitis--a randomized controlled trial, The Journal of rheumatology, 17, 228-233, 1990
Was the study apparently free of other problems that could put it at a high risk of bias?	YES
Risk of Bias	Patients age stratified for block randomisation. Assessors were tested regarding blinding - results indicated they did not know group allocation
Other information	n/a

Table 131: Maseiro et al., 2014

Bibliographic reference	Masiero, S., Pol, P., Bonaldo, L., Pigatto, M., Ramonda, R., Lubrano, E., Punzi, L., Maffuli, N. Supervised training and home-based rehabilitation in patients with stabilized ankylosing spondylitis on TNF inhibitor treatment: controlled clinical trial with a 12-month follow-up. Clinical Rehabilitation, 28 (6): 562-572, 2014
Population	People with ankylosing spondylitis undergoing treatment with TNF inhibitors
Setting	Outpatients recruited from a hospital Rheumatology department, Italy
Study type	Quasi-randomised controlled clinical trial
Aim of the study	To assess the 12-month's follow-up effects on pain, mobility, and physical function outcomes of a supervised training and home-based rehabilitation for ankylosing spondylitis patients stabilized with TNF-inhibitor therapy.
Study dates	Not reported
Source of funding	This research received no specific grant from any funding agency in the public, commercial, or not-for-profit sectors.
Sample size	81 people were eligible of whom 12 declined to participate. 69 were randomly assigned to treatment of whom 64 completed the full study.
Characteristics	Rehabilitation group age, yrs (mean (SD)): 49.11 (11.8) male (%): 80.0 duration of complaints, yrs (mean (SD)): 19.3 (9.2) time from diagnosis, years (mean (SD)): 9.11 (6.9) infliximab/etanercept/adalimumab (n): 10/5/6 Education-behavioural group

Bibliographic reference	Masiero, S., Pol, P., Bonaldo, L., Pigatto, M., Ramonda, R., Lubrano, E., Punzi, L., Maffuli, N. Supervised training and home-based rehabilitation in patients with stabilized ankylosing spondylitis on TNF inhibitor treatment: controlled clinical trial with a 12-month follow-up. Clinical Rehabilitation, 28 (6): 562-572, 2014
	age, yrs (mean (SD)): 43.85 (8.1) male (%): 85.0 duration of complaints, yrs (mean (SD)): 15.6 (6.7) time from diagnosis, years (mean (SD)): 7.41 (4.7) infliximab/etanercept/adalimumab (n): 10/7/5/ Control group age, yrs (mean (SD)): 46.15 (10.3) male (%): 80.9 duration of complaints, yrs (mean (SD)): 18.94 (9.6) time from diagnosis, years (mean (SD)): 9.15 (4.23) infliximab/etanercept/adalimumab (%): 10/6/5
Inclusion Criteria	Being treated with a standard dose of infliximab (5 mg/kg every six weeks) or etanercept (25 mg twice/week) or adalimumab (40mg every two weeks) for at least nine months and did not NSAIDs on a continuous basis presented with a stable clinical picture in example, with a change in the Bath Ankylosing Spondylitis Disease Activity Index of ±1/10 units in the previous three months aged between 18 and 65 years did not present severe functional impairment affecting independence in activities of daily living (such as walking or dressing); no other associated osteoarticular pathologies (e.g. rheumatoid arthritis, hip prosthesis).
Exclusion Criteria	complete ankylosis of the spine participation in rehabilitation treatment in the previous three months or rehabilitation treatments other than the one envisaged by the trial variations in the standard biological therapy regimens during the study period discontinuation of TNF-inhibitor therapy medical condition impairing function (e.g. heart disease) patients who declined to consent to the study.
Methods	Allocation via numerical sequence (participant 1 in rehabilitation group, participant 2 in education group, participant 3 in the control group etc.). Blinding: metrologist collecting data was blinded to treatment allocation. No other blinding is reported

Bibliographic reference	**Masiero, S., Pol, P., Bonaldo, L., Pigatto, M., Ramonda, R., Lubrano, E., Punzi, L., Maffuli, N. Supervised training and home-based rehabilitation in patients with stabilized ankylosing spondylitis on TNF inhibitor treatment: controlled clinical trial with a 12-month follow-up. Clinical Rehabilitation, 28 (6): 562-572, 2014**
	Analysis: Intention to treat analysis was carried out. Participants were assessed at baseline, after 6 weeks, and at 12 months Intervention: Rehabilitation group Initial education component followed by exercise program developed by an interdisciplinary team. Educational programme involved two meetings spaced two weeks apart, each lasting three hours and organised for groups of 8-12 people. Information was provided on the condition, pain and stress mechanisms and their control, and identification of problems with everyday activities. Exercise component involved 12 twice-weekly sessions of 60 minutes each delivered by a physiotherapist in a group setting (6-8 patients). At the end of the programme, participants were encouraged to perform the exercises at home at least 3 times a week. Participants received a phone call from a member of the team every 3 weeks until the end of the trial to encourage them to perform the exercises. Education-behavioural group: received only the educational programme described above Control group: no intervention but continued on standard biological therapy
Results	Rehabilitation group (n=21): BASMI (mean (SD)): Baseline: 4.7 (1.1); 12 months: 3.8 (1.4) BASFI (mean (SD)): Baseline: 3.0 (1.5); 12 months: 2.2 (1.3) BASDAI (mean (SD)): Baseline: 3.8 (1.6); 12 months: 2.2 (1.3) Education-behaviour group (n=22): BASMI (mean (SD)): Baseline: 3.8 (1.1); 12 months: 3.6 (2.1) BASFI (mean (SD)):

Bibliographic reference	Masiero, S., Pol, P., Bonaldo, L., Pigatto, M., Ramonda, R., Lubrano, E., Punzi, L., Maffuli, N. Supervised training and home-based rehabilitation in patients with stabilized ankylosing spondylitis on TNF inhibitor treatment: controlled clinical trial with a 12-month follow-up. Clinical Rehabilitation, 28 (6): 562-572, 2014
	Baseline: 2.7 (1.6); 12 months: 2.4 (2.4) BASDAI (mean (SD)): Baseline: 2.9 (1.2); 12 months: 2.8 (2.1) Control group (n=21): BASMI (mean (SD)): Baseline: 4.0 (1.3); 12 months: 4.1 (1.6) BASFI (mean (SD)): Baseline: 2.9 (1.7); 12 months: 3.0 (2.0) BASDAI (mean (SD)): Baseline: 3.1 (1.7); 12 months: 3.2 (2.2)
Limitations	No other limitations
Other information	Risk of bias assessment Was the allocation sequence adequately generated? no Was allocation adequately concealed? no Was knowledge of the allocated intervention adequately prevented during the study? unclear Were incomplete outcome data adequately addressed? yes Are reports of the study free of suggestion of selective outcome reporting? yes Was the study apparently free of other problems that could put it at a high risk of bias? yes Overall risk of bias:

Bibliographic reference	Masiero, S., Pol, P., Bonaldo, L., Pigatto, M., Ramonda, R., Lubrano, E., Punzi, L., Maffuli, N. Supervised training and home-based rehabilitation in patients with stabilized ankylosing spondylitis on TNF inhibitor treatment: controlled clinical trial with a 12-month follow-up. Clinical Rehabilitation, 28 (6): 562-572, 2014
	Serious risk of bias due to suboptimal/under-reported methods in treatment allocation and blinding

Table 132: Rodriguez-Lozano et al., 2013

Bibliographic reference	Rodriguez-Lozano,Carlos, Juanola,Xavier, Cruz-Martinez,Juan, Pena-Arrebola,Andres, Mulero,Juan, Gratacos,Jordi, Collantes,Eduardo, Spondyloarthropathies Study Group of the Spanish Society of Rheumatology, Outcome of an education and home-based exercise programme for patients with ankylosing spondylitis: a nationwide randomized study, Clinical and experimental rheumatology, 31, 739-748, 2013
Country/ies where the study was carried out	Spain
Study type	Randomised controlled trial
Aim of the study	To assess the impact of a structured education and home exercise programme in daily practice patients with ankylosing spondylitis.
Study dates	Not reported. Presented in part at a 2010 conference. Submitted and published 2013.
Source of funding	Educational project received funding from the Spanish Society of Rheumatology
Sample size	At recruitment there were 391 in each arm. At follow up there were 381 in the education group and 375 in the control group. Only patients with follow up data were analysed
Characteristics	Diagnostic Criteria Ankylosing Spondylitis diagnosed on the basis of the modified New York criteria Baseline Characteristics Education/exercise intervention (n=381): male (%): 71 age (mean (sd)): 45(12) disease duration, years (mean(sd)): 17(10) current pharmacological treatment (%) Analgesics: 12.9

Bibliographic reference	**Rodriguez-Lozano,Carlos, Juanola,Xavier, Cruz-Martinez,Juan, Pena-Arrebola,Andres, Mulero,Juan, Gratacos,Jordi, Collantes,Eduardo, Spondyloarthropathies Study Group of the Spanish Society of Rheumatology, Outcome of an education and home-based exercise programme for patients with ankylosing spondylitis: a nationwide randomized study, Clinical and experimental rheumatology, 31, 739-748, 2013**
	Regular NSAIDs: 74.5 Corticosteroids: 3.4 DMARDs: 15.5 Sulfasalazine: 7.9 Methotrexate: 6.3 Biologic agents: 38.3 Regular physical exercise (>=1 day/week) (%): 47.8 Control (n=375): male (%): 73 age (mean (sd)):46(11) disease duration, years (mean(sd)): 18(11) current pharmacological treatment (%) Analgesics: 10.1 Regular NSAIDs: 76.3 Corticosteroids: 4.5 DMARDs: 22.6 Sulfasalazine: 10.9 Methotrexate: 10.9 Biologic agents: 39.7 Regular physical exercise (>=1 day/week) (%): 50.7
Inclusion criteria	Patients with confirmed diagnosis of AS (mod NY) attending outpatient departments at one of 24 participating hospitals in Spain Patients aged 18-70
Exclusion criteria	Patients with very severe AS, with significant loss of motion and ankylosis precluding physical exercise. Patients with diagnosis of other spondyloarthritis Patients with concomitant diseases in which exercise could be contraindicated
Details	Randomisation and allocation concealment

Bibliographic reference	**Rodriguez-Lozano,Carlos, Juanola,Xavier, Cruz-Martinez,Juan, Pena-Arrebola,Andres, Mulero,Juan, Gratacos,Jordi, Collantes,Eduardo, Spondyloarthropathies Study Group of the Spanish Society of Rheumatology, Outcome of an education and home-based exercise programme for patients with ankylosing spondylitis: a nationwide randomized study, Clinical and experimental rheumatology, 31, 739-748, 2013**
	Allocation concealment by opaque envelope. Each participating hospital was sent these envelopes by a central agency and contained a consecutive numeration and assignation case which was unknown to the investigators. Measurements Participants in both groups were asked to complete a weekly diary card in which they indicated the number of days they took NSAIDS and the number of exercised performed including aerobics and sports. Patients from the intervention group also recorded the % of the recommended exercise programme that they actually carried out each week. Pain and global assessments on VASs were performed at the end of each month Both groups received monthly phone calls to remind them to complete the patient diary. Intervention group received concurrent reminder to carry out the recommended exercises. Study assessments performed at baseline and after final visit at 24 weeks. These were performed by both groups as questionnaires. Participants in the intervention group also evaluated different aspects of the exercise programme, using VASs,. Analysis Sample size calculation was performed with significance level of 5% and power of 80%, assuming a mean BASDAI score of 4.5 in the control group and 3.5 in the intervention group. Final results reported were limited to those with data in the initial and final visits. Variables were compared with the chi squared test, Student's t-test, or Mann-Whitney U test. Within-group differences were examined with Student's t-test of the Wilcoxon signed rank test for continuous data and the McNemar's test or Stuart-Maxwell test for categorical variables. Between group differences were assessed with the Mann-Whitney U test. ANCOVA analysis was also performed with adjustment for a selection of baseline characteristics. Although this was a multicentre study, the article did not report whether this was performed as a cluster-randomised trial or whether any between-centre variation was examined in the analysis
Interventions	The study period was 24 weeks. Education/exercise group Participants in this arm divided into groups of 10, to attended educational sessions. Allowed to bring one family member to these sessions Intervention comprised: 30 minutes, led by rheumatologist, containing information about musculoskeletal system and the disease (pathophysiology, disease process, genetics, symptoms, prognosis, pharmacological management)

Bibliographic reference	Rodriguez-Lozano,Carlos, Juanola,Xavier, Cruz-Martinez,Juan, Pena-Arrebola,Andres, Mulero,Juan, Gratacos,Jordi, Collantes,Eduardo, Spondyloarthropathies Study Group of the Spanish Society of Rheumatology, Outcome of an education and home-based exercise programme for patients with ankylosing spondylitis: a nationwide randomized study, Clinical and experimental rheumatology, 31, 739-748, 2013
	30 minutes, led by rheumatology nurse, with information about general disease management (rest, aids, ergonomics, proper diet, alcohol and tobacco avoidance, sexuality and pregnancy) Psychological support information provided by pre-recorded interview with a psychologist 60 minute session with physiotherapist, reviewing the purposes of exercises, followed by on-site practice session to carry out the most difficult exercises with the help of the physiotherapist Exercise intervention was to be carried out at home. Comprised stretching, deep breathing, spinal extension, and range of motion exercises for the three spine segments, shoulders and hips Education and exercise programme received as printed handouts and a DVD. Comprised 30 home exercises and 10 water exercises, developed by a rehabilitation specialist. Leaflet containing 2007 American College of Sports Medicine and American Heart Association recommendations about physical activity and public health for adults was also received. Control group Followed usual pharmacological and rheumatological treatments recommended by rheumatologist in charge No further intervention apart from general clinical recommendations
Results	All measures reported are changes from baseline (mean (95% CI)) Pain Total pain (0-10 cm VAS) Exercise: -0.76 (-0.82 to -0.47) Control: -0.37 (-0.55 to -0.19) Nocturnal pain (0-10cm VAS) Exercise: -0.70 (-0.94 to -0.47) Control: -0.46 (-0.71 to -0.21) Adverse events Not reported Joint mobility Not reported Physical function

<table>
<tr><th>Bibliographic reference</th><th>Rodriguez-Lozano,Carlos, Juanola,Xavier, Cruz-Martinez,Juan, Pena-Arrebola,Andres, Mulero,Juan, Gratacos,Jordi, Collantes,Eduardo, Spondyloarthropathies Study Group of the Spanish Society of Rheumatology, Outcome of an education and home-based exercise programme for patients with ankylosing spondylitis: a nationwide randomized study, Clinical and experimental rheumatology, 31, 739-748, 2013</th></tr>
<tr><td></td><td>Not reported

Quality of life
ASQoL (0-18 scale)
Exercise: -0.98 (-1.29 to -0.68)
Control: -0.23 (-0.54 to 0.07)

Imaging
Not reported

Composite measures
BASDAI (0-10 scale)
Exercise: -0.65 (-0.82 to -0.47)
Control: -0.37 (-0.55 to -0.19)
BASFI (0-10 scale)
Exercise: -0.54 (-0.68 to -0.40)
Control: -0.21 (-0.36 to -0.007)
Patient's global assessment (0-10 cm VAS)
Exercise: -0.75 (-0.98 to -0.53)
Control: -0.36 (-0.58 to -0.13)</td></tr>
<tr><td>Pain</td><td>Pain<table><tr><td></td><td>Mean</td><td>SD</td><td>Total</td></tr><tr><td>Experimental</td><td>-0.76</td><td>2.29</td><td>381</td></tr><tr><td>Control</td><td>-0.44</td><td>2.37</td><td>375</td></tr></table></td></tr>
<tr><td>BASDAI</td><td>BASDAI<table><tr><td></td><td>Mean</td><td>SD</td><td>Total</td></tr><tr><td>Experimental</td><td>-0.65</td><td>1.74</td><td>381</td></tr></table></td></tr>
</table>

Bibliographic reference	Rodriguez-Lozano,Carlos, Juanola,Xavier, Cruz-Martinez,Juan, Pena-Arrebola,Andres, Mulero,Juan, Gratacos,Jordi, Collantes,Eduardo, Spondyloarthropathies Study Group of the Spanish Society of Rheumatology, Outcome of an education and home-based exercise programme for patients with ankylosing spondylitis: a nationwide randomized study, Clinical and experimental rheumatology, 31, 739-748, 2013
	Control -0.37 1.78 375
BASFI	BASFI Mean SD Total Experimental -0.54 1.39 381 Control -0.21 1.74 375
ASQoL	ASQoL Mean SD Total Experimental -0.98 3.04 381 Control -0.23 3.01 375
Was the allocation sequence adequately generated?	YES
Was allocation adequately concealed?	YES
Was knowledge of the allocated intervention adequately prevented during the study?	UNCLEAR
Were incomplete outcome data adequately addressed?	NO
Are reports of the study free of suggestion of selective outcome reporting?	YES
Was the study apparently free of other problems that could put it at a high risk of bias?	YES

Bibliographic reference	Rodriguez-Lozano,Carlos, Juanola,Xavier, Cruz-Martinez,Juan, Pena-Arrebola,Andres, Mulero,Juan, Gratacos,Jordi, Collantes,Eduardo, Spondyloarthropathies Study Group of the Spanish Society of Rheumatology, Outcome of an education and home-based exercise programme for patients with ankylosing spondylitis: a nationwide randomized study, Clinical and experimental rheumatology, 31, 739-748, 2013
Risk of Bias	Investigators blinded to allocation process but report is unclear on whether they were also blinded to intervention status during assessment. Unclear whether the participants lost to follow up where representative of those who completed the study.
Other information	Standard deviations manually calculated by KM from confidence intervals according to Cochrane handbook section 7.7.3.2

Table 133: Sweeney et al., 2002

Bibliographic reference	Sweeney,Siobhan, Taylor,Gordon, Calin,Andrei, The effect of a home based exercise intervention package on outcome in ankylosing spondylitis: a randomized controlled trial, The Journal of rheumatology, 29, 763-766, 2002
Country/ies where the study was carried out	UK
Study type	Randomised controlled trial
Aim of the study	To evaluate the effectiveness over a period of 6 months of an intervention package aimed at promoting self-care and regular long-term exercise
Study dates	Not reported. Submitted for publication 2001, published 2002.
Source of funding	Grants from BUPA, National Ankylosing Spondylitis Society, John Coates Charitable Trust, Col W.W. Pilkington Trust
Sample size	100 patients per group (200 total) were recruited. At follow up there were 75 in the intervention group and 80 in the control group. Only data on the followed-up patients are reported.
Characteristics	For patients still included at follow up: Intervention (n=75) age, years: 46.5 male (n): 51; female (n) :24 disease duration (years): 21.1 Control (n=80)

Bibliographic reference	Sweeney,Siobhan, Taylor,Gordon, Calin,Andrei, The effect of a home based exercise intervention package on outcome in ankylosing spondylitis: a randomized controlled trial, The Journal of rheumatology, 29, 763-766, 2002
	age, years: 45.9 male (n): 53; female (n): 27 disease duration (years): 21.9
Inclusion criteria	The 200 patients initially recruited were sampled at random from the investigators' database of 4569 people who were either outpatients of the Royal National Hospital for Rheumatic diseases Bath, or members of the National Ankylosing Spondylitis Society. All were between the ages of 16-65
Exclusion criteria	Not reported
Details	Diagnostic criteria Diagnostic criteria were not reported. All members of database had completed a questionnaire at entry including questions on date of diagnosis and onset of symptoms. Data were validated in a subset of these, confirming diagnosis in 98% of cases. Measurements Data were recorded at baseline and 6 months. Outcome measures were BASFI, BASDAI, BASG, exercise self-efficacy, Stanford Self-Efficacy scale and quantity of AS mobility and aerobic exercise per week (minutes). Analysis Independent t-tests and Mann-Whitney U tests used on pre- and post-test change scores for each individual
Interventions	Intervention was delivered by mail and consisted of: exercise/educational video containing introduction led by a consultant rheumatologist an exercise regime suitable for all stages of AS concluding discussion involving a health psychologist, physiotherapist and patient, discussing barriers to exercise and methods of maintaining regular adherence. An educational booklet An exercise progress wall chart and reminder stickers
Results	All values reported as mean (sd)

Bibliographic reference	Sweeney,Siobhan, Taylor,Gordon, Calin,Andrei, The effect of a home based exercise intervention package on outcome in ankylosing spondylitis: a randomized controlled trial, The Journal of rheumatology, 29, 763-766, 2002
	Pain Stanford Self-Efficacy, pain Exercise: 6 months: 6.80(1.21); change from baseline: 0.31(1.49) Control: 6 months: 6.24(1.1); change from baseline: 0.21(1.54) Adverse events Not reported Joint mobility Not reported Physical function Not reported Quality of life Not reported Imaging Not reported Composite measures BASDAI Exercise: 6 months: 3.65 (2.00); change from baseline: -0.33(1.87) Control: 6 months: 3.49(2.16); change from baseline: -0.58(0.58) BASFI Exercise: 6 months: 3.06(2.35); change from baseline:-0.43(1.78) Control: 6 months: 3.43(2.61); change from baseline: -0.23(1.89) BASGI

<table>
<tr><th>Bibliographic reference</th><th>Sweeney,Siobhan, Taylor,Gordon, Calin,Andrei, The effect of a home based exercise intervention package on outcome in ankylosing spondylitis: a randomized controlled trial, The Journal of rheumatology, 29, 763-766, 2002</th></tr>
<tr><td></td><td>Exercise: 6 months: 3.60(2.61); change from baseline: -0.21(2.86)
Control: 6 months: 3.61(2.81); change from baseline: -0.35(2.56)</td></tr>
<tr><td>Pain</td><td>Pain<table><tr><td></td><td>Mean</td><td>SD</td><td>Total</td></tr><tr><td>Experimental</td><td>0.31</td><td>1.49</td><td>75</td></tr><tr><td>Control</td><td>0.21</td><td>1.54</td><td>80</td></tr></table></td></tr>
<tr><td>BASDAI</td><td>BASDAI<table><tr><td></td><td>Mean</td><td>SD</td><td>Total</td></tr><tr><td>Experimental</td><td>-0.33</td><td>1.87</td><td>75</td></tr><tr><td>Control</td><td>-0.58</td><td>0.58</td><td>80</td></tr></table></td></tr>
<tr><td>BASFI</td><td>BASFI<table><tr><td></td><td>Mean</td><td>SD</td><td>Total</td></tr><tr><td>Experimental</td><td>-0.43</td><td>1.78</td><td>75</td></tr><tr><td>Control</td><td>-0.23</td><td>1.89</td><td>80</td></tr></table></td></tr>
<tr><td>BASG</td><td>BASG</td></tr>
</table>

Bibliographic reference	**Sweeney,Siobhan, Taylor,Gordon, Calin,Andrei, The effect of a home based exercise intervention package on outcome in ankylosing spondylitis: a randomized controlled trial, The Journal of rheumatology, 29, 763-766, 2002**
	<table><tr><td></td><td>Mean</td><td>SD</td><td>Total</td></tr><tr><td>Experimental</td><td>-0.21</td><td>2.86</td><td>75</td></tr><tr><td>Control</td><td>-0.35</td><td>2.56</td><td>80</td></tr></table>
Was the allocation sequence adequately generated?	UNCLEAR
Was allocation adequately concealed?	UNCLEAR
Was knowledge of the allocated intervention adequately prevented during the study?	UNCLEAR
Were incomplete outcome data adequately addressed?	NO
Are reports of the study free of suggestion of selective outcome reporting?	YES
Was the study apparently free of other problems that could put it at a high risk of bias?	YES
Risk of Bias	Quite a lot of participants dropped out (25% intervention, 20% control), with a slightly higher dropout rate amongst men and amongst control participants.
Other information	Query - is standard deviation of BASDAI mean change in control group a typo?

E.3.3 Hydrotherapy for spondyloarthritis

Review Question 16

- What is the effectiveness of hydrotherapy compared with standard care for managing spondyloarthritis?

Randomised Controlled Trials

Table 134: Altan et al., 2006

Bibliographic reference	Altan,L., Bingol,U., Aslan,M., Yurtkuran,M., The effect of balneotherapy on patients with ankylosing spondylitis, Scandinavian journal of rheumatology, 35, 283-289, 2006
Country/ies where the study was carried out	Turkey
Study type	Randomised controlled trial
Aim of the study	To compare the effect of balneotherapy on physical activity and quality of life as well as the symptoms of pain and stiffness with exercise alone in the short and medium term.
Study dates	Not reported. Study was submitted and accepted 2005, published 2006.
Source of funding	Not reported
Sample size	60 patients (6 were lost to follow up)
Diagnostic criteria	modified New York
Inclusion criteria	Diagnosed AS with a moderate degree of pain (between 4 to 7 according to the VAS), stiffness and a score of 2 or higher (according to the 1-5 score) for patient's global evaluation.
Exclusion criteria	Active peripheral arthritis secondary fibromyalgia syndrome total spinal ankylosis ESR>50mm/h or CRP>10 times normal value Previously receiving balneotherapy in last 12 month
Characteristics	All patients had ankylosing spondylitis with a moderate degree of pain, but no systemic problems contra-indicating hydrotherapy or exercise. No baseline demographic (age, sex) or disease-characterising (duration of symptoms etc.) data were reported for either group or for the study population as a whole. Patients were allowed to continue previous medication but were required not to use supplementary drugs or change the usual dosages through the study period of 24 weeks.
Interventions	Balneotherapy+exercise (n=28) Daily outpatient balneotherapy, once a day for 3 weeks

Bibliographic reference	Altan,L., Bingol,U., Aslan,M., Yurtkuran,M., The effect of balneotherapy on patients with ankylosing spondylitis, Scandinavian journal of rheumatology, 35, 283-289, 2006
	30 mins of early morning bathing in spa water, followed by 2 hours of bed rest. Water was heated to 39°C Exercises: participants given instructions on exercise and requested to repeat this once a day for 30 minutes for the study duration (24 weeks). Home exercise programme comprised respiration-postural exercises and dorsal/lumbar extension exercises Exercise only group (n=26) This group did not receive balneotherapy, but did received the same exercise instructions as the other group. Patient's compliance with the exercise programme was monitored by monthly phone calls and a control examination at month 3.
Randomisation, allocation, blinding	No details of randomisation method were reported. Physician carrying out evaluations was blinded.
Details	Patient evaluations were carried out at baseline, 3 weeks and 24 weeks by a physician who was blinded to the patients. Pain assessed using VAS. Morning stiffness evaluated on 4 point scale: 0=no stiffness, 1=less than 15 mins, 2=between 15 and 30 mins, 3=more than 30 mins. Quality of life was measured using the Nottingham Health profile. Changes in outcome measures were assessed with the Wilcoxen test. Comparison of results between the two groups was performed using the Mann-Whitney U-test.
Missing data handling/loss to follow up	Two patients in group I did not complete due to personal reasons, four in group II did not complete due to difficulty complying with exercise programme.
Results	Daily pain (VAS) Balneotherapy + exercise: baseline: 3.46(2.11); week 3: 1.96(1.37); week 24:1.92(1.32); change from baseline: -1.68(2.05) Exercise: baseline: 3.53(1.55); week 3: 2.0(1.44); week 24: 2.11(1.58); change from baseline: -1.42(1.42) Night pain (VAS) Balneotherapy + exercise: baseline: 5.0(1.9); week 3: 3.26(1.67); week 24: 2.82(1.84); change from baseline: -2.44(1.61) Exercise: baseline: 4.77(1.17); week 3: 3.23(1.53); week 24: 3.0(1.83); change from baseline: -1.77(1.82) Morning stiffness (0-4 scale) Balneotherapy + exercise: baseline: 1.57(0.74); week 3: 1.03(0.51); week 24: 1.12(0.33); change from baseline: -0.48(0.71) Exercise: baseline: 2.04(0.66); week 3: 1.31(0.47); week 24: 1.27(0.45); change from baseline: -0.76(0.65) NB: This was collected on an ordinal scale but analysed by the authors as a continuous variable Adverse events

Bibliographic reference	Altan,L., Bingol,U., Aslan,M., Yurtkuran,M., The effect of balneotherapy on patients with ankylosing spondylitis, Scandinavian journal of rheumatology, 35, 283-289, 2006
	Paper reports that no side effects of either treatment protocol were recorded Joint / Spinal mobility Not reported Physical function Not reported Quality of life NHP (total score, 0-600) (mean(sd)) Balneotherapy+exercise: baseline: 134.5(78.83); week 3: 55.74(52.93); week 24: 70.49(82.74); change from baseline: -58.92(72.11) Exercise: baseline: 136.46(112.78); week 3: 108.76(114.49); week 24: 80.63(100.14); change from baseline: -55.82(68.71) Imaging Not reported Composite measures BASFI (mean(sd)) Balneotherapy + exercise: baseline: 1.28(1.15); week 3: 0.50(0.73); week 24: 0.38(0.57); change from baseline: -0.73(0.88) Exercise: baseline: 0.91(0.75); week 3: 0.61(0.6); week 24: 0.54(0.71); change from baseline: -0.36(0.64) BASDAI (mean(sd)) Balneotherapy + exercise: baseline: 3.42(1.57); week 3: 1.11(0.77); week 24: 1.49(1.37); change from baseline: -1.77(1.70) Exercise: baseline: 3.05(1.58); week 3: 1.78(0.98); week 24: 1.62(1.40); change from baseline: -1.43(1.50)
BASFI/Dougados FI	BASFI/Dougados FI <table><tr><td></td><td>Mean</td><td>SD</td><td>Total</td></tr><tr><td>Experimental</td><td>-0.73</td><td>0.88</td><td>28</td></tr></table>

Bibliographic reference	Altan,L., Bingol,U., Aslan,M., Yurtkuran,M., The effect of balneotherapy on patients with ankylosing spondylitis, Scandinavian journal of rheumatology, 35, 283-289, 2006
	Control | -0.36 | 0.64 | 26
ASQoL/HAQ/NHP	ASQoL/HAQ/NHP | | Mean | SD | Total | | Experimental | -58.92 | 72.11 | 28 | | Control | -55.82 | 68.71 | 26 |
Pain	Pain | | Mean | SD | Total | | Experimental | -1.68 | 2.05 | 28 | | Control | -1.42 | 1.42 | 26 |
BASDAI	BASDAI | | Mean | SD | Total | | Experimental | -1.77 | 1.70 | 28 | | Control | -1.43 | 1.50 | 26 |
Overall Risk of Bias	No information about baseline characteristics of each group means success of randomisation cannot be assessed.
Other information	Some of the change scores from baseline for group I are potentially discrepant.

Bibliographic reference	Altan,L., Bingol,U., Aslan,M., Yurtkuran,M., The effect of balneotherapy on patients with ankylosing spondylitis, Scandinavian journal of rheumatology, 35, 283-289, 2006
	Morning stiffness measures were omitted from our meta-analysis as they were inappropriately handled in the study.
Was the allocation sequence adequately generated?	UNCLEAR
Was allocation adequately concealed?	UNCLEAR
Was knowledge of the allocated intervention adequately prevented during the study?	UNCLEAR
Were incomplete outcome data adequately addressed?	YES
Are reports of the study free of suggestion of selective outcome reporting?	NO
Was the study apparently free of other problems that could put it at a high risk of bias?	NO

Table 135: Ciprian et al., 2013

Bibliographic reference	Ciprian,Luca, Lo Nigro,Alessandro, Rizzo,Michela, Gava,Alessandra, Ramonda,Roberta, Punzi,Leonardo, Cozzi,Franco, The effects of combined spa therapy and rehabilitation on patients with ankylosing spondylitis being treated with TNF inhibitors, Rheumatology international, 33, 241-245, 2013
Country/ies where the study was carried out	Padova, Italy
Study type	Randomised controlled trial
Aim of the study	To assess the effects on physical function and quality of life of combined spa therapy and rehabilitation in the management of patients with ankylosing spondylitis being treated with anti-TNF agents.
Study dates	Not stated. Article submitted March 2011, published September 2011.
Source of funding	Not reported
Sample size	30 patients (15 intervention group, 15 control)

Bibliographic reference	Ciprian,Luca, Lo Nigro,Alessandro, Rizzo,Michela, Gava,Alessandra, Ramonda,Roberta, Punzi,Leonardo, Cozzi,Franco, The effects of combined spa therapy and rehabilitation on patients with ankylosing spondylitis being treated with TNF inhibitors, Rheumatology international, 33, 241-245, 2013
Diagnostic criteria	Not stated. Patients fulfilled "the classification criteria for the diagnosis of AS".
Inclusion criteria	Attendees of the Rheumatological unit of the University of Padova Treated with TNF inhibitors for at least 3 months
Exclusion criteria	None reported
Characteristics	Spa treatment group (n=15) 14 males, 1 female age (mean(sd)): 47.8(10) disease duration, years (mean(sd)): 13.9(8.6) HLA B27+ve (n): 13 treated with etanercept (n): 11 treated with infliximab (n): 4 Control group (n=15) 14 males, 1 female age (mean(sd)):45.6(11.8) disease duration, years (mean(sd)): 13.2(8.8) HLA B27+ve (n): 14 treated with etanercept (n): 10 treated with infliximab (n): 5
Interventions	All study participants had been taking TNF inhibitors for at least 3 months prior to the start of the trial, and continued taking them throughout the trial period. Use of NSAIDs or corticosteroids was not permitted during that time in either group. Only oral paracetamol was permitted if necessary. Intervention group 10 sessions of spa therapy and rehab over a 10 week period Sessions performed in morning and comprised two parts: mud-pack (40-55°C) applied to entire spinal area for 15 minutes followed by immersion to neck level in thermal bath tank at 37-38°C for 10 minutes group rehab session for an hour in a pool of thermal water (32-34°C) under the supervision of a specialist physiotherapist. Included exercises for spine mobilisation (flex/extension and torsion of the trunk), exercises for muscular spine strengthening and respiratory kinesitherapy.

Bibliographic reference	**Ciprian,Luca, Lo Nigro,Alessandro, Rizzo,Michela, Gava,Alessandra, Ramonda,Roberta, Punzi,Leonardo, Cozzi,Franco, The effects of combined spa therapy and rehabilitation on patients with ankylosing spondylitis being treated with TNF inhibitors, Rheumatology international, 33, 241-245, 2013**
	Thermal water contained 6g/l mineral salts, obtained from a well at 73°C. Mud was a mixture of natural clay (94%) and organic substances (6%) produced by maceration of a range of microorganisms in special tanks irrigated by a continuous flow of thermal water Control group No details of control group reported. Assumed (KMc) to be standard care
Randomisation, allocation, blinding	Participants were randomly assigned in a 1:1 ratio by investigators independent of spa staff. No further detail reported.
Details	Spa treatment patients were evaluated at baseline, at the end of the spa treatment period, and at 3 and 6 months after the treatment. Control patients assessed at same time. Outcome measurements were standard instruments (Bath Indices, HAQ, 10cm VAS for pain). Descriptive data were expressed as mean and standard deviation. Wilcoxen test used to compare to baseline values the data collected at each time point. A p value threshold of <0.05 was used for statistical significance.
Missing data handling/loss to follow up	No loss to follow up reported.
Results	Pain Back pain intensity (10cm VAS*) (mean(sd)) Intervention: baseline: 23.11(16.27); 2 weeks: 20.22(11.56); 3 months: 17.33(9.24); 6 months: 14.89(9.49) Control: baseline: 26.31(16.39); 2 weeks: 21.15(14.45); 3 months: 26.31(16.39); 6 months: 21.15(14.45) *Numbers given here as reported. Have assumed them to be mm despite VAS described as 10cm.[KMc] Adverse events Not reported Joint / Spinal mobility Not reported Physical function Not reported Quality of life

<table>
<tr><th>Bibliographic reference</th><th>Ciprian,Luca, Lo Nigro,Alessandro, Rizzo,Michela, Gava,Alessandra, Ramonda,Roberta, Punzi,Leonardo, Cozzi,Franco, The effects of combined spa therapy and rehabilitation on patients with ankylosing spondylitis being treated with TNF inhibitors, Rheumatology international, 33, 241-245, 2013</th></tr>
<tr><td></td><td>HAQ (mean(sd))
Intervention: baseline: 0.80(0.54); 2 weeks: 0.56(0.42); 3 months: 0.66(0.46); 6 months: 0.62(0.50)
Control: baseline: 0.76(0.63); 2 weeks: 0.69(0.59); 3 months: 0.80(0.73); 6 months: 0.77(0.60)

Imaging
Not reported

Composite measures
BASMI (mean(sd))
Intervention: baseline: 5.11(3.03); 2 weeks: 3.56(2.91); 3 months: 3.81(2.51); 6 months: 3.98(3.16)
Control: baseline: 4.15(1.40); 2 weeks: 3.92(1.19); 3 months: 4.25(1.66); 6 months: 4.02(1.24)

BASDAI (mean(sd))
Intervention: baseline: 2.86(1.76); 2 weeks: 1.83(1.04); 3 months: 2.12(1.44); 6 months: 2.20(1.18)
Control: baseline: 2.86(1.76); 2 weeks: 2.20(1.31); 3 months: 2.66(1.68); 6 months:2.40(1.51)

BASFI
Only reported as a graph, raw numbers not provided</td></tr>
<tr><td>BASMI</td><td>BASMI<table><tr><td></td><td>Mean</td><td>SD</td><td>Total</td></tr><tr><td>Experimental</td><td>3.98</td><td>3.16</td><td>15</td></tr><tr><td>Control</td><td>4.02</td><td>1.24</td><td>15</td></tr></table></td></tr>
<tr><td>ASQoL/HAQ/NHP</td><td>ASQoL/HAQ/NHP</td></tr>
</table>

Bibliographic reference	**Ciprian,Luca, Lo Nigro,Alessandro, Rizzo,Michela, Gava,Alessandra, Ramonda,Roberta, Punzi,Leonardo, Cozzi,Franco, The effects of combined spa therapy and rehabilitation on patients with ankylosing spondylitis being treated with TNF inhibitors, Rheumatology international, 33, 241-245, 2013**
	<table><tr><td></td><td>Mean</td><td>SD</td><td>Total</td></tr><tr><td>Experimental</td><td>0.62</td><td>0.50</td><td>15</td></tr><tr><td>Control</td><td>0.77</td><td>0.60</td><td>15</td></tr></table>
Pain	Pain <table><tr><td></td><td>Mean</td><td>SD</td><td>Total</td></tr><tr><td>Experimental</td><td>14.89</td><td>9.49</td><td>15</td></tr><tr><td>Control</td><td>21.15</td><td>14.45</td><td>15</td></tr></table>
BASDAI	BASDAI <table><tr><td></td><td>Mean</td><td>SD</td><td>Total</td></tr><tr><td>Experimental</td><td>2.20</td><td>1.18</td><td>15</td></tr><tr><td>Control</td><td>2.40</td><td>1.51</td><td>15</td></tr></table>
Overall Risk of Bias	Randomisation performed by investigators other than the spa staff. It is not clear what other roles these investigators took on e.g. whether they were the assessors.
Other information	Mean change not reported, so values at 6 months were used for meta-analysis, as study was considered to be well balanced at baseline.
Was the allocation sequence adequately generated?	UNCLEAR

Bibliographic reference	Ciprian,Luca, Lo Nigro,Alessandro, Rizzo,Michela, Gava,Alessandra, Ramonda,Roberta, Punzi,Leonardo, Cozzi,Franco, The effects of combined spa therapy and rehabilitation on patients with ankylosing spondylitis being treated with TNF inhibitors, Rheumatology international, 33, 241-245, 2013
Was allocation adequately concealed?	UNCLEAR
Was knowledge of the allocated intervention adequately prevented during the study?	NO
Were incomplete outcome data adequately addressed?	YES
Are reports of the study free of suggestion of selective outcome reporting?	YES
Was the study apparently free of other problems that could put it at a high risk of bias?	YES

Table 136: Cozzi et al., 2007

Bibliographic reference	Cozzi,Franco, Podswiadek,Marta, Cardinale,Gabriella, Oliviero,Francesca, Dani,Lara, Sfriso,Paolo, Punzi,Leonardo, Mud-bath treatment in spondylitis associated with inflammatory bowel disease--a pilot randomised clinical trial, Joint, bone, spine : revue du rhumatisme, 74, 436-439, 2007
Country/ies where the study was carried out	Padova, Italy
Study type	Randomised controlled trial
Aim of the study	To evaluate the effects and the tolerability of mud packs and thermal baths in a group of patients with spondylitis and Crohn's disease or ulcerative colitis.
Study dates	Not reported. Paper submitted 2006, published 2007.
Source of funding	Not reported
Sample size	24 participants (12 intervention group, 12 control) with spondylitis and inflammatory bowel disease
Diagnostic criteria	All participants fulfilled ESSG diagnostic criteria. IBD diagnosed by clinical, endoscopic, histological and radiological criteria
Inclusion criteria	Patients at the Rheumatology unit of the University of Padova

Bibliographic reference	Cozzi,Franco, Podswiadek,Marta, Cardinale,Gabriella, Oliviero,Francesca, Dani,Lara, Sfriso,Paolo, Punzi,Leonardo, Mud-bath treatment in spondylitis associated with inflammatory bowel disease--a pilot randomised clinical trial, Joint, bone, spine : revue du rhumatisme, 74, 436-439, 2007
	Without active peripheral arthritis or active IBD (CDAI>150 or Powell-Tuck index>4)
Exclusion criteria	Active peripheral arthritis
Characteristics	Prior to study start, 17 patients were in treatment with 5-ASA and 7 with sulfasalazine for at least 3 months prior. There was good management of peripheral arthritis and IBD but poor management of spondylitis (BASDAI>30) Mud-bath treatment group (n=12) gender (n female): 6 age (years (mean(sd)): 47.8(10.0) IBD duration (years (mean(sd)): 8.9(6.3) spondylitis duration (years (mean(sd)): 6.8(6.5) Crohn's disease (n): 5 Ulcerative colitis (n): 7 Control group (n=12) gender (n female): 7 age (years (mean(sd)): 41.4(11.8) IBD duration (years (mean(sd)): 6.8(3.5) spondylitis duration (years (mean(sd)): 5.6(1.9) Crohn's disease (n): 6 Ulcerative colitis (n): 6
Interventions	Participants in both groups were not permitted to take NSAIDs or corticosteroids during the study period. Oral paracetamol administered as necessary Intervention group 12 sessions of mud paths and thermal baths over a period of 2 weeks Sessions comprised two parts: mud-pack (42-45°C) applied to entire spinal area for 15 minutes daily in the morning immersion in thermal water at 37-38°C for 10 minutes

Bibliographic reference	**Cozzi,Franco, Podswiadek,Marta, Cardinale,Gabriella, Oliviero,Francesca, Dani,Lara, Sfriso,Paolo, Punzi,Leonardo, Mud-bath treatment in spondylitis associated with inflammatory bowel disease--a pilot randomised clinical trial, Joint, bone, spine : revue du rhumatisme, 74, 436-439, 2007**
	Thermal water contained 6g/l mineral salts, obtained from a well at 73°C. Mud was a mixture of natural clay (94%) and organic substances (6%) produced by maceration of a range of microorganisms in special tanks irrigated by a continuous flow of thermal water Control group No intervention described
Randomisation, allocation, blinding	Patients were randomised in 1:1 ratio Investigators assessing the patients were independent of the spa staff. Evaluations carried out by blinded investigator who was not involved in treatment allocation. To achieve partial blinding of participants they were not informed of the comparison between groups.
Details	Patients in both groups were assessed at baseline, end of treatment period, 12 weeks and 24 weeks. Outcome measures relating to spondylitis (including BASFI, BASDAI50 and BASDAI20) were collected. IBD activity was monitored by CDAI or Powell-Tuck Index. Wilcoxen signed rank test used to compare variables at each time point. Chi sq or Fisher's exact test were used to calculate statistical significances between the BASDAI50/20 improvement of patients in the intervention and control groups. p values of <0.05 were considered statistically significant
Missing data handling/loss to follow up	No loss to follow up reported
Results	Pain VAS for back pain (mean(sd)) Mud-bath treatment: baseline: 36.1(18.6); 2 weeks: 19.5(17.4); 12 weeks: 25.2(19.7); 24 weeks: 28.4(19.5) Control: baseline: 39.8(15.9); 2 weeks: 42.2(21.8); 12 weeks: 42.2(20.3); 24 weeks: 43.8(17.2) Adverse events Not reported Joint/spinal mobility Not reported Physical function Not reported

<table>
<tr><th>Bibliographic reference</th><th>Cozzi,Franco, Podswiadek,Marta, Cardinale,Gabriella, Oliviero,Francesca, Dani,Lara, Sfriso,Paolo, Punzi,Leonardo, Mud-bath treatment in spondylitis associated with inflammatory bowel disease--a pilot randomised clinical trial, Joint, bone, spine : revue du rhumatisme, 74, 436-439, 2007</th></tr>
<tr><td></td><td>Quality of life
Not reported

Imaging
Not reported

Composite measures
BASFI (mean(sd))
Mud-bath treatment: baseline: 26.8(16.2); 2 weeks: 14.7(7.9); 12 weeks: 21.5(18.4); 24 weeks: 20.5(18.5)
Control: baseline: 22.1(18.5); 2 weeks: 24.6(22.9); 12 weeks: 26.6(25.4); 24 weeks: 26.0(24.3)
BASDAI* (mean(sd))
Mud-bath treatment: baseline: 40.6(21.5); 2 weeks: 25.4(12.9); 12 weeks: 28.1(16.3); 24 weeks: 29.1(14.2)
Control: baseline: 43.6(19.8); 2 weeks: 46.1(20.4); 12 weeks: 45.6(24.9); 24 weeks: 42.1(20.6)
*Assumed to be BASDAI50 but slightly unclear</td></tr>
<tr><td>BASFI/Dougados FI</td><td>BASFI/Dougados FI<table><tr><td></td><td>Mean</td><td>SD</td><td>Total</td></tr><tr><td>Experimental</td><td>-6.30</td><td>24.30</td><td>12</td></tr><tr><td>Control</td><td>3.90</td><td>24.30</td><td>12</td></tr></table></td></tr>
<tr><td>Pain</td><td>Pain<table><tr><td></td><td>Mean</td><td>SD</td><td>Total</td></tr><tr><td>Experimental</td><td>-7.70</td><td>19.50</td><td>12</td></tr><tr><td>Control</td><td>4.00</td><td>19.50</td><td>12</td></tr></table></td></tr>
<tr><td>Adverse events</td><td></td></tr>
</table>

Bibliographic reference	**Cozzi,Franco, Podswiadek,Marta, Cardinale,Gabriella, Oliviero,Francesca, Dani,Lara, Sfriso,Paolo, Punzi,Leonardo, Mud-bath treatment in spondylitis associated with inflammatory bowel disease--a pilot randomised clinical trial, Joint, bone, spine : revue du rhumatisme, 74, 436-439, 2007**
BASDAI	BASDAI | | Mean | SD | Total | | Experimental | -11.50 | 21.50 | 12 | | Control | -1.50 | 21.50 | 12 |
Overall Risk of Bias	Reporting of BASDAI changes in table 2 is ambiguous
Other information	SDs for mean change manually imputed as largest SD of baseline/endpoint for that outcome across two groups [KMc]
Was the allocation sequence adequately generated?	UNCLEAR
Was allocation adequately concealed?	UNCLEAR
Was knowledge of the allocated intervention adequately prevented during the study?	YES
Were incomplete outcome data adequately addressed?	UNCLEAR
Are reports of the study free of suggestion of selective outcome reporting?	YES
Was the study apparently free of other problems that could put it at a high risk of bias?	YES

Table 137: Gurcay et al., 2008

Bibliographic reference	Gurcay,Eda, Yuzer,Serdil, Eksioglu,Emel, Bal,Ajda, Cakci,Aytul, Stanger bath therapy for ankylosing spondylitis: illusion or reality?, Clinical rheumatology, 27, 913-917, 2008
Country/ies where the study was carried out	Ankara,Turkey
Study type	Randomised controlled trial
Aim of the study	To clinically evaluate the short-term effects of Stanger bath therapy in conjunction with conventional exercise on spinal mobility, functional capacity, disease activity, and quality of life outcomes in AS patients and to compare with results in patients receiving conventional exercise alone.
Study dates	Not reported. Paper submitted and published 2008.
Source of funding	Not reported
Sample size	58 patients recruited, one withdrew during course of the study.
Diagnostic criteria	Modified New York
Inclusion criteria	Attendees of Physical Therapy and Rehabilitation clinic
Exclusion criteria	People with severe comorbidity of the heart, lung, liver or kidneys Total spinal ankylosis Previously received hydrotherapy within 1 year ESR>50mm/h or CRP more than ten times normal value
Characteristics	Patients were allowed to continue their previous medication but were requested not to use supplementary drugs or change the usual dosages during the 3 week study period. Bath therapy group (n=29) age, years (mean(sd)): 40.2(10.38) female, n(%): 2(6.9) disease duration (mean(sd)): 16.21(10.22) clinical type peripheral, n(%): 6(20.7) axial, n(%):15(51.7) periphic and axial, n(5): 8(27.6) Control group (n=28) age, years (mean(sd)): 41.3(8.59)

Bibliographic reference	Gurcay,Eda, Yuzer,Serdil, Eksioglu,Emel, Bal,Ajda, Cakci,Aytul, Stanger bath therapy for ankylosing spondylitis: illusion or reality?, Clinical rheumatology, 27, 913-917, 2008
	female, n(%): 6(21.4) disease duration (mean(sd)):13.53(9.33) clinical type periphic, n(%): 2(7.1) axial, n(%): 17(60.7) periphic and axial, n(5): 9(32.1)
Interventions	Group 1 (bath therapy), n=29 exercise programme and bath therapy for 20 mins/day for 15 sessions over 3 week period exercise programme: Taught by physiotherapist to each patient individually, then carried out unsupervised at home. Comprised range of motion, muscle strengthening, respiration and postural exercises. Stanger bath therapy: Bath made of synthetic materials, and had 9 electrodes which could be activated in transverse, longitudinal or transverse-diagonal form. . NaCL added to water to increase conductivity (0.2-0.5% ratio). DD current used and intensity was assigned according to patient's tingling sensation on body surface. Tap water was used at temperature of 36-37°C Group 2 (control), n=28 exercise programme as above
Randomisation, allocation, blinding	Randomisation via opaque envelopes on 1:1 basis. Physician collecting measurements was blinded to treatment allocation.
Details	Personal and clinical data collected by questionnaire. Bath therapy was applied by a physiotherapist. Exercises were also taught by a physiotherapist, on an individual basis. Outcome measures were collected by a physician blinded to treatment allocation. Mean values compared using Student's t test or Mann-Whitney U test where appropriate. Pre- and post-treatment differences evaluated using Wilcoxen sign rank test within groups. For categorical comparisons, chi sq tests or Fisher's exact test used where appropriate. P values of <0.05 were accepted as statistically significant.
Missing data handling/loss to follow up	One patient withdrew due to personal reasons (bath therapy group). Baseline characteristics and results only presented on the remaining 57 patients.
Results	Pain Not reported Adverse events

Bibliographic reference	Gurcay,Eda, Yuzer,Serdil, Eksioglu,Emel, Bal,Ajda, Cakci,Aytul, Stanger bath therapy for ankylosing spondylitis: illusion or reality?, Clinical rheumatology, 27, 913-917, 2008
	Paper states that no side effects occurred Joint / Spinal mobility Not reported Physical function Not reported Quality of life ASQoL (mean(sd)) Bath therapy+exercise: baseline: 10.17(3.02); 3 weeks: 6.96(2.80); mean difference: -3.21(2.29) Exercise only: baseline: 8.11(0.05); 3 weeks: 6.96(3.71); mean difference: -1.14(1.11) Imaging Not reported Composite measures BASMI (mean(sd)) Bath therapy+exercise: baseline: 4.69(2.46); 3 weeks: 3.94(2.42); mean difference: -0.74(0.89) Exercise only: baseline: 4.46(3.08); 3 weeks: 4.29(3.05); mean difference: -0.18(0.55) BASDAI (mean(sd)) Bath therapy+exercise: baseline: 4.96(1.88); 3 weeks: 2.75(1.56); mean difference: -2.20(1.39) Exercise only: baseline: 3.20(1.63); 3 weeks: 2.61(1.41); mean difference: -0.59(0.71) BASFI (mean(sd)) Bath therapy+exercise: baseline: 4.72(1.76); 3 weeks: 2.87(1.78); mean difference: -1.84(1.07) Exercise only: baseline: 3.20(1.63); 3 weeks: 2.61(1.41); mean difference: -0.48(0.73)
BASFI/Dougados FI	BASFI/Dougados FI

Bibliographic reference	Gurcay,Eda, Yuzer,Serdil, Eksioglu,Emel, Bal,Ajda, Cakci,Aytul, Stanger bath therapy for ankylosing spondylitis: illusion or reality?, Clinical rheumatology, 27, 913-917, 2008
	<table><tr><td></td><td>Mean</td><td>SD</td><td>Total</td></tr><tr><td>Experimental</td><td>-1.84</td><td>1.07</td><td>29</td></tr><tr><td>Control</td><td>-0.48</td><td>0.73</td><td>28</td></tr></table>
BASMI	BASMI <table><tr><td></td><td>Mean</td><td>SD</td><td>Total</td></tr><tr><td>Experimental</td><td>-0.74</td><td>0.89</td><td>29</td></tr><tr><td>Control</td><td>-0.18</td><td>0.55</td><td>28</td></tr></table>
ASQoL/HAQ/NHP	ASQoL/HAQ/NHP <table><tr><td></td><td>Mean</td><td>SD</td><td>Total</td></tr><tr><td>Experimental</td><td>-3.21</td><td>2.29</td><td>29</td></tr><tr><td>Control</td><td>-1.14</td><td>1.11</td><td>28</td></tr></table>
BASDAI	BASDAI <table><tr><td></td><td>Mean</td><td>SD</td><td>Total</td></tr><tr><td>Experimental</td><td>-2.20</td><td>1.39</td><td>29</td></tr><tr><td>Control</td><td>-0.59</td><td>0.71</td><td>28</td></tr></table>
Other information	n/a

Bibliographic reference	Gurcay,Eda, Yuzer,Serdil, Eksioglu,Emel, Bal,Ajda, Cakci,Aytul, Stanger bath therapy for ankylosing spondylitis: illusion or reality?, Clinical rheumatology, 27, 913-917, 2008
Was the allocation sequence adequately generated?	UNCLEAR
Was allocation adequately concealed?	YES
Was knowledge of the allocated intervention adequately prevented during the study?	UNCLEAR
Were incomplete outcome data adequately addressed?	YES
Are reports of the study free of suggestion of selective outcome reporting?	YES
Was the study apparently free of other problems that could put it at a high risk of bias?	YES

Table 138: Yurtkuran et al., 2005

Bibliographic reference	Yurtkuran,Merih, Ay,Alev, Karakoc,Yuksel, Improvement of the clinical outcome in Ankylosing spondylitis by balneotherapy, Joint, bone, spine : revue du rhumatisme, 72, 303-308, 2005
Country/ies where the study was carried out	Turkey
Study type	Randomised controlled trial
Aim of the study	To show the efficacy of balneotherapy and balneotherapy+NSAID use in ankylosing spondylitis
Study dates	Not reported. Paper submitted and published 2004.
Source of funding	Not reported
Sample size	61 participants at baseline (21 in balneotherapy(BT), 20 BT+NSAID, 20 NSAID). Either 5 or 6 were withdrawn during course of study (see 'Missing data handling/loss to follow up' section)
Diagnostic criteria	New York criteria

Bibliographic reference	Yurtkuran,Merih, Ay,Alev, Karakoc,Yuksel, Improvement of the clinical outcome in Ankylosing spondylitis by balneotherapy, Joint, bone, spine : revue du rhumatisme, 72, 303-308, 2005
Inclusion criteria	Outpatients of Ataturk Balneotherapy and Rehabilitation centre
Exclusion criteria	Active periphic arthritis or systemic involvement
Characteristics	None of the patients had peripheral arthritis or other systemic involvement. BT+NSAID group (n=20) age (mean(sd)): 51(7) sex (F/M): 4/16 Illness duration, years (mean(sd)): 12(5) Bilateral grade II-III sacroiliitis (n): 12 Grade III/IV sacroiliitis (n): 8 NSAID group (n=21) age (mean(sd)): 50(11) sex (F/M): 3/17 Illness duration, years (mean(sd)): 9(6) Bilateral grade II-III sacroiliitis (n): 11 Grade III/IV sacroiliitis (n): 9
Interventions	Patients were asked to cease taking NSAIDs for one week prior to study start. All participants were instructed to do respiratory and postural correction exercises for the 6 month study duration (20 minutes per day). In addition, the groups were given interventions as follows: Group 1 (BT), n=21: Balneotherapy comprising immersion into a heated bath (water at 37°) of springwater in a therapeutic pool. Bathing lasted 20 mins per day, 5 days per week for 3 weeks. Group 2 (BT+NSAID), n=20: As group 1, plus 1000mg naproxen and 400mcg misoprostol per day. Group 3 (NSAID), n=20: 1000mg naproxen and 400mcg misoprostol per day. After the three weeks of intervention, patients were not given any NSAID medication unless clinical activation occurred. Participants were followed clinically by phone and home visits for the remainder of the 6 months.
Randomisation, allocation, blinding	Single-blinded. Evaluation was conducted by three physicians of which two were 'blind to the study'. Patients were randomly allocated to one of three groups - details of randomisation not reported

Bibliographic reference	Yurtkuran,Merih, Ay,Alev, Karakoc,Yuksel, Improvement of the clinical outcome in Ankylosing spondylitis by balneotherapy, Joint, bone, spine : revue du rhumatisme, 72, 303-308, 2005
Details	Measurements were carried out at baseline, post-treatment, and 2 months after study start by three physicians of whom two (who did the physical examination and pain evaluation) were blind to the study. Variables chosen in the study were from the ASAS core set. Pain was measured on a VAS (1-100), morning stiffness was measured in minutes, finger-floor distance in cm and lumbar flexibility with a functional index One-way ANOVA was used to compare most baseline characteristics between groups, with Chi Sq used for comparing sex and Kruskal-Wallis for pain measurements. Freidman nonparametric repeated measures ANOVA test and Dunn's multiple comparisons test was used to compare the change scores.
Missing data handling/loss to follow up	During the post-treatment monitoring period, 5 patients were found to have peripheral arthritis, require medication, and were thus removed from the study (2 from BT group, 1 from BT+NSAID group, 3 from NSAID group) [NB: numbers here as reported in paper but this is inconsistent as to whether 5 or 6 were excluded]
Results	Pain Morning pain (VAS) BT+NSAID: baseline: 39.0(25.4); post-treatment: 17.9(16.2); 6 months: 14.5(14.4); change score at 6 months:-24.5(22.7) NSAID: baseline: 38.1(21.7); post-treatment: 25.2(19.7); 6 months: 23.8(19.7); change score at 6 months: -14.3(25.7) *NB: change score here appears to have been transposed in the paper's table 6 with that of nocturnal pain Nocturnal pain (VAS) BT+NSAID: baseline: 45.2(30.4); post-treatment: 22.1(20.2); 6 months: 17.1(18.8); change score at 6 months: -28.0(21.2) NSAID: baseline: 43.0(31.3); post-treatment: 28.0(20.7); 6 months: 22.1(13.2); change score at 6 months: -20.8(19.5) NB: change score here appears to have been transposed in the paper's table 6 with that of morning pain Duration of morning stiffness (minutes) BT+NSAID: baseline: 40.3(51.4); post-treatment: 13.0(20.5); 6 months: 10.2(15.4); change score at 6 months: -30.1(17.4) NSAID: baseline: 24.9(45.3); post-treatment: 16.8(22.7); 6 months: 16.0(25.2); change score at 6 months: -8.8 Adverse events Moderate gastro-intestinal side effects (dyspepsy, nausea, abdominal pain) in 10 participants (four in group 2, six in group 3) Joint/spinal mobility Finger-floor distance (cm) BT+NSAID: baseline: 3.6(5.0); post-treatment: 1.7(3.0); 6 months: 2.6(3.9); change score at 6 months: -0.9(5.0)

<table>
<tr><th>Bibliographic reference</th><th>Yurtkuran,Merih, Ay,Alev, Karakoc,Yuksel, Improvement of the clinical outcome in Ankylosing spondylitis by balneotherapy, Joint, bone, spine : revue du rhumatisme, 72, 303-308, 2005</th></tr>
<tr><td></td><td>NSAID: baseline: 4.4(4.9); post-treatment: 3.9(5.0); 6 months: 3.9(5.0); change score at 6 months: -0.5(4.3)

Physical function
Functional index (ref: Dougados 1988)
BT+NSAID: baseline: 29(13); post-treatment: 15(20); 6 months: 21(17); change score at 6 months: -0.2(1.8)
NSAID: baseline: 23(17); post-treatment: 22(11); 6 months: 24(19); change score at 6 months: 0.0(2.6)

Quality of life
Not reported

Imaging
Not reported

Composite measures
Not reported</td></tr>
<tr><td>BASFI/Dougados FI</td><td>BASFI/Dougados FI<table><tr><td></td><td>Mean</td><td>SD</td><td>Total</td></tr><tr><td>Experimental</td><td>-0.20</td><td>1.80</td><td>19</td></tr><tr><td>Control</td><td>0.00</td><td>2.60</td><td>18</td></tr></table></td></tr>
<tr><td>Finger-floor distance</td><td>Finger-floor distance<table><tr><td></td><td>Mean</td><td>SD</td><td>Total</td></tr><tr><td>Experimental</td><td>-0.90</td><td>5.00</td><td>19</td></tr><tr><td>Control</td><td>-0.50</td><td>4.30</td><td>18</td></tr></table></td></tr>
<tr><td>Pain</td><td>Pain<table><tr><td></td><td>Mean</td><td>SD</td><td>Total</td></tr><tr><td>Experimental</td><td>-24.50</td><td>22.70</td><td>19</td></tr></table></td></tr>
</table>

Bibliographic reference	Yurtkuran,Merih, Ay,Alev, Karakoc,Yuksel, Improvement of the clinical outcome in Ankylosing spondylitis by balneotherapy, Joint, bone, spine : revue du rhumatisme, 72, 303-308, 2005
	Control -14.30 25.70 18
Overall Risk of Bias	Some discrepancies in numbers e.g. text says 61 patients enrolled, but baseline table indicates 62; text says 5 patients were withdrawn but numbers add up to 6. Table 6 change scores for morning and nocturnal pain look likely to have been transposed
Was the allocation sequence adequately generated?	UNCLEAR
Was allocation adequately concealed?	UNCLEAR
Was knowledge of the allocated intervention adequately prevented during the study?	UNCLEAR
Were incomplete outcome data adequately addressed?	NO
Are reports of the study free of suggestion of selective outcome reporting?	YES
Was the study apparently free of other problems that could put it at a high risk of bias?	NO

Observational studies

Table 139: Robertson & Davis, 2004

Bibliographic reference	Robertson,L.P., Davis,M.J., A longitudinal study of disease activity and functional status in a hospital cohort of patients with ankylosing spondylitis, Rheumatology, 43, 1565-1568, 2004
Country/ies where the study was carried out	Cornwall, UK
Study type	Retrospective cohort
Aim of the study	To provide information on the course and natural history of ankylosing spondylitis.

Bibliographic reference	Robertson,L.P., Davis,M.J., A longitudinal study of disease activity and functional status in a hospital cohort of patients with ankylosing spondylitis, Rheumatology, 43, 1565-1568, 2004
Study dates	1996 to 2001
Source of funding	Not reported
Sample size	Case notes of 112 patients screened. 74 had completed an adequate number of questionnaires and were included.
Diagnostic criteria	Modified New York
Inclusion criteria	Completion of at least 3 patient questionnaires from 1996 to 2001 Patients of Royal Cornwall Hospital, Truro ankylosing spondylitis diagnosed with modified New York criteria
Exclusion criteria	Completing fewer than 3 questionnaires in the period
Characteristics	mean age, years (sd): 48.5 (11.24) mean disease duration, years (sd): 21.1(10.63) female, n(%): 18 (24.3) psoriasis, n(%): 7 (9.5) IBD, n(%): 7 (9.5) Iritis, n(%): 29 (39.2) peripheral joint disorder, n(%): 39 (52.7) regular NSAIDs, n(%): 58 (78.3) DMARD treatment, n(%): 4 (5.4)
Interventions	17 people (23%) reported via questionnaire receiving 'regular hydrotherapy. No further detail given.
Randomisation, allocation, blinding	n/a
Details	BASDAI and BASFI (0-100 scale) were analysed cross-sectionally and longitudinally for the whole cohort and for subgroups. The Kolmogorov-Smirnov test was used to assess normality of distribution. For cross sectional analysis, unpaired t-tests were used. For the longitudinal analysis, paired t-tests, change per year and area under the curve per year were used.
Missing data handling/loss to follow up	38 out of 112 cases excluded from analysis for not having a minimum number of questionnaires returned in the period
Results	Pain Not reported Adverse events not reported

Bibliographic reference	Robertson,L.P., Davis,M.J., A longitudinal study of disease activity and functional status in a hospital cohort of patients with ankylosing spondylitis, Rheumatology, 43, 1565-1568, 2004
	Joint/spinal mobility Not reported Physical Function Not reported Imaging Not reported Composite measures BASFI Mean (95% CI) change in BASFI scores (paired t-test): regular hydrotherapy: 3.98 (-5.0 to 12.9), p=0.4 no regular hydrotherapy: 7.03 (1.9, 12.2), p=0.01 BASDAI Only reported as a whole-cohort level measure
Overall Risk of Bias	Analysis was restricted to those with at least 3 BASDAI/BASFI questionnaire responses but the reported mean change in BASFI does not adjust for duration of follow up (which could be from 3-5 years). No information is presented about the baseline characteristics of people who were excluded from the study.
Other information	n/a
Was the allocation sequence adequately generated?	--
Was allocation adequately concealed?	--
Was knowledge of the allocated intervention adequately prevented during the study?	NO
Were incomplete outcome data adequately addressed?	NO

Bibliographic reference	Robertson,L.P., Davis,M.J., A longitudinal study of disease activity and functional status in a hospital cohort of patients with ankylosing spondylitis, Rheumatology, 43, 1565-1568, 2004
Are reports of the study free of suggestion of selective outcome reporting?	YES
Was the study apparently free of other problems that could put it at a high risk of bias?	NO

Table 140: Tishler et al., 1995

Bibliographic reference	Tishler,M., Brostovski,Y., Yaron,M., Effect of spa therapy in Tiberias on patients with ankylosing spondylitis, Clinical rheumatology, 14, 21-25, 1995
Country/ies where the study was carried out	Israel/Tiberius
Study type	Quasi-randomised non-controlled intervention
Aim of the study	To evaluate the effectiveness of spa therapy, including hot mineral baths and mud packs from Tiberius springs on patients with AS.
Study dates	Not reported. Study submitted 1993, published 1995
Source of funding	Not reported
Sample size	14 people
Diagnostic criteria	Modified New York
Inclusion criteria	Randomly selected from a group of people regularly followed at the Tel Aviv Medical Centre. Active disease defined by night pains and morning stiffness using analgesics and/or NSAIDs regularly patients taking sulfasalazine or methotrexate had been using them for at least three months prior to study entry
Exclusion criteria	uncontrolled blood pressure unbalanced ischemic heart disease severe peripheral vascular disease total hip replacement
Characteristics	mean age (range): 45.3 (33 to 65) mean disease duration, years (range): 13.6 (2 to 18) females (n): 3 drugs in use

Bibliographic reference	Tishler,M., Brostovski,Y., Yaron,M., Effect of spa therapy in Tiberias on patients with ankylosing spondylitis, Clinical rheumatology, 14, 21-25, 1995
	NSAIDs (n): 12 Analgesics (n): 8 Methotrexate (n): 2 sulfasalazine (n): 2
Interventions	Daily mineral water baths (38°C) for 20 mins. Daily mud packs to lower back for 20 mins at initial temperature of 45°C. Total duration was 2 weeks. Patients were allowed to change NSAID and analgesic doses following improvement of worsening of symptoms. No change in type of NSAIDs was allowed
Randomisation, allocation, blinding	No detail of randomisation/allocation method was provided. This was a pilot study in which everyone involved received the intervention therefore there was no blinding.
Details	Assessment by same rheumatologist seven days prior to arrival at spa hotel, after one week of therapy, at end of treatment (2 weeks) and at 4, 8 and 12 weeks from start of treatment. At each assessment the following were measured: during of morning stiffness (min), modified Schober test (cm), chest expansion (cm), finger-floor distance (cm), patient's assessment of disease severity (-3 to +3 scale), physician assessment on same scale, full blood count, ESR, CRP and electrophoresis of blood proteins. Statistical analysis by ANOVA test with repeated measures. Comparisons tested using Fisher's test.
Missing data handling/loss to follow up	None reported
Results	Most results were presented in graphs. Text reporting tended to be limited to the biggest change for that outcome Pain Morning stiffness, duration (mins) (mean, sd) baseline: 38 (7) 1 week: presented graphically, better than baseline, worse than week 2 2 weeks: 15 (4) 4 weeks: presented graphically, better than baseline, worse than week 2 8 weeks: presented graphically, better than baseline, worse than week 2 12 weeks: presented graphically, better than baseline, worse than week 2 Finger-floor distance, cm (mean, sd) baseline: 27 (3) 1 week: presented graphically, better than baseline, worse than week 4 2 weeks: presented graphically, better than baseline, worse than week 4

Bibliographic reference	Tishler,M., Brostovski,Y., Yaron,M., Effect of spa therapy in Tiberias on patients with ankylosing spondylitis, Clinical rheumatology, 14, 21-25, 1995
	4 weeks: 13(4) 8 weeks: presented graphically, better than baseline, worse than week 4 12 weeks: presented graphically, better than baseline, worse than week 4 No other outcomes of interest were reported numerically
Overall Risk of Bias	Text/numerical reporting of results tended to be limited to the biggest change for that outcome, rather than at a consistent time point
Other information	n/a
Was the allocation sequence adequately generated?	UNCLEAR
Was allocation adequately concealed?	UNCLEAR
Was knowledge of the allocated intervention adequately prevented during the study?	NO
Were incomplete outcome data adequately addressed?	YES
Are reports of the study free of suggestion of selective outcome reporting?	NO
Was the study apparently free of other problems that could put it at a high risk of bias?	YES

Table 141: Annegret & Thomas, 2013

Bibliographic reference	Annegret,Franke, Thomas,Franke, Long-term benefits of radon spa therapy in rheumatic diseases: results of the randomised, multi-centre IMuRa trial, Rheumatology international, 33, 2839-2850, 2013
Country/ies where the study was carried out	Germany
Study type	Randomised controlled trial of radon therapy (we extracted data on control group only)

Bibliographic reference	Annegret,Franke, Thomas,Franke, Long-term benefits of radon spa therapy in rheumatic diseases: results of the randomised, multi-centre IMuRa trial, Rheumatology international, 33, 2839-2850, 2013
Aim of the study	To compare radon bath therapy with radon-free control in Rheumatic diseases (back pain, osteoarthritis, rheumatoid arthritis, ankylosing spondylitis or multiple indications).
Study dates	April 2009 to June 2011.
Source of funding	External financial support was given by EURADON, overtaking the role of sponsor without intervening in scientific planning and reporting of results
Sample size	A total of 320 people were randomised to the control group of whom 19 had ankylosing spondylitis or other (unspecified) spondyloarthropathies. The intervention group contained a total of 332 people of whom 20 had ankylosing spondylitis or other (unspecified) spondyloarthropathies.
Diagnostic criteria	No formal diagnostic criteria were reported; diagnosis was assumed to be correct on the basis of referral from family doctors who had a long-standing familiarity with the medical history of the referred patients. Article later states that some participants self-referred to study via advertisements, though does not clarify how diagnosis was validated in those cases.
Inclusion criteria	Geographic proximity to treatment centre chronic or recurrent pain lasting longer than 6 months and mean pain levels >= 3 on initial assessment with numerical rating scale (NRS) age >18 years Sufficient knowledge of German language
Exclusion criteria	Radon therapy in previous 9 months advanced cardiac insufficiency (above NYHA II) hypertension grade 3 severe ventricular arrhythmia myocardial infarction or stroke known thermal uticaria any contraindication against whole-body thermo-neutral water immersion current exacerbations of the inflammation in inflammatory rheumatism malignant tumours under current oncological treatment pregnancy acute infections other generally accepted contraindications against spa therapy
Characteristics	Of the 20 people in the control arm classified as having ankylosing spondylitis: n female: 3 age, mean(sd): 59.6(12.9) baseline pain assessment (numerical rating scale): 5.50(2.18)

Bibliographic reference	Annegret,Franke, Thomas,Franke, Long-term benefits of radon spa therapy in rheumatic diseases: results of the randomised, multi-centre IMuRa trial, Rheumatology international, 33, 2839-2850, 2013
	baseline functional capacity as measured by BASMI: 3.9(2.3)
Interventions	The control group received tap-water baths (12 baths, within a 3-4 week period (i.e. every 2-3 days) at 36-38°C, of 20 minutes duration. To encourage adherence, the control group were assigned to a waiting list for active treatment after the study was complete. Slight adaptations to dose (in intervention group) and frequency were allowed. Continuation of stable medication and/or physical therapy use was allowed during the study.
Randomisation, allocation, blinding	Randomisation stratified by centre, rheumatic indication and initial pain level. Randomisation was externally performed using a computer-generated random allocation sequence. Investigator, therapists and patients were blinded to treatment, except for those who received speleotherapy or control. Administrative/technical staff that did not have patient contacts ensured the correct allocation of baths according to individual time tables of patients.
Details	Self-assessed pain levels were reported on numerical rating scales from 0-10. SF-12 was used to measure quality of life. BASFI was applied to the AS patients. Patients were additionally asked to report all inter-current events (e.g. hospitalisations), adverse events and all pharmacological therapies. Post-hoc review of medication data carried out by experienced physician. Outcomes were measured at baseline, at end of treatment, and every 3 months for the next nine months. A sample size calculation was conducted prior to study start to estimate the number of participants required, taking into account potential drop-out rate. Analysis was performed on an intention-to-treat basis on all randomised patients with at least one study intervention. 'Last observation carried forward' was used for handling missing data at given time points. Repeated measures ANCOVA was used for assessing changes to pain scores. For other outcomes, hierarchical analysis was performed, with Fisher's exact test used for examination of rates of medication reduction.
Missing data handling/loss to follow up	Loss to follow up clearly reported per group at each time point. Analysis was performed on an intention-to-treat basis on all randomised patients with at least one study intervention. 'Last observation carried forward' was used for handling missing data at given time points.
Results	Control group only, Ankylosing spondylitis only, n=19 Pain NRS self-assessment (0-10), mean(sd) Baseline: 5.50(2.18) Follow up not reported in disease-specific subgroups Adverse events Adverse events across both treatment groups and all disease types were reported by 32 patients, though some were not of a clinical nature. Of those that were, there were 19 where a causal role of the intervention was considered plausible (13 in intervention group, 6 in the control). Of the 6 in the control group. 1 reported aggravation of pain, 1 hypertension, 1 fatigue

Bibliographic reference	Annegret,Franke, Thomas,Franke, Long-term benefits of radon spa therapy in rheumatic diseases: results of the randomised, multi-centre IMuRa trial, Rheumatology international, 33, 2839-2850, 2013
	and 3 were unspecified by the authors. All were of mild to moderate severity. In the whole study population, hospitalisation occurred in 3 patients but in none of these cases was it considered to be attributable to the treatment. Joint/spinal mobility Not reported Physical function Not reported Quality of life SF-12, mean (sd) Not reported in disease-specific subgroups Imaging Not reported Composite measures BASFI Baseline (mean(sd)): 3.9(2.3) Change scores: end of treatment: -0.11(0.86); 3 months: -0.08(0.79); 6 months: -0.22(1.01); 9 months: 0.22(0.92)
Overall Risk of Bias	
Other information	n/a
Was the allocation sequence adequately generated?	YES
Was allocation adequately concealed?	YES
Was knowledge of the allocated intervention adequately prevented during the study?	UNCLEAR
Were incomplete outcome data adequately addressed?	YES

Bibliographic reference	Annegret,Franke, Thomas,Franke, Long-term benefits of radon spa therapy in rheumatic diseases: results of the randomised, multi-centre IMuRa trial, Rheumatology international, 33, 2839-2850, 2013
Are reports of the study free of suggestion of selective outcome reporting?	UNCLEAR
Was the study apparently free of other problems that could put it at a high risk of bias?	YES

Table 142: Aydemir et al., 2010

Bibliographic reference	Aydemir,Koray, Tok,Fatih, Peker,Fatma, Safaz,Ismail, Taskaynatan,Mehmet Ali, Ozgul,Ahmet, The effects of balneotherapy on disease activity, functional status, pulmonary function and quality of life in patients with ankylosing spondylitis, Acta Reumatologica Portuguesa, 35, 441-446, 2010
Country/ies where the study was carried out	Turkey
Study type	Non-randomised, uncontrolled intervention study
Aim of the study	To increase knowledge of balneotherapy for the treatment of AS.
Study dates	Not reported. Published 2010
Source of funding	Not reported
Sample size	28 people
Diagnostic criteria	modified New York
Inclusion criteria	No detail was reported on where patients were recruited from Therapy with sulfasalazine 2000 mg/d and indomethacin 75 mg/d for at least 6 months AS diagnosed by modified New York criteria
Exclusion criteria	use of DMARDs (except sulfasalazine) or biologics in previous 6 months spa treatment during previous 6 months history of orthopaedic surgery COPD coronary artery disease congestive heart failure hypertension
Characteristics	age (mean(sd)): 24.39 (2.97) disease duration, years (mean(sd)): 4.71(1.86)

Bibliographic reference	**Aydemir,Koray, Tok,Fatih, Peker,Fatma, Safaz,Ismail, Taskaynatan,Mehmet Ali, Ozgul,Ahmet, The effects of balneotherapy on disease activity, functional status, pulmonary function and quality of life in patients with ankylosing spondylitis, Acta Reumatologica Portuguesa, 35, 441-446, 2010**
	27 male, 1 female
Interventions	Spa treatment 5 days/week for 3 weeks 37°C therapeutic pool (30 mins/day) including underwater exercises 20 minutes ventilation exercises after pool session Then 20 minutes of postural exercises
Randomisation, allocation, blinding	No randomisation/allocation. No detail of assessor blinding was given.
Details	Measures made at baseline and 1 month
Missing data handling/loss to follow up	No missing data or loss to follow up reported
Results	Pain SF-36 bodily pain domain baseline: 43.48; 1 month: 42.59, p=0.575 Adverse events Not reported Joint/spinal mobility No relevant outcomes reported Physical function SF-36 physical functioning domain baseline: 48.33; 1 month: 46.48, p=0.412 Quality of life SF-36 was used: reported values for separate domains only, not whole score. Imaging Not reported Composite measures

Bibliographic reference	Aydemir,Koray, Tok,Fatih, Peker,Fatma, Safaz,Ismail, Taskaynatan,Mehmet Ali, Ozgul,Ahmet, The effects of balneotherapy on disease activity, functional status, pulmonary function and quality of life in patients with ankylosing spondylitis, Acta Reumatologica Portuguesa, 35, 441-446, 2010
	BASDAI (mean (no reported sd)) baseline: 5.3; 1 month: 4.9, p>0.05 BASFI baseline: 4; 1 month: 4.2, p not reported BASMI baseline: 3.23; 1 month: 2.29, p=0.48
Overall Risk of Bias	Standard deviations not reported, nor exact p values for non-significant results, so difficult to fully interpret some of the data.
Other information	n/a
Was the allocation sequence adequately generated?	--
Was allocation adequately concealed?	--
Was knowledge of the allocated intervention adequately prevented during the study?	NO
Were incomplete outcome data adequately addressed?	YES
Are reports of the study free of suggestion of selective outcome reporting?	YES
Was the study apparently free of other problems that could put it at a high risk of bias?	YES

Table 143: Colina et al., 2009

Bibliographic reference	Colina,M., Ciancio,G., Garavini,R., Conti,M., Trotta,F., Govoni,M., Combination treatment with etanercept and an intensive spa rehabilitation program in active ankylosing spondylitis, International journal of immunopathology and pharmacology, 22, 1125-1129, 2009
Country/ies where the study was carried out	Italy
Study type	Non-randomised controlled intervention study
Aim of the study	To compare and evaluate the effects of anti-TNF alpha agent etanercept and spa rehabilitation vs etanercept alone on function, disability, and quality of life in a group of patients with active AS.
Study dates	Enrolment between September 2006 and August 2007.
Source of funding	Grant provided by CARIFE
Sample size	60 people (30 opted to enter the rehabilitation programme in addition to receiving etanercept
Diagnostic criteria	Modified New York
Inclusion criteria	previous NSAID therapy failure (given for at least 3 months) BASFI score >=4 persistently high markers of inflammation global health visual analogue scale score or pain VAS of >=40 (on a 0-100 scale)
Exclusion criteria	Not reported
Characteristics	Combination therapy (etanercept+rehabilitation) group at baseline (n=30): age, mean(sd): 40.7(7.2) duration of disease, mean(sd): 8.4(3.2) peripheral arthritis(n): 7 skin involvement (n): 1 ocular involvement (n): 0 HLA-B27+ve (n): 23
Interventions	Both groups received etanercept for 2 months After 2 months, 30 patients consented to enrolment to a 7 day rehabilitation programme. These patients were self-selecting. The remaining patients continued on etanercept alone The rehabilitation programme was conducted in a thermal baths centre by expert physiotherapists under the supervision of a physiatrist and included hydro-kinesitherapy sessions (30 mins): flex/extension of trunk and lower limbs, truck torsion and twist shoulder joints, controlled relaxation of the spine respiratory fitness sessions (30 mins) massotherapy

Bibliographic reference	Colina,M., Ciancio,G., Garavini,R., Conti,M., Trotta,F., Govoni,M., Combination treatment with etanercept and an intensive spa rehabilitation program in active ankylosing spondylitis, International journal of immunopathology and pharmacology, 22, 1125-1129, 2009
	muscular strengthening exercises with active and passive kinesitherapy postural education (40 mins) education on home treatment
Randomisation, allocation, blinding	n/a
Details	Descriptive data were presented. T-test for paired and unpaired data
Missing data handling/loss to follow up	Not reported
Results	Pain Not reported Adverse events None observed Joint/spinal mobility Not reported Quality of life EQ-5D (0-100) Baseline (both groups combined): 16(4.8) combination group: 2 months: 22 (p=NS); 5 months: 32 (p=NS); 8 months: 33 (p<0.05) Physical function Not reported Imaging Not reported Composite measures BASDAI, mean(sd)

Bibliographic reference	Colina,M., Ciancio,G., Garavini,R., Conti,M., Trotta,F., Govoni,M., Combination treatment with etanercept and an intensive spa rehabilitation program in active ankylosing spondylitis, International journal of immunopathology and pharmacology, 22, 1125-1129, 2009
	Baseline (both groups combined):7.3(1.9) BASFI, mean(SD) Baseline (both groups combined): 6.9(1.6) combination group: 2 months: 5.6(2.2); 5 months: 1.9 (p<0.05), 8 months: 2.1 (p<0.05)
Overall Risk of Bias	
Other information	
Was the allocation sequence adequately generated?	--
Was allocation adequately concealed?	--
Was knowledge of the allocated intervention adequately prevented during the study?	NO
Were incomplete outcome data adequately addressed?	UNCLEAR
Are reports of the study free of suggestion of selective outcome reporting?	UNCLEAR
Was the study apparently free of other problems that could put it at a high risk of bias?	NO

Table 144: Eppeland et al., 2013

Bibliographic reference	Eppeland,Siv Grodal, Diamantopoulos,Andreas P., Soldal,Dag Magnar, Haugeberg,Glenn, Short term in-patient rehabilitation in axial spondyloarthritis - the results of a 2-week program performed in daily clinical practice, BMC research notes, 6, 185-, 2013
Ref Id	200138
Country/ies where the study was carried out	Norway

Bibliographic reference	Eppeland,Siv Grodal, Diamantopoulos,Andreas P., Soldal,Dag Magnar, Haugeberg,Glenn, Short term in-patient rehabilitation in axial spondyloarthritis - the results of a 2-week program performed in daily clinical practice, BMC research notes, 6, 185-, 2013
Study type	Retrospective cross-sectional study
Aim of the study	To evaluate the short-term effect of an in-patient 2-weeks rehabilitation and exercise program on self-reported outcome and physical functions in axial-SpA patients, within the frame of standard routine and clinical care.
Study dates	Jan 2007 to June 2011
Source of funding	Not reported
Sample size	87 patients
Diagnostic criteria	All patients fulfilled ASAS diagnostic criteria and had sacroiliitis confirmed by imaging.
Inclusion criteria	Patients attending Hospital of Southern Norway Participated in and completed a 2-week rehabilitation programme. Diagnosed ax-SpA with imaging confirmed sacroiliitis >=18 years old Referral by rheumatologist
Exclusion criteria	Severe comorbidities Severe reduced exercise tolerance
Characteristics	60 men, 27 women mean age (sd): 49.2(10.0) disease duration, years (sd): 14.4(11.9) HLA-B27 positive: 92.5% imaging: X-ray: 72 patients with available radiographs of whom 64 had radiographic sacroiliitis MRI: 18 with MRI-confirmed sacroiliitis (non-radiographic) CT: 5 with CT-confirmed sacroiliitis (non-radiographic) Drugs NSAIDs: 62.1% anti-TNFs: 17.2% (10 etanercept, 3 infliximab, 2 adalimumab)
Interventions	Intensive rehabilitation programme delivered by a multidisciplinary team (rheumatologist, physiotherapist, occupational therapist, social worker, secretary) Delivered 5 days/week for 2 weeks Daily programme involving water exercises (30 minutes)

Bibliographic reference	Eppeland,Siv Grodal, Diamantopoulos,Andreas P., Soldal,Dag Magnar, Haugeberg,Glenn, Short term in-patient rehabilitation in axial spondyloarthritis - the results of a 2-week program performed in daily clinical practice, BMC research notes, 6, 185-, 2013
	basic exercises for movement, muscle strength and stability, balance and co-ordination (45 mins) Endurance exercises (40 mins) Individual physiotherapy including massage, stretching, mobilisation/articulation and advice on specific exercises to enhance a good body posture. Exercises delivered in groups of 4 people but with focus on meeting individual patient goals
Randomisation, allocation, blinding	Randomisation/allocation: n/a Physiotherapist involved in patient assessment did not analyse the data
Details	Group comparisons: student's t-test or non-parametric Wilcoxon test. Skewed data were presented with medians (IQR) as appropriate. All patients were assessed to some degree at baseline and 2 weeks. Some additionally had data on selected outcomes collected at a follow up outpatient appointment.
Missing data handling/loss to follow up	8 patients started the rehab programme but did not complete, for various reasons. For each outcome, a different number of patients had available data. No imputation was attempted
Results	Pain Not reported Adverse events Not reported Joint / Spinal mobility Finger-floor distance, cm n=49 baseline mean (sd): 15.1(14.0); 2 weeks: 9.1(12.7) p<0.001 baseline median (IQR): 11.0(25.0); 2 weeks: 0 (16) p<0.001 Physical function Not reported Quality of life Not reported

Bibliographic reference	Eppeland,Siv Grodal, Diamantopoulos,Andreas P., Soldal,Dag Magnar, Haugeberg,Glenn, Short term in-patient rehabilitation in axial spondyloarthritis - the results of a 2-week program performed in daily clinical practice, BMC research notes, 6, 185-, 2013
	Imaging Not reported Composite measures BASFI (0-10) n=59 baseline mean (sd): 3.1(1.9); 2 weeks: 2.3(2.0), p<0.001 48 patients had long-term follow up data (mean time period 9.3 (sd=6.9) months). baseline mean (sd): 3.2(2.0); long term follow-up: 3.5(2.6), p=0.31 BASDAI (0-10) n=57 baseline mean (sd): 4.3(2.2); 2 weeks 3.1(2.1), p<0.001 48 patients had long-term follow up data (mean time period 9.3 (sd=6.9) months). baseline mean (sd): 4.1(2.3); long-term follow up: 4.4(2.2), p<0.24 BASMI (0-10) n=87 baseline mean (sd): 3.2(2.4); 2 weeks 2.3(3.4), p<0.001 48 patients had long-term follow up data (mean time period 9.3 (sd=6.9) months). baseline mean (sd): 3.3(2.6); long-term follow up: 2.7(2.5), p<0.02
Overall Risk of Bias	It is unclear whether missing outcome data (for 2 weeks or long term follow up) are missing at random
Other information	n/a
Was the allocation sequence adequately generated?	--
Was allocation adequately concealed?	--
Was knowledge of the allocated intervention adequately prevented during the study?	NO

Bibliographic reference	Eppeland,Siv Grodal, Diamantopoulos,Andreas P., Soldal,Dag Magnar, Haugeberg,Glenn, Short term in-patient rehabilitation in axial spondyloarthritis - the results of a 2-week program performed in daily clinical practice, BMC research notes, 6, 185-, 2013
Were incomplete outcome data adequately addressed?	NO
Are reports of the study free of suggestion of selective outcome reporting?	YES
Was the study apparently free of other problems that could put it at a high risk of bias?	YES

Table 145: van Tubergen et al., 2001

Bibliographic reference	van Tubergen,A., Landewe,R., van der Heijde,D., Hidding,A., Wolter,N., Asscher,M., Falkenbach,A., Genth,E., The,H.G., van der Linden,S., Combined spa-exercise therapy is effective in patients with ankylosing spondylitis: a randomized controlled trial, Arthritis and rheumatism, 45, 430-438, 2001
Ref Id	200207
Country/ies where the study was carried out	Austria/Netherlands
Study type	Randomised controlled trial, with three arms, of which we considered evidence from the control group
Aim of the study	To assess the efficacy of spa therapy combined with exercise therapy in addition to standard treatment with anti-inflammatory drugs and weekly group exercise physical therapy alone in patients with AS.
Study dates	Rehabilitation phase of study took place in April 1999. Study submitted in 2000, published 2001
Source of funding	Not reported
Sample size	40 people in the control group at baseline, 39 at study endpoint (week 40).
Diagnostic criteria	Modified New York. Radiographs of sacroiliac joints checked for sacroiliitis.
Inclusion criteria	modified New York criteria reported pain and stiffness or functional limitations for at least 3 months before entry able to stay away from home and work for 3 consecutive pre-planned weeks
Exclusion criteria	inability or unwillingness to participate in weekly group physical therapy pregnancy

Bibliographic reference	van Tubergen,A., Landewe,R., van der Heijde,D., Hidding,A., Wolter,N., Asscher,M., Falkenbach,A., Genth,E., The,H.G., van der Linden,S., Combined spa-exercise therapy is effective in patients with ankylosing spondylitis: a randomized controlled trial, Arthritis and rheumatism, 45, 430-438, 2001
	claustrophobia severe-comorbidity of the heart, lung, liver or kidneys a diagnosis of AS more than 20 years prior to study date
Characteristics	Control group (n=40): female (n): 6 age, mean(sd): 48(10) disease duration, years , mean(sd): 10(6) duration of complaints, years, mean(sd): 15(8) NSAIDs (n): 4 Sulfasalazine (n): 5 Uveitis (ever, n):20 Inflammatory bowel disease (ever, n): 10 Psoriasis (ever, n): 4
Interventions	Control group: Once a week physical therapy comprising: 1 hr group physical exercises 1 hr sports 1 hr hydrotherapy After the intervention group treatment period (3 weeks) was over, all groups carried out group physical therapy sessions weekly. During intervention and follow up period, all patients were allowed to continue their usual drug treatment, and were allowed to increase or decrease the amount of anti-inflammatory drugs. Patients in this group were offered the treatment at the end of the study period.
Randomisation, allocation, blinding	Randomisation by computer-generated random number list prepared by rheumatologist not further involved in the study.
Details	All outcome measures collected by self-assessment questionnaires. Sample size calculation was carried out. Analysis was intention to treat. Results were expressed as a pooled index of change. For each component of this, the change compared to baseline per unit time was calculated per patient. Mean change per standard period of each group was divided by the pooled standard deviation of the change at the endpoint for that instrument.

Bibliographic reference	van Tubergen,A., Landewe,R., van der Heijde,D., Hidding,A., Wolter,N., Asscher,M., Falkenbach,A., Genth,E., The,H.G., van der Linden,S., Combined spa-exercise therapy is effective in patients with ankylosing spondylitis: a randomized controlled trial, Arthritis and rheumatism, 45, 430-438, 2001
Missing data handling/loss to follow up	Analysis was intention to treat. Missing answers in questionnaires were followed up and obtained where possible by telephone or mail. Where this was unsuccessful, manual imputation of missing data, following the instructions of the authors of each instrument, was used.
Results	Pain Pain (0-10) baseline (mean (sd)): 4.8(2.8) changes from baseline (mean(sd)): 4weeks: 0.0(2.3); 16 weeks: 0.3(2.7); 28 weeks: 0.0(2.7); 40 weeks: -0.2(2.1) Morning stiffness, mins baseline (median (IQR)): 30(10; 60) changes from baseline (median(IQR)): 4weeks: 4(0;10); 16 weeks: 3(-6;15); 28 weeks: 0(-15;10); 40 weeks: 0(-13;14) Adverse events Not reported Joint/spinal mobility Not reported Physical function Not reported Quality of life ASQoL (0-18) baseline (median (IQR)): 8.0(3.0;11.8) changes from baseline (median (IQR)): 4 weeks: 1.0(-1.0;2.0); 16 weeks: 0.0(-1.1;1.8); 28 weeks: 0.0(-1.0;2.1); 40 weeks: 0.0(-1.0;1.8) Imaging Not reported Composite measures

Bibliographic reference	van Tubergen,A., Landewe,R., van der Heijde,D., Hidding,A., Wolter,N., Asscher,M., Falkenbach,A., Genth,E., The,H.G., van der Linden,S., Combined spa-exercise therapy is effective in patients with ankylosing spondylitis: a randomized controlled trial, Arthritis and rheumatism, 45, 430-438, 2001
	BASFI (0-10) baseline (mean (sd)): 4.2(2.1) changes from baseline (mean(sd)): 4 weeks: 0.0(1.1); 16 weeks: 0.0(1.6); 28 weeks: -0.1(1.7); 40 weeks: -0.1(1.3) BASDAI (0-10) baseline (mean (sd)): 4.5(2.0) changes from baseline (mean(sd)): 4 weeks: 0.3(1.7); 16 weeks: 0.6(2.1); 28 weeks: 0.8(1.7); 40 weeks: 0.4(1.5)
Overall Risk of Bias	
Other information	n/a
Was the allocation sequence adequately generated?	YES
Was allocation adequately concealed?	YES
Was knowledge of the allocated intervention adequately prevented during the study?	NO
Were incomplete outcome data adequately addressed?	YES
Are reports of the study free of suggestion of selective outcome reporting?	YES
Was the study apparently free of other problems that could put it at a high risk of bias?	YES

E.3.4 Acupuncture for spondyloarthritis

Review Question 17

- What is the effectiveness of acupuncture compared with sham acupuncture and standard care for managing spondyloarthritis?

Table 146: Jia et al., 2006

Bibliographic reference	**Jia,Jie, Wang,Qiyin, Zhang,Tiehan, Li,Jun, Treatment of ankylosing spondylitis with medicated moxibustion plus salicylazosulfapyridine and methotrexate--a report of 30 cases, Journal of traditional Chinese medicine = Chung i tsa chih ying wen pan / sponsored by All-China Association of Traditional Chinese Medicine, Academy of Traditional Chinese MedicineJ Tradit Chin Med, 26, 26-28, 2006**
Ref Id	200059
Country/ies where the study was carried out	China(?)
Study type	Three arm randomised controlled trial
Aim of the study	To evaluate the therapeutic effect of medicated moxibustion plus administration of salicylazosulfapyridine (SASP) and methotrexate (MTX) for treatment of active ankylosing spondylitis (AS)
Study dates	July 1998 to Dec 2003
Source of funding	Not stated
Sample size	90, with 30 in each of 3 treatment arms
Characteristics	See baseline table below
Baseline	Baseline

	Acupuncture	Control
Gender (M/F)	22/8	23/7
Age - Mean (SD)	22.6 (5.1)	22.0 (5.4)
Duration - Mean (SD)	4.3 years (3.5)	4.4 years (3.2)

Bibliographic reference	**Jia,Jie, Wang,Qiyin, Zhang,Tiehan, Li,Jun, Treatment of ankylosing spondylitis with medicated moxibustion plus salicylazosulfapyridine and methotrexate--a report of 30 cases, Journal of traditional Chinese medicine = Chung i tsa chih ying wen pan / sponsored by All-China Association of Traditional Chinese Medicine, Academy of Traditional Chinese MedicineJ Tradit Chin Med, 26, 26-28, 2006**
	X-ray grade (I-IV) | I:3, II:11, III:14, IV:2 | I:2, II:13, III:11, IV:4 Current treatment | Not reported | Not reported Diagnosis | Not reported | Not reported Diagnostic criteria | Not reported | Not reported
Inclusion criteria	Not stated
Exclusion criteria	Not stated
Details	No reported details of patient recruitment, allocation/randomisation, or how outcomes were measured.
Interventions	Group A (control): Methotrexate (MTX) was injected intravenously once a week, with a starting dosage of 5 mg per week, increasing to 10-15 mg per week in a 3-week period. Simultaneously, salicylazosulfapyridine (SASP) was administered tid orally, with a starting dosage of 0.25g per week, which was increased to 0.75-1.0g per week in a 3-week period. Both medications lasted over 6 months. Group B (acupuncture): For Group B, MTX and SASP plus acupuncture at bilateral Fengchi (GB20), Dazhui (GV14), bilateral Pishu (BL20), bilateral Geshu (BL17), Shenzhu (GV12), bilateral Shenshu (BL23), Mingmen (GV4), Yaoyangguan (GV3), bilateral Zusanli (ST36) and bilateral Taixi (KI3) were taken as the main therapeutic method. #28 filiform needles of 5 cun in length were inserted into the points when the patient was lying prone. The needles were retained for 30 minutes when a needling sensation was experienced, during which the needles were manipulated once every 10 minutes. Acupuncture was performed once every other day for 3 successive courses (2 months each course with an interval of 5 days). Group C omitted here as neither acupuncture not standard care

Bibliographic reference	Jia,Jie, Wang,Qiyin, Zhang,Tiehan, Li,Jun, Treatment of ankylosing spondylitis with medicated moxibustion plus salicylazosulfapyridine and methotrexate--a report of 30 cases, Journal of traditional Chinese medicine = Chung i tsa chih ying wen pan / sponsored by All-China Association of Traditional Chinese Medicine, Academy of Traditional Chinese MedicineJ Tradit Chin Med, 26, 26-28, 2006
Results	Reported outcomes. Pain Morning stiffness (min) Control: pre: 40.94±36.75 post:9.70±6.21 difference: 30.57±29.78 Acupuncture: pre: 41.12±36.78 post:9.18±6.01 difference: 31.97±30.17 p* (between-group difference)>0.05 Swollen and painful peripheral joints (n) Control: pre: 3.20±1.52 post:1.02±1.32 difference: 2.38±0.39 Acupuncture: pre: 3.03±1.54 post:1.01±1.39 difference: 2.41±0.39 p (between-group difference)>0.05 Adverse events Not reported Joint/spinal mobility Sacroiliitis index Control: pre: 5.31±1.52 post: 2.82±1.49 difference 2.99±0.19 Acupuncture: pre: 5.29±1.70 post: 1.82±1.53 difference 4.03±0.21 p (between-group difference)<0.01 Schober test (cm) Control: pre: 3.31±1.29 post: 3.29±1.27 difference: 0.63±0.11 Acupuncture: pre: 3.30±1.37 post: 3.88±1.99 difference: 1.02±0.72 p (between-group difference)<0.01 Chest expansion (cm) Control: pre: 3.81±0.69 post: 3.99±0.95 difference: 0.27±0.31 Acupuncture: pre: 3.77±0.71 post: 3.90±0.87 difference: 0.29±0.18 p (between-group difference)>0.05

Bibliographic reference	Jia,Jie, Wang,Qiyin, Zhang,Tiehan, Li,Jun, Treatment of ankylosing spondylitis with medicated moxibustion plus salicylazosulfapyridine and methotrexate--a report of 30 cases, Journal of traditional Chinese medicine = Chung i tsa chih ying wen pan / sponsored by All-China Association of Traditional Chinese Medicine, Academy of Traditional Chinese MedicineJ Tradit Chin Med, 26, 26-28, 2006
	Occipital wall test** (cm) Group A: pre: 4.44±1.39 post: 2.82±1.33 difference: 1.97±0.11 Acupuncture: pre: 4.49±1.41 post: 1.12±1.37 difference: 3.37±0.31 p (between-group difference)<0.01 Finger-ground distance (cm) Control: pre: 14.09±18.23 post: 10.23±11.10 difference:4.19±8.36 Acupuncture: pre: 14.23±17.11 post: 6.52±8.73 difference: 9.10±9.07 p (between-group difference)<0.05 Physical function Not reported Quality of life Not reported Imaging Not reported Composite measures none *figure legend unclear on p-values as it assigns same significance level to two different symbols **Possibly a mistranslation of "occiput wall test"
Morning stiffness (continuous)	Morning stiffness (continuous) <table><tr><td></td><td>Mean</td><td>SD</td><td>Total</td></tr><tr><td>Experimental</td><td>-31.97</td><td>29.78</td><td>30</td></tr></table>

Bibliographic reference	Jia,Jie, Wang,Qiyin, Zhang,Tiehan, Li,Jun, Treatment of ankylosing spondylitis with medicated moxibustion plus salicylazosulfapyridine and methotrexate--a report of 30 cases, Journal of traditional Chinese medicine = Chung i tsa chih ying wen pan / sponsored by All-China Association of Traditional Chinese Medicine, Academy of Traditional Chinese MedicineJ Tradit Chin Med, 26, 26-28, 2006
	Control: -30.57; 29.78; 30
Swollen and painful peripheral joins	Swollen and painful peripheral joins Experimental: Mean -2.41; SD 0.39; Total 30 Control: Mean -2.38; SD 0.39; Total 30
Schober test	Schober test Experimental: Mean 1.02; SD 0.72; Total 30 Control: Mean -0.63; SD 0.11; Total 30
Sacroiliitis index	Sacroiliitis index Experimental: Mean -4.03; SD 0.21; Total 30 Control: Mean -2.99; SD 0.19; Total 30
Chest expansion	Chest expansion

Bibliographic reference	Jia,Jie, Wang,Qiyin, Zhang,Tiehan, Li,Jun, Treatment of ankylosing spondylitis with medicated moxibustion plus salicylazosulfapyridine and methotrexate--a report of 30 cases, Journal of traditional Chinese medicine = Chung i tsa chih ying wen pan / sponsored by All-China Association of Traditional Chinese Medicine, Academy of Traditional Chinese MedicineJ Tradit Chin Med, 26, 26-28, 2006
	<table><tr><td></td><td>Mean</td><td>SD</td><td>Total</td></tr><tr><td>Experimental</td><td>0.29</td><td>0.18</td><td>30</td></tr><tr><td>Control</td><td>0.27</td><td>0.31</td><td>30</td></tr></table>
Occiput wall test	Occiput wall test<table><tr><td></td><td>Mean</td><td>SD</td><td>Total</td></tr><tr><td>Experimental</td><td>-3.37</td><td>0.31</td><td>30</td></tr><tr><td>Control</td><td>-1.97</td><td>0.11</td><td>30</td></tr></table>
Finger-floor distance	Finger-floor distance<table><tr><td></td><td>Mean</td><td>SD</td><td>Total</td></tr><tr><td>Experimental</td><td>-9.10</td><td>9.07</td><td>30</td></tr><tr><td>Control</td><td>-4.19</td><td>8.36</td><td>30</td></tr></table>
Pain	n/a
Stiffness	n/a
Was the allocation sequence adequately generated?	UNCLEAR
Was allocation adequately concealed?	UNCLEAR

Bibliographic reference	Jia,Jie, Wang,Qiyin, Zhang,Tiehan, Li,Jun, Treatment of ankylosing spondylitis with medicated moxibustion plus salicylazosulfapyridine and methotrexate--a report of 30 cases, Journal of traditional Chinese medicine = Chung i tsa chih ying wen pan / sponsored by All-China Association of Traditional Chinese Medicine, Academy of Traditional Chinese MedicineJ Tradit Chin Med, 26, 26-28, 2006
Was knowledge of the allocated intervention adequately prevented during the study?	UNCLEAR
Were incomplete outcome data adequately addressed?	UNCLEAR
Are reports of the study free of suggestion of selective outcome reporting?	YES
Was the study apparently free of other problems that could put it at a high risk of bias?	YES
Risk of Bias	Limited reporting of baseline participant characteristics - hard to assess potential for selection bias. No details of blinding or allocation method reported. No details of missing outcome or baseline data reported.
Other information	Obtained article is a translation. There are some possible typographic errors in the results reporting, particularly with respect to p values.

Table 15: Mayrhofer et al., 1990	
Bibliographic reference	Mayrhofer,F., Broll,H., Eberl,R., Ebner,W., Klein,G., Rainer,F., Schorsch,G., Thumb,N., Tenoxicam versus diclofenac in patients with ankylosing spondylitis. A double-blind study, Drug Investigation, 2, 52-53, 1990
Country/ies where the study was carried out	Austria
Study type	Double blind, randomised
Aim of the study	Not reported
Study dates	Not reported
Source of funding	Not reported
Sample size	n=57
Inclusion criteria	Not reported

Bibliographic reference	Jia,Jie, Wang,Qiyin, Zhang,Tiehan, Li,Jun, Treatment of ankylosing spondylitis with medicated moxibustion plus salicylazosulfapyridine and methotrexate--a report of 30 cases, Journal of traditional Chinese medicine = Chung i tsa chih ying wen pan / sponsored by All-China Association of Traditional Chinese Medicine, Academy of Traditional Chinese MedicineJ Tradit Chin Med, 26, 26-28, 2006
Exclusion criteria	Not reported
Details	Patients were randomised (10 patients per centre, 5 on tenoxicam, 5 on diclofenac). After a washout period of at least 3 days patients were randomly allocated treatment groups. Treatment was for 21 days and patients also took part in a physical therapy programme as part of the study. Clinical assessment performed prior to treatment and on days 7,14 and 21.
Interventions	Tenoxicam 20mg/day (n=28) Diclofenac 100mg/day (n=29, calculated by analyst)
Characteristics	Baseline characteristics: 49 men, 8 women Age range: 22-67 (mean 42) 82% people HLA B27 positive
Results	Pain intensity (VAS scale): This data was presented in graphical form only for lumbosacral pain on movement, made into discrete data (e.g. >50% improvement), therefore this data could not be reported here. Lumbosacral pain during the day and lumbosacral pain at night was stated to be improved similarly in both groups, but no data was presented within the paper. Withdrawals due to adverse events: Tenoxicam: n=0 Diclofenac: n=3 Withdrawals due to lack of efficacy of study drug: Tenoxicam: n=3 Diclofenac: n=2
Overall Risk of Bias	Inclusion and exclusion criteria not reported. Outcomes not reported fully, data could not be analysed.
Was the allocation sequence adequately generated?	UNCLEAR
Was allocation adequately concealed?	UNCLEAR
Was knowledge of the allocated intervention	UNCLEAR

Bibliographic reference	Jia,Jie, Wang,Qiyin, Zhang,Tiehan, Li,Jun, Treatment of ankylosing spondylitis with medicated moxibustion plus salicylazosulfapyridine and methotrexate--a report of 30 cases, Journal of traditional Chinese medicine = Chung i tsa chih ying wen pan / sponsored by All-China Association of Traditional Chinese Medicine, Academy of Traditional Chinese MedicineJ Tradit Chin Med, 26, 26-28, 2006
adequately prevented during the study?	
Were incomplete outcome data adequately addressed?	UNCLEAR
Are reports of the study free of suggestion of selective outcome reporting?	NO
Was the study apparently free of other problems that could put it at a high risk of bias?	UNCLEAR

Table 147: Lomen et al., 1986

Bibliographic reference	Lomen,P.L., Turner,L.F., Lamborn,K.R., Brinn,E.L., Flurbiprofen in the treatment of ankylosing spondylitis. A comparison with indomethacin, The American journal of medicine, 80, 127-132, 1986
Country/ies where the study was carried out	USA
Study type	Randomised, double blind study
Aim of the study	Not reported
Study dates	Not reported
Source of funding	Not reported
Sample size	n=60
Inclusion criteria	Patients between 18-60 years with definitive diagnosis of AS. Clinical and radiographic feature included pain and stiffness in the lumbar region for more than 3 months, major limitation of motion in the lumbar spine in all 3 planes, pain and stiffness in the thoracic region for more than 3 months, limitation of chest expansion, night pain, history or evidence of iritis or its sequelae, bilateral sacroiliac disease on radiographic examination.
Exclusion criteria	Not reported.
Details	Study duration = 26 weeks. All previous anti-inflammatory medications were discontinued upon entry into the study for a washout period of at least 48 hours to allow for exacerbation of symptoms. Assignment to the two treatment groups was in accordance with a

Bibliographic reference	Lomen,P.L., Turner,L.F., Lamborn,K.R., Brinn,E.L., Flurbiprofen in the treatment of ankylosing spondylitis. A comparison with indomethacin, The American journal of medicine, 80, 127-132, 1986
	standardised randomisation schedule. Treatment was double blind, bottles for the two groups were identical with attached decoding labels. Efficacy assessed at one week, patient was withdrawn from the study before the end of the 1st week if a serious AE occurred. Dose could be escalated at 1 week. De-escalation of dose was always encouraged to determine the minimum effective dose for each patient, and there was a de-escalation schedule.
Interventions	Flurbiprofen 50mg capsules, three times daily (total initial daily dose 150mg). Assessment of efficacy after 1 week. If poor control of symptoms and no AEs, dose escalated to maximum maintenance dose of 200mg Flurbiprofen (50mg, four times daily). This regimen was continued throughout the study in patients whose symptoms remained adequately controlled and who were not experiencing side effects. In patients whose symptoms were not adequately controlled on the maintenance dose, and experienced no serious AEs, after treatment for 1 week at the maintenance dose, the total daily dose was increased to 250mg Flurbiprofen (100mg, 50mg, 50mg, 50mg divided doses) These doses - the low escalation regimen- could be taken for a total of 14 days during the study, either consecutively or following an exacerbation whilst on the maintenance dose. If the low dose escalation regimen was required for more than a total of 14 days, the patient was withdrawn from the study. In patients who did not gain adequate symptom control on 250mg after 1 week, the dose was increased to 300mg (100mg, 50mg, 50mg, 100mg divided doses). This dose could not be taken for more than 4 days. If symptoms did not subside after this time the patient was withdrawn from the study. Indomethacin 25mg capsules, three times daily (total initial daily dose 75mg). Assessment of efficacy after 1 week. If poor control of symptoms and no AEs, dose escalated to maximum maintenance dose of 100mg Indomethacin (25mg, four times daily). This regimen was continued throughout the study in patients whose symptoms remained adequately controlled and who were not experiencing side effects. In patients whose symptoms were not adequately controlled on the maintenance dose, and experienced no serious AEs, after treatment for 1 week at the maintenance dose, the total daily dose was increased to 125mg Indomethacin (50mg, 25mg, 25mg, 25mg divided doses). These doses - the low escalation regimen- could be taken for a total of 14 days during the study, either consecutively or following an exacerbation whilst on the maintenance dose. If the low dose escalation regimen was required for more than a total of 14 days, the patient was withdrawn from the study. In patients who did not gain adequate symptom control on 125mg after 1 week, the dose was increased to 150mg (50mg, 25mg, 25mg, 50mg divided doses). This dose could not be taken for more than 4 days. If symptoms did not subside after this time the patient was withdrawn from the study.
Characteristics	Baseline characteristics: No statistically significant differences between groups for race, Steinbrocker functional class, sex, age and duration of disease or patients and investigators week 0 assessment of disease. No statistically significant differences between the two groups for previous therapy for AS.

Bibliographic reference	Lomen,P.L., Turner,L.F., Lamborn,K.R., Brinn,E.L., Flurbiprofen in the treatment of ankylosing spondylitis. A comparison with indomethacin, The American journal of medicine, 80, 127-132, 1986

Parameter	Flurbiprofen	Indomethacin
n	30	27
ethnicity:		
white	30	26
NR	0	1
Sex: m/f	26/4	24/3
Age (yrs)		
20-29	6	8
30-39	11	10
40-49	8	4
50-59	3	4
>60	2	1
Duration of disease:		
0-4	6	7
5-9	5	8
10-14	7	2
15-19	4	3
20-24	4	5
25-29	1	0
>30	3	2

Results

Pain

Efficacy measurement	Flurbiprofen	Indomethacin

Bibliographic reference	**Lomen,P.L., Turner,L.F., Lamborn,K.R., Brinn,E.L., Flurbiprofen in the treatment of ankylosing spondylitis. A comparison with indomethacin, The American journal of medicine, 80, 127-132, 1986**

	n at 26 weeks	Mean improvement	Median improvement	n at 26 weeks	Mean improvement	Median improvement
Night pain (0-3)	24	1.3	1.0	29	1.3	1.0
Spinal pain (0-4)	23	1.5	2.0	21	1.5	2.0
Rest pain (0-6)	24	1.9	2.0	21	1.8	2.0
Motion pain (0-6)	25	2.0	2.0	21	2.2	2.0

Withdrawals due to adverse events:
Flurbiprofen: n=1
Indomethacin: n=1
Withdrawals due to lack of efficacy of study drug:
Flurbiprofen: n=2
Indomethacin: n=1

Overall Risk of Bias

Study drugs were titrated, therefore participants on different doses.
Randomisation not described.
Not clear whether those withdrawn in the first week due to AEs are recorded as having AES, therefore potential bias and under-reporting.
Only mean values reported for pain outcome, no SD or SEM.
Paper indicates ITT analysis, but not clear what happens to missing data.
No details on exclusion criteria for study.

Other information

Whenever possible, comparisons were made with baseline measurements (week 0), if these were unavailable the pre-washout or initial values were used.
For efficacy analyses only, analyses were performed on baseline to final change scores (final visit defined as last report on study drug for a patient regardless of when it occurred. (ITT).

2-tailed paired t tests were conducted on efficacy measurements; ANOVA were performed on baseline measurements an on key follow up change scores for efficacy. 2 sided Fisher's test was used in a few instances and the 2 sample Wilcoxon test was used extensively.
Dosage summary of study drugs:

	Flurbiprofen	Indomethacin

Bibliographic reference	Lomen,P.L., Turner,L.F., Lamborn,K.R., Brinn,E.L., Flurbiprofen in the treatment of ankylosing spondylitis. A comparison with indomethacin, The American journal of medicine, 80, 127-132, 1986		
	QID regimen (4 x daily)		
	Total n of patients following QID regimen	20	17
	Mean % of total days on QID regimen for those following that regimen	76.6	67.8
	TID regimen (3 x daily)		
	Total n of patients following TID regimen	30	26*
	Mean % of total days on TID regimen for those following that regimen	40.3	55.7
	BID regimen (2 x daily)		
	Total n of patients following BID regimen	10	8
	Mean % of total days on BID regimen for those following that regimen	16.7	7.9
	Range of % total days on BID regimen for those following that regimen	0.5-94.1	0.5- 23.4
Was the allocation sequence adequately generated?	UNCLEAR		
Was allocation adequately concealed?	UNCLEAR		
Was knowledge of the allocated intervention adequately prevented during the study?	YES		

Bibliographic reference	Lomen,P.L., Turner,L.F., Lamborn,K.R., Brinn,E.L., Flurbiprofen in the treatment of ankylosing spondylitis. A comparison with indomethacin, The American journal of medicine, 80, 127-132, 1986
Were incomplete outcome data adequately addressed?	UNCLEAR
Are reports of the study free of suggestion of selective outcome reporting?	UNCLEAR
Was the study apparently free of other problems that could put it at a high risk of bias?	NO

Table 148: Mayrhofer et al., 1990

Bibliographic reference	Mayrhofer,F., Broll,H., Eberl,R., Ebner,W., Klein,G., Rainer,F., Schorsch,G., Thumb,N., Tenoxicam versus diclofenac in patients with ankylosing spondylitis. A double-blind study, Drug Investigation, 2, 52-53, 1990
Country/ies where the study was carried out	Austria
Study type	Double blind, randomised
Aim of the study	Not reported
Study dates	Not reported
Source of funding	Not reported
Sample size	n=57
Inclusion criteria	Not reported
Exclusion criteria	Not reported
Details	Patients were randomised (10 patients per centre, 5 on tenoxicam, 5 on diclofenac). After a washout period of at least 3 days patients were randomly allocated treatment groups. Treatment was for 21 days and patients also took part in a physical therapy programme as part of the study.

Bibliographic reference	Mayrhofer,F., Broll,H., Eberl,R., Ebner,W., Klein,G., Rainer,F., Schorsch,G., Thumb,N., Tenoxicam versus diclofenac in patients with ankylosing spondylitis. A double-blind study, Drug Investigation, 2, 52-53, 1990
	Clinical assessment performed prior to treatment and on days 7,14 and 21.
Interventions	Tenoxicam 20mg/day (n=28) Diclofenac 100mg/day (n=29, calculated by analyst)
Characteristics	Baseline characteristics: 49 men, 8 women Age range: 22-67 (mean 42) 82% people HLA B27 positive
Results	Pain intensity (VAS scale): This data was presented in graphical form only for lumbosacral pain on movement, made into discrete data (e.g. >50% improvement), therefore this data could not be reported here. Lumbosacral pain during the day and lumbosacral pain at night was stated to be improved similarly in both groups, but no data was presented within the paper. Withdrawals due to adverse events: Tenoxicam: n=0 Diclofenac: n=3 Withdrawals due to lack of efficacy of study drug: Tenoxicam: n=3 Diclofenac: n=2
Overall Risk of Bias	Inclusion and exclusion criteria not reported. Outcomes not reported fully, data could not be analysed.
Was the allocation sequence adequately generated?	UNCLEAR
Was allocation adequately concealed?	UNCLEAR
Was knowledge of the allocated intervention adequately prevented during the study?	UNCLEAR

Bibliographic reference	Mayrhofer,F., Broll,H., Eberl,R., Ebner,W., Klein,G., Rainer,F., Schorsch,G., Thumb,N., Tenoxicam versus diclofenac in patients with ankylosing spondylitis. A double-blind study, Drug Investigation, 2, 52-53, 1990
Were incomplete outcome data adequately addressed?	UNCLEAR
Are reports of the study free of suggestion of selective outcome reporting?	NO
Was the study apparently free of other problems that could put it at a high risk of bias?	UNCLEAR

Table 149: Nahir & Scharf, 1980

Bibliographic reference	Nahir,A.M., Scharf,Y., A comparative study of diclofenac and sulindac in ankylosing spondylitis, Rheumatology and rehabilitation, 19, 189-198, 1980
Country/ies where the study was carried out	Israel
Study type	Double blind, single centre trial.
Aim of the study	To compare the efficacy and tolerability of diclofenac sodium (Voltaren) 150mg daily and Sulindac 400mg daily in people with AS.
Study dates	Not reported
Source of funding	Not reported
Sample size	n=62
Inclusion criteria	Patients were currently receiving treatment at the Rheumatology out-patient department of the Rambam medical centre. All had radiographic evidence of sacroiliitis and clinically active disease. All patients demonstrated spinal pain, decreased range of motion in some part of the spine and an increased ESR.

Bibliographic reference	**Nahir,A.M., Scharf,Y., A comparative study of diclofenac and sulindac in ankylosing spondylitis, Rheumatology and rehabilitation, 19, 189-198, 1980**
Exclusion criteria	Patients with hepatic, renal, gastric disease or previous intolerance to indomethacin were excluded.
Details	After a 7 day washout period, where no anti-inflammatory/ analgesic medication was permitted, the patients were randomly assigned to the 2 treatment groups.
Interventions	Diclofenac 150mg daily: 50mg, 3 x daily plus sulindac placebo 2 x daily Sulindac 400mg daily: Sulindac 200mg, 3 x daily plus diclofenac placebo 3 x daily
Characteristics	Baseline characteristics

Parameter	Diclofenac	Sulindac	Total
Age (yrs) mean (range)	37 (26-58)	37 (20-57)	37 (20-58)
Sex: m/f (%)	30 (97)/1 (3)	30 (97)/1 (3)	60/2
Duration of illness:			
1-5 years	10 (32%)	13 (42%)	23 (37%)
>5 years	21 (68%)	18 (58%)	39 (63%)
Criteria for active disease:			
Increased muscle spasm in back: n, (%)	29 (94)	28 (93)	57 (93)
Decreased ROM in some part of spine: n, (%)	31 (100)	30 (100)	61 (100)
Increased ESR: n, (%)	30 (97)	29 (97)	59 (97)

Bibliographic reference	**Nahir,A.M., Scharf,Y., A comparative study of diclofenac and sulindac in ankylosing spondylitis, Rheumatology and rehabilitation, 19, 189-198, 1980**
	Not stated: n / - / 1 / 1
Results	Pain (100mm VAS), mean (SD) Pre washout: Diclofenac 43 (18) n=30; Sulindac 52 (18) n=29 Baseline: Diclofenac 85 (9) n=31; Sulindac 88 (8) n=31 Day 28: Diclofenac 25* (19) n=30; Sulindac 36* (21) n=30 *significant difference between groups on day 28 in favour of diclofenac Withdrawals due to adverse events: Diclofenac: n=0 Sulindac: n=1 Withdrawals due to lack of efficacy: Diclofenac: n=1 Sulindac: n=0
Overall Risk of Bias	Not reported whether ITT analysis, no information provided on statistics used to analyse data.
Was the allocation sequence adequately generated?	UNCLEAR
Was allocation adequately concealed?	UNCLEAR
Was knowledge of the allocated intervention	YES

Bibliographic reference	Nahir,A.M., Scharf,Y., A comparative study of diclofenac and sulindac in ankylosing spondylitis, Rheumatology and rehabilitation, 19, 189-198, 1980
adequately prevented during the study?	
Were incomplete outcome data adequately addressed?	UNCLEAR
Are reports of the study free of suggestion of selective outcome reporting?	UNCLEAR
Was the study apparently free of other problems that could put it at a high risk of bias?	UNCLEAR

Table 150: Pasero et al., 1994

Bibliographic reference	Pasero,G., Ruju,G., Marcolongo,R., Senesi,M., Seni,U., Mannoni,A., Accardo,S., Seriolo,B., Colombo,B., Ligniere,G.C., Consoli,G., De,Santis D., Ferri,S., Amoresano,C., Frizziero,L., Reta,M., Giorgianni,G., Martorana,U., Termine,S., Mattara,L., Franceschini,M., Oriente,P., Scarpa,R., Perpignano,G., Bogliolo,A., Torri,G., Trotta,F., Govoni,F., Aceclofenac versus naproxen in the treatment of ankylosing spondylitis: A double-blind, controlled study, Current Therapeutic Research - Clinical and Experimental, 55, 833-842, 1994
Country/ies where the study was carried out	Italy
Study type	Double blind, multicentre, controlled study
Aim of the study	To assess the efficacy and tolerability of Aceclofenac and naproxen sodium in the treatment of AS.
Study dates	Not reported
Source of funding	Not reported
Sample size	n=130 (n=126 fully complied with the inclusion criteria).
Inclusion criteria	Both sexes, aged 20-50 years, with active definite AS. AS defined by presence of spinal and/or sacroiliac pain and back muscle spasm and/or decreased spinal motion or increased ESR. with a negative test for faecal occult blood. Definite AS was defined by presence of grade 2, 3, or 4 sacroiliitis confirmed by radiography and at least 2 of the following clinical criteria. lumbar or dorsal/ lumbar junction pain

<table>
<tr><th>Bibliographic reference</th><th>Pasero,G., Ruju,G., Marcolongo,R., Senesi,M., Seni,U., Mannoni,A., Accardo,S., Seriolo,B., Colombo,B., Ligniere,G.C., Consoli,G., De,Santis D., Ferri,S., Amoresano,C., Frizziero,L., Reta,M., Giorgianni,G., Martorana,U., Termine,S., Mattara,L., Franceschini,M., Oriente,P., Scarpa,R., Perpignano,G., Bogliolo,A., Torri,G., Trotta,F., Govoni,F., Aceclofenac versus naproxen in the treatment of ankylosing spondylitis: A double-blind, controlled study, Current Therapeutic Research - Clinical and Experimental, 55, 833-842, 1994</th></tr>
<tr><td></td><td>and stiffness of over 3 months duration; major limitation of motion of the lumbar spine in 3 directions - flexion/extension, lateral bending and rotation; pain and stiffness in the thoracic region of over 3 months duration; limited chest expansion; nocturnal pain with morning predominance and/or morning stiffness and/or pain in one or both buttocks.</td></tr>
<tr><td>Exclusion criteria</td><td>Patients with other arthropathies, CV, neoplastic, GI or renal diseases, or treated with drugs that could interfere with the study drugs were excluded. Pregnant or nursing women, women receiving hormonal contraception and patients, who in the opinion of the investigators would be unable to comply fully with trial requirements.</td></tr>
<tr><td>Details</td><td>Study duration 3 months.
Patients were randomised to treatment with aceclofenac or naproxen</td></tr>
<tr><td>Interventions</td><td>Aceclofenac 200mg/ day (n=63, 60 fully complied)
100mg, twice daily.
Naproxen 1g/ day (n=66, 60 fully complied)
500mg, twice daily.</td></tr>
<tr><td>Characteristics</td><td>Baseline characteristics:
Groups similar for all characteristics apart from significant difference (p<0.05) between hand to floor distance (by split plot ANOVA). All values mean (SD)
<table>
<tr><td>Parameter</td><td>Aceclofenac (n=60)</td><td>Naproxen (n=66)</td></tr>
<tr><td>Age (yrs)</td><td>39.10 (7.93)</td><td>38.50 (8.94)</td></tr>
<tr><td>Sex (m/f)</td><td>50/10</td><td>57/9</td></tr>
<tr><td>Disease onset (months)</td><td>89.77 (74.22)</td><td>85.82 (85.39)</td></tr>
<tr><td>Pain (VAS)</td><td>52.80 (20.27)</td><td>53.48 (21.95)</td></tr>
<tr><td>Pain on movement (score 0-3)</td><td>1.92 (0.74)</td><td>1.79 (0.79)</td></tr>
<tr><td>Pain at rest (score 0-3)</td><td>1.48 (0.77)</td><td>1.56 (0.81)</td></tr>
</table></td></tr>
<tr><td>Results</td><td>Spontaneous pain (measured on 100mm VAS, 0= no pain, 100= unbearable pain). Mean values, data estimated from graph (no raw data provided in study).
<table>
<tr><td></td><td>Aceclofenac</td><td>Naproxen</td></tr>
</table></td></tr>
</table>

Bibliographic reference	**Pasero,G., Ruju,G., Marcolongo,R., Senesi,M., Seni,U., Mannoni,A., Accardo,S., Seriolo,B., Colombo,B., Ligniere,G.C., Consoli,G., De,Santis D., Ferri,S., Amoresano,C., Frizziero,L., Reta,M., Giorgianni,G., Martorana,U., Termine,S., Mattara,L., Franceschini,M., Oriente,P., Scarpa,R., Perpignano,G., Bogliolo,A., Torri,G., Trotta,F., Govoni,F., Aceclofenac versus naproxen in the treatment of ankylosing spondylitis: A double-blind, controlled study, Current Therapeutic Research - Clinical and Experimental, 55, 833-842, 1994**
	<table><tr><td>Baseline</td><td>53</td><td>53</td></tr><tr><td>3 months</td><td>25</td><td>29</td></tr></table> n=13 patients withdrew from the study - no information provided as to whether this was due to AEs or lack of efficacy.
Overall Risk of Bias	Lack of detail on intervention.
Other information	Variation within and between groups was studied by split- plot analysis of variance and Tukey test, Friedman and Mann-Whitney U, and student's t test for parametric variables. The ANOVA, Friedman and Mann Whitney U and Chi squared test were performed for nonparametric variables.
Was the allocation sequence adequately generated?	UNCLEAR
Was allocation adequately concealed?	UNCLEAR
Was knowledge of the allocated intervention adequately prevented during the study?	UNCLEAR
Were incomplete outcome data adequately addressed?	UNCLEAR
Are reports of the study free of suggestion of selective outcome reporting?	UNCLEAR
Was the study apparently free of other problems that could put it at a high risk of bias?	UNCLEAR

Table 151: Rejholec et al., 1980

Bibliographic reference	Rejholec,V., Vapaatalo,H., Tokola,O., Gothoni,G., Tolfenamic acid in rheumatoid arthritis and ankylosing spondylitis, Scandinavian journal of rheumatology.Supplement, Suppl 33, 50-, 1980
Country/ies where the study was carried out	Finland
Study type	RCT
Aim of the study	Not reported.
Study dates	Not reported.
Source of funding	Not reported.
Sample size	n=50
Inclusion criteria	Diagnosis verified clinically and radiographically. Patients were treated with various anti-inflammatory analgesics in the 3 months preceding the trial.
Exclusion criteria	Not reported.
Details	Treatment period was 6 months.
Interventions	Tolfenamic acid Administered in dose of 200mg, 3 x daily. Indomethacin 25mg doses, 3 x daily Drugs were administered in gelatine capsules of identical appearance.
Characteristics	Baseline characteristics: not reported whether variance SD, SE etc.

Parameter	Tolfenamic acid	Indomethacin
n	25	25
Men/ women	21/4	22/3
Age, yrs (mean)	38.6 (2.6)	35.6 (2.7)
Duration of disease, yrs (mean)	13.9 (2.4)	10.4 (2.1)

Results: Pain (0-3 scale:0= no pain; 1= slight, occasional; 2= inconsistent, tolerable; 3= continuous, severe).
Mean values presented. Data estimated from graphical data by analyst as raw data was not presented in the paper.

	Tolfenamic acid	Indomethacin

Bibliographic reference	Rejholec,V., Vapaatalo,H., Tokola,O., Gothoni,G., Tolfenamic acid in rheumatoid arthritis and ankylosing spondylitis, Scandinavian journal of rheumatology.Supplement, Suppl 33, 50-, 1980
	<table><tr><td>Baseline</td><td>1.9</td><td>1.3</td></tr><tr><td>6 months</td><td>0.7</td><td>1.2</td></tr></table> Withdrawals due to adverse events: Tolfenamic acid: n=0 Indomethacin: n=4 Withdrawals due to lack of efficacy: Not reported
Overall Risk of Bias	Data on pain was estimated from graphical data as the paper did not present the raw data.
Was the allocation sequence adequately generated?	UNCLEAR
Was allocation adequately concealed?	UNCLEAR
Was knowledge of the allocated intervention adequately prevented during the study?	YES
Were incomplete outcome data adequately addressed?	UNCLEAR
Are reports of the study free of suggestion of selective outcome reporting?	UNCLEAR
Was the study apparently free of other problems that could put it at a high risk of bias?	UNCLEAR

Table 152: Schwarzer et al., 1990

Bibliographic reference	Schwarzer,A.C., Cohen,M., Arnold,M.H., Kelly,D., McNaught,P., Brooks,P.M., Tenoxicam compared with diclofenac in patients with ankylosing spondylitis, Current medical research and opinion, 11, 648-653, 1990
Country/ies where the study was carried out	Australia
Study type	Randomised comparative trial
Aim of the study	Not reported
Study dates	Not reported
Source of funding	Roche
Sample size	n=24
Inclusion criteria	Age 16-65 years, diagnosis of definite or probably AS according to the New York criteria (1966). Patients suitable for study entry entered a 3 day washout period when usual NSAID drug therapy was ceased. Only patients noticing an increase in back pain and stiffness were allocated to treatment.
Exclusion criteria	Patients with spinal arthritis showing active manifestations (articular or not), spinal arthritis secondary to intestinal lesion or Bechet's syndrome, disc lesions in spinal arthritis, ulcers or severe organic disease (e.g. hepatic, cardiac)known intolerance to other NSAIDs, current treatment with anticoagulants, patients treated in previous 2 months with radiotherapy, gold, thorium, immunosuppressives or steroids.
Details	After 3 day run in, patient's randomly allocated to Tenoxicam or Diclofenac groups. Patients assessed prior to commencement and at 2,4,6,8 and 12 weeks after the start of treatment.
Interventions	20mg Tenoxicam daily 100mg Diclofenac (2 x 50g doses per day) Patients were allocated to study drug for 12 weeks.
Characteristics	Baseline characteristics

	Tenoxicam	Diclofenac
Number studied	12	12
Male/ female, n	12	9/3
Age (years, mean)	42	40
Duration of disease (years, mean)	9	7
Duration of stiffness (minutes, mean)	30	60

<table>
<tr><th>Bibliographic reference</th><th>Schwarzer,A.C., Cohen,M., Arnold,M.H., Kelly,D., McNaught,P., Brooks,P.M., Tenoxicam compared with diclofenac in patients with ankylosing spondylitis, Current medical research and opinion, 11, 648-653, 1990</th></tr>
<tr><td>Results</td><td>Diurnal pain [score 0 (none) - 3 (severe)], mean (SD)
<table>
<tr><td></td><td>Tenoxicam</td><td>Diclofenac</td></tr>
<tr><td>Baseline</td><td>1.8 (0.8)</td><td>1.8 (0.8)</td></tr>
<tr><td>Week 12</td><td>1.3 (0.8)</td><td>0.9 (0.6)</td></tr>
</table>
Global assessment at week 12, mean (SD)
<table>
<tr><td></td><td>Tenoxicam</td><td>Diclofenac</td></tr>
<tr><td>Investigators</td><td>2.5 (2.1)</td><td>2.4 (1.2)</td></tr>
<tr><td>Patients</td><td>2.3 (2.0)</td><td>1.6 (1.2)</td></tr>
</table>
Withdrawals due to adverse events:
Only 1 due to serious adverse event (depression); paper does not state which group the patient withdrew from.

Withdrawals due to lack of efficacy (n)
<table>
<tr><td>Tenoxicam</td><td>Diclofenac</td></tr>
<tr><td>4</td><td>3</td></tr>
</table></td></tr>
<tr><td>Overall Risk of Bias</td><td>Does not reported allocation concealment or randomisation.
Does not state whether ITT analysis
Large number of dropouts.</td></tr>
<tr><td>Other information</td><td>Unpaired t test and Mann Whitney test used for comparison of drug groups for continuous measures
Fishers exact test used for comparing groups for categorical measures. For ordered categorical measures an exact probability test for a difference in trend across the ordered variable between the 2 drugs was performed. Paired t tests and sign tests were used to analyse the differences from the baseline measurements within each drug group.</td></tr>
<tr><td>Was the allocation sequence adequately generated?</td><td>UNCLEAR</td></tr>
<tr><td>Was allocation adequately concealed?</td><td>UNCLEAR</td></tr>
<tr><td>Was knowledge of the allocated intervention</td><td>UNCLEAR</td></tr>
</table>

Bibliographic reference	Schwarzer,A.C., Cohen,M., Arnold,M.H., Kelly,D., McNaught,P., Brooks,P.M., Tenoxicam compared with diclofenac in patients with ankylosing spondylitis, Current medical research and opinion, 11, 648-653, 1990
adequately prevented during the study?	
Were incomplete outcome data adequately addressed?	UNCLEAR
Are reports of the study free of suggestion of selective outcome reporting?	UNCLEAR
Was the study apparently free of other problems that could put it at a high risk of bias?	UNCLEAR

Table 153: Shipley et al., 1980

Bibliographic reference	Shipley,M., Berry,H., Bloom,B., A double-blind cross-over trial of indomethacin, fenoprofen and placebo in ankylosing spondylitis, with comments on patient assessment, Rheumatology and rehabilitation, 19, 122-125, 1980
Country/ies where the study was carried out	UK
Study type	Double blind, double dummy placebo controlled crossover trial.
Aim of the study	To assess efficacy and safety of Indomethacin and Fenoprofen in people with AS.
Study dates	Not reported
Source of funding	Dista products Ltd provided the capsules for the study.
Sample size	n=19
Inclusion criteria	Patients with symptomatic AS, diagnosed by clinical and radiological criteria.
Exclusion criteria	None
Details	3 x 2 week treatment periods, therefore 6 week study period. A standard number of paracetamol tablets was provided at the beginning of every treatment period in addition to the trial capsules. Allocation of patients was randomised. No washout periods were included. Patients were seen and assessed in the late afternoon by a single observer at the beginning of the trial and then fortnightly for 6 weeks.
Interventions	Placebo: No details on dosage provided

<table>
<tr><th>Bibliographic reference</th><th>Shipley,M., Berry,H., Bloom,B., A double-blind cross-over trial of indomethacin, fenoprofen and placebo in ankylosing spondylitis, with comments on patient assessment, Rheumatology and rehabilitation, 19, 122-125, 1980</th></tr>
<tr><td></td><td>Fenoprofen:
600mg, three times daily
Indomethacin:
50mg, three times daily</td></tr>
<tr><td>Characteristics</td><td>n=19
Age (yrs),mean (range): 38 (21-53)
Sex (m/f): 18/1</td></tr>
<tr><td>Results</td><td>Pain (VAS): (Pain over the previous fortnight was assessed by the patients).
<table>
<tr><td></td><td>Placebo</td><td>Fenoprofen</td><td>Indomethacin</td></tr>
<tr><td>Mean</td><td>4.48</td><td>2.95</td><td>2.22</td></tr>
<tr><td>Difference from placebo</td><td>-</td><td>-1.53</td><td>-2.26</td></tr>
<tr><td>p</td><td>-</td><td><0.05</td><td><0.01</td></tr>
</table>
Withdrawals due to adverse events:
n= 0
Withdrawals due to lack of efficacy:
n=1 during placebo period.</td></tr>
<tr><td>Overall Risk of Bias</td><td>Patients continued with regular analgesic medication.
Lack of baseline characteristics.
3 patients failed to complete the trial; unclear how missing data assessed.
No SD/SE/95%CI reported for pain outcomes.
No details on how placebo given - not clear whether adequate to maintain blinding.</td></tr>
<tr><td>Other information</td><td>Returned tablets were counted to assess adherence.
14 of the 19 patients took regular medication in addition to study medication: 8 took indomethacin, 2 took naproxen, 1 took Phenylbutazone, 1 ibuprofen and 2 distalgesic.</td></tr>
<tr><td>Was the allocation sequence adequately generated?</td><td>UNCLEAR</td></tr>
<tr><td>Was allocation adequately concealed?</td><td>UNCLEAR</td></tr>
<tr><td>Was knowledge of the allocated intervention</td><td>UNCLEAR</td></tr>
</table>

Bibliographic reference	Shipley,M., Berry,H., Bloom,B., A double-blind cross-over trial of indomethacin, fenoprofen and placebo in ankylosing spondylitis, with comments on patient assessment, Rheumatology and rehabilitation, 19, 122-125, 1980
adequately prevented during the study?	
Were incomplete outcome data adequately addressed?	UNCLEAR
Are reports of the study free of suggestion of selective outcome reporting?	UNCLEAR
Was the study apparently free of other problems that could put it at a high risk of bias?	UNCLEAR

Table 154: Sieper et al., 2008

Bibliographic reference	Sieper,J., Klopsch,T., Richter,M., Kapelle,A., Rudwaleit,M., Schwank,S., Regourd,E., May,M., Comparison of two different dosages of celecoxib with diclofenac for the treatment of active ankylosing spondylitis: results of a 12-week randomised, double-blind, controlled study, Annals of the rheumatic diseases, 67, 323-329, 2008
Country/ies where the study was carried out	Germany, 47 investigational centres
Study type	Randomised, double blind, controlled study.
Aim of the study	To demonstrate the non- inferiority of celecoxib compared with diclofenac in patients with Ankylosing Spondylitis
Study dates	Not reported.
Source of funding	Sponsored by Pfizer.
Sample size	n=458
Inclusion criteria	Age range of 18-75 years, confirmed diagnosis of AS according to modified New York criteria, presence of axial involvement, no peripheral involvement (apart from hips or shoulders), the need for daily treatment with NSAIDs. Acute episode of moderate to severe pain at baseline (>40mm on 100mm VAS scale) and with an increase in pain VAS of >30% compared to screening visit after cessation of NSAID treatment.
Exclusion criteria	Present or previous episodes of inflammatory bowel disease or a history of upper GI ulcers within the previous year and confirmed by endoscopy were regarded as exclusion criteria.
Details	People with AS recruited by rheumatologists in outpatient units or in private practice.

<table>
<tr><th>Bibliographic reference</th><td>Sieper,J., Klopsch,T., Richter,M., Kapelle,A., Rudwaleit,M., Schwank,S., Regourd,E., May,M., Comparison of two different dosages of celecoxib with diclofenac for the treatment of active ankylosing spondylitis: results of a 12-week randomised, double-blind, controlled study, Annals of the rheumatic diseases, 67, 323-329, 2008</td></tr>
<tr><td></td><td>Eligible subjects entered a 2 week washout phase of 2-14 days during which all NSAIDs and other analgesics were withdrawn.
Eligible subjects randomised 1:1:1 to double dummy study medication (capsules of celecoxib, diclofenac and matching placebo) for oral administration over a treatment period of 12 weeks. Concomitant treatment with DMARDS (if used at a stable dose for at least 3 months prior to study start and no change planned during the study period) and prednisolone equivalents of >10mg/day at stable doses were permitted. The concomitant administration of proton pump inhibitors was allowed at the discretion of the investigators.</td></tr>
<tr><td>Interventions</td><td>Celecoxib 200mg twice a day
Celecoxib 200mg once a day
Diclofenac 75mg slow release (SR), twice a day</td></tr>
<tr><td>Characteristics</td><td>n=458 (69% male, n=317)
Mean age 44.8 years (range 18-77 years)</td></tr>
<tr><td>Results</td><td>VAS pain (100mm VAS scale)
<table>
<tr><td></td><td>Celecoxib 200mg once a day</td><td>Celecoxib 200mg twice a day</td><td>Diclofenac 75mg twice a day</td></tr>
<tr><td>Baseline, mean (SD)</td><td>65.6 (14.9)</td><td>68.1 (16.4)</td><td>64.3 (16.6)</td></tr>
<tr><td>Week 12, mean (SD)</td><td>37.4 (25.6)</td><td>38.7 (24.9)</td><td>33.8 (27.1)</td></tr>
<tr><td>Mean change from baseline, mean (SD)</td><td>-28.2 (27.2)</td><td>-29.8 (25.1)</td><td>-30.8 (25.6)</td></tr>
<tr><td>LS mean treatment contrast, mean (SEM)</td><td>2.9 (2.7)</td><td>2.1 (2.8)</td><td>NA</td></tr>
<tr><td>95%CI for the treatment contrast</td><td>-2.4, 8.2</td><td>-3.3, 7.6</td><td>NA</td></tr>
</table>
Global assessment of disease activity (o (inactive)- 10 (highly active))
<table>
<tr><td></td><td>Celecoxib 200mg once a day</td><td>Celecoxib 200mg twice a day</td><td>Diclofenac 75mg twice a day</td></tr>
</table></td></tr>
</table>

<table>
<tr><th>Bibliographic reference</th><th>Sieper,J., Klopsch,T., Richter,M., Kapelle,A., Rudwaleit,M., Schwank,S., Regourd,E., May,M., Comparison of two different dosages of celecoxib with diclofenac for the treatment of active ankylosing spondylitis: results of a 12-week randomised, double-blind, controlled study, Annals of the rheumatic diseases, 67, 323-329, 2008</th></tr>
<tr><td></td><td>
<table>
<tr><td>Baseline, mean (SD)</td><td>6.1 (1.8)</td><td>6.5 (1.7)</td><td>6.1 (1.8)</td></tr>
<tr><td>Week 12, mean (SD)</td><td>4.1 (2.4)</td><td>4.3 (2.5)</td><td>3.8 (2.6)</td></tr>
<tr><td>Mean change from baseline, mean (SD)</td><td>-2.0 (2.7)</td><td>-2.2 (2.5)</td><td>-2.3 (2.6)</td></tr>
<tr><td>LS mean treatment contrast, mean (SEM)</td><td>0.3 (0.3)</td><td>0.3 (0.3)</td><td>NA</td></tr>
<tr><td>95%CI for the treatment contrast</td><td>-0.2, 0.8</td><td>-0.2, 0.8</td><td>NA</td></tr>
</table>
Withdrawals due to adverse events
<table>
<tr><td></td><td>celecoxib 200mg qd</td><td>celecoxib 200 mg bid</td><td>Diclofenac 75mg SR bid</td></tr>
<tr><td>12 weeks</td><td>8/153</td><td>12/150</td><td>15/155</td></tr>
</table>
Withdrawals due to lack of efficacy (the analysis of premature withdrawal was based on the allocation of 1 primary reason for withdrawal in the case of multiple reasons - 14 patients had an additional specification of "lack of efficacy" but were allocated to another (primary) category. The paper states that the number of patients with lack of efficacy was comparable between treatment groups)
<table>
<tr><td></td><td>celecoxib 200mg qd</td><td>celecoxib 200 mg bid</td><td>Diclofenac 75mg SR bid</td></tr>
<tr><td>12 weeks</td><td>5</td><td>5</td><td>4</td></tr>
</table>
</td></tr>
<tr><td>Overall Risk of Bias</td><td>Allocation concealment not reported.
>10% dropouts in each group, though these were equally distributed between groups.</td></tr>
<tr><td>Other information</td><td>Primary analysis performed hierarchically in the per protocol population. Primary and secondary efficacy variables were analysed using several ANCOVA models. For the primary analysis (Global pain intensity at week 12), baseline, VAS and age were used as covariates, and sex, treatment and pooled centre as factors. The safety analysis was performed descriptively.
Study adequately powered.</td></tr>
<tr><td>Was the allocation sequence adequately generated?</td><td>UNCLEAR</td></tr>
</table>

Bibliographic reference	Sieper,J., Klopsch,T., Richter,M., Kapelle,A., Rudwaleit,M., Schwank,S., Regourd,E., May,M., Comparison of two different dosages of celecoxib with diclofenac for the treatment of active ankylosing spondylitis: results of a 12-week randomised, double-blind, controlled study, Annals of the rheumatic diseases, 67, 323-329, 2008
Was allocation adequately concealed?	UNCLEAR
Was knowledge of the allocated intervention adequately prevented during the study?	UNCLEAR
Were incomplete outcome data adequately addressed?	YES
Are reports of the study free of suggestion of selective outcome reporting?	YES
Was the study apparently free of other problems that could put it at a high risk of bias?	YES

Table 155: Sturrock & Hart, 1974

Bibliographic reference	Sturrock,R.D., Hart,F.D., Double-blind cross-over comparison of indomethacin, flurbiprofen, and placebo in ankylosing spondylitis, Annals of the Rheumatic Diseases, 33, 129-131, 1974
Country/ies where the study was carried out	UK
Study type	Double blind, crossover
Aim of the study	Not reported
Study dates	Not reported
Source of funding	Financial support of the Arthritis and Rheumatism Council for Research.
Sample size	n=24 (20 completed the trial)

Bibliographic reference	**Sturrock,R.D., Hart,F.D., Double-blind cross-over comparison of indomethacin, flurbiprofen, and placebo in ankylosing spondylitis, Annals of the Rheumatic Diseases, 33, 129-131, 1974**
Inclusion criteria	Negative sheep cell agglutination test, fulfilled the criteria for the diagnosis of ankylosing spondylosis (Bennett and Wood, 1968)
Exclusion criteria	History of peptic ulcers, intolerance to indomethacin, concurrent steroid therapy.
Details	Patients were randomly allocated to one of 6 treatment sequences. The capsules were of identical size shape and colouring. A return capsule count was made at the end of each treatment period. The use of paracetamol tablets was allowed during the course of the trial and the number taken daily was recorded on a pain diary. The trial period consisted of three, 2 - week treatment intervals. Assessments taken at the end of each 2 week period.
Interventions	Indomethacin 25mg, three times a day Flurbiprofen 50mg, three times a day Placebo
Characteristics	n= 24 (21 male, 3 female) Mean age (years) 43.2 Mean duration of disease (yrs) 16.5
Results	Subjective impression of pain (VAS)

Comparison	indomethacin	Placebo	Flurbiprofen	Difference	S.E	No. of cases	t	Probability
Placebo vs indomethacin	1.30	1.77		0.47	0.23	19	2.08	p=0.05
Placebo vs flurbiprofen		1.77	1.16	0.61	0.20	19	2.98	p<0.01
Indomethacin vs flurbiprofen	1.30		1.16	0.14	0.17	19	0.79	p>0.02

Mean daily pain scores

Bibliographic reference	Sturrock,R.D., Hart,F.D., Double-blind cross-over comparison of indomethacin, flurbiprofen, and placebo in ankylosing spondylitis, Annals of the Rheumatic Diseases, 33, 129-131, 1974

Comparison	Wilcoxon's T	No. of cases	Critical 5% value of T	Probability	
Placebo vs indomethacin	77	19	53	p>0.1	favours indomethacin
Placebo vs flurbiprofen	32	17	34	0.05>p>0.02	favours flurbiprofen
Indomethacin vs flurbiprofen	51.5	19	53	0.05>p>0.02	favours flurbiprofen

Withdrawals:
4 in total;
2 on indomethacin (indigestion and nausea)
1 on Flurbiprofen (vertigo)
1 during placebo (severe exacerbation of pain and stiffness)

Overall Risk of Bias	Very small trial. Unclear whether ITT analysis. Allocation concealment not reported.
Other information	Unclear whether there was a washout period between the three treatment periods.
Was the allocation sequence adequately generated?	UNCLEAR
Was allocation adequately concealed?	UNCLEAR

Bibliographic reference	Sturrock,R.D., Hart,F.D., Double-blind cross-over comparison of indomethacin, flurbiprofen, and placebo in ankylosing spondylitis, Annals of the Rheumatic Diseases, 33, 129-131, 1974
Was knowledge of the allocated intervention adequately prevented during the study?	UNCLEAR
Were incomplete outcome data adequately addressed?	UNCLEAR
Are reports of the study free of suggestion of selective outcome reporting?	UNCLEAR
Was the study apparently free of other problems that could put it at a high risk of bias?	UNCLEAR

Table 156: Sydnes, 1981

Bibliographic reference	Sydnes,O.A., Comparison of piroxicam with indomethacin in ankylosing spondylitis: a double-blind crossover trial, The British journal of clinical practice, 35, 40-44, 1981
Country/ies where the study was carried out	Norway, 13 rheumatology departments.
Study type	Double blind, crossover
Aim of the study	To assess the efficacy and tolerability of Piroxicam and Indomethacin.
Study dates	Not reported
Source of funding	Not reported

Bibliographic reference	Sydnes,O.A., Comparison of piroxicam with indomethacin in ankylosing spondylitis: a double-blind crossover trial, The British journal of clinical practice, 35, 40-44, 1981
Sample size	n=93
Inclusion criteria	Patients of either sex, aged 18-70 years suffering from classical or definite AS, as defined by the American Rheumatism Association were included. All patients had active disease requiring treatment with NSAIDs.
Exclusion criteria	History of primary disease of less than 6 months duration, AS associated with psoriasis, systematically or intra-articularly administered corticosteroids in the preceding 3 months, anticipated corticosteroid requirement during the course of the trial, pregnancy or nursing mothers, blood, liver or renal abnormalities unrelated to the primary disease, peptic ulceration or severe dyspepsia in the preceding 12 months, known hypersensitivity to NSAID
Details	A double blind, crossover design was used. The order in which the drugs were given was randomised with a restriction to ensure a balance between treatments and orders. At the first visit, patients underwent clinical examination and any NSAID and analgesics except paracetamol were stopped and patients received placebo for one week. Those patients meeting the selection criteria were entered into the trial. The duration of each drug treatment was 4 weeks; the treatment periods were separated by 1 week of placebo. Patients attended for assessment after 1, 5, 6 and 10 weeks; as far as possible at the same hour of the day and seen by the same observer on each occasion. If during a placebo period, pain or morning stiffness worsened considerably, the investigator was allowed to shorten the period and proceed immediately to the next treatment as scheduled. A fixed dose of all study drugs was given to patients throughout the trial. All capsules were identical in appearance and supplied in dosing boxes, each box containing capsules for one week. At return, a capsule count was undertaken. Paracetamol was permitted as an escape medication. Those patients receiving physiotherapy continued with this, unchanged, throughout the entire trial period.
Interventions	Piroxicam One capsule (20mg) taken in the evening, 2 placebo capsules taken to maintain blinding. Indomethacin One 25mg capsule, taken 3 times daily
Characteristics	Baseline characteristics (on patients remaining in study only - no details on 6 patients who discontinued): Male: 67; mean age (years):39 Female: 20; mean age (years): 41 Total n: 87; mean age (years): 40
Results	Pain [mean(SEM)]

Parameter	Sequence A	Sequence B	Results

Bibliographic reference	Sydnes,O.A., Comparison of piroxicam with indomethacin in ankylosing spondylitis: a double-blind crossover trial, The British journal of clinical practice, 35, 40-44, 1981

	Placebo	Piroxicam	placebo	Indomethacin	Placebo	Indomethacin	Placebo	Piroxicam	
Peripheral joint pain at rest*	3.6 (0.5)	2.5 (0.4)	3.7 (0.5)	3.2 (0.4)	3.7 (0.3)	3.2 (0.4)	4.3 (0.4)	2.4 (0.3)	P>I p>0.01
Peripheral joint pain on movement*	5.0 (0.5)	3.3 (0.4)	4.4 (0.4)	3.7 (0.4)	3.7 (0.3)	3.0 (0.4)	4.6 (0.4)	2.4 (0.3)	P>I 0.05<p<0.1
Pain in tendon attachments*	3.8 (0.5)	2.2 (0.4)	3.7 (0.4)	2.8 (0.4)	3.6 (0.4)	3.2 (0.4)	4.2 (0.4)	2.2 (0.4)	P>I p<0.02
Back pain+	5.0 (0.4	3.2 (0.4)	4.6 (0.4)	3.7 (0.4)	5.0 (0.3)	3.8 (0.4)	5.7 (0.4)	2.8 (0.3)	P>I p<0.01
Overall condition**	3.3 (0.1)	2.3 (0.1)	3.0 (0.1)	2.4 (0.1)	3.3 (0.1)	2.6 (0.1)	3.3 (0.1)	2.1 (0.1)	P>I p<0.03

*measured on VAS scale of 0 [very good] to 10 [very bad]),
+ not reported what scale back pain was measure on)
** 5 Grades; 1= very good - 5=very bad

Withdrawals due to adverse events
n=1 withdrew during treatment with Indomethacin
Withdrawals due to lack of efficacy of study medication
n=1 hospitalised for flare of disease activity (not stated during which intervention).

Overall Risk of Bias	The ability of the investigator to shorten any placebo period and move to active treatment is a source of bias; not reported how many participants this occurred with. Lack of information on baseline characteristics. No baseline information on 6 patients who discontinued study.

Bibliographic reference	Sydnes,O.A., Comparison of piroxicam with indomethacin in ankylosing spondylitis: a double-blind crossover trial, The British journal of clinical practice, 35, 40-44, 1981
Other information	Comparisons in efficacy between the 2 medications made by using student's T test, each patient being their own control between measurements of each active treatment period.
Was the allocation sequence adequately generated?	UNCLEAR
Was allocation adequately concealed?	UNCLEAR
Was knowledge of the allocated intervention adequately prevented during the study?	YES
Were incomplete outcome data adequately addressed?	UNCLEAR
Are reports of the study free of suggestion of selective outcome reporting?	UNCLEAR
Was the study apparently free of other problems that could put it at a high risk of bias?	UNCLEAR

Table 157: Tannenbaum et al., 1984

Bibliographic reference	Tannenbaum,H., DeCoteau,W.E., Esdaile,J.M., A double blind multicenter trial comparing piroxicam and indomethacin in ankylosing spondylitis with long-term follow-up, Current Therapeutic Research - Clinical and Experimental, 36, 426-435, 1984
Country/ies where the study was carried out	Canada
Study type	Randomised, double blind parallel study
Aim of the study	To compare the efficacy and safety of piroxicam with indomethacin in the therapy of patients with AS. Compliance was also assessed.
Study dates	Not reported
Source of funding	Not reported
Sample size	n=55
Inclusion criteria	AS diagnosed by a history of morning stiffness, low back pain with limitation of motion, sacroiliitis radiologically graded according to New York criteria. Patient had to be aged between 18-65 years, and have active disease as evidenced by spinal and/or sacroiliac pain and one or more of the following:1. muscle spasm in the back; 2. decreased range of motion of some part of the spine; 3. increased ESR. A history of uveitis and detection of HLA-B27 histocompatibility antigen was also considered as positive evidence of disease (but absence of these did not preclude the diagnosis of AS).
Exclusion criteria	Patients with other arthropathies or diseases closely related to AS, such as psoriatic arthritis were excluded, as were patients with active haematological, GI, renal or hepatic disease, pregnant or nursing women.
Details	Double blind phase, 12 weeks duration. Undertaken at 4 rheumatology centres. Patients underwent a placebo washout period of up to 7 days (average length was 5 days). The washout terminated when there was an exacerbation of symptoms. Patients randomised to either indomethacin or piroxicam. As the two drugs were not identical, the double dummy technique was used. Depending on the clinical response, it was possible to increase or decrease the dose of the drug without breaking blinding.
Interventions	Indomethacin (n=27) 100mg (25mg capsules) divided into 3 doses: 25mg at 08.00 and 12.00, and 50mg at 22.00. The dose could be adjusted between 75mg - 125mg. In addition to indomethacin tablets, patients received placebo capsules identical to piroxicam. Piroxicam (n=28) 20mg (in 10mg capsules) once a day at 8.00. The dose could be lowered to 10mg, but could not be increased beyond 20mg per day. In addition to piroxicam tablets, patients received placebo capsules identical to indomethacin.

<table>
<tr><th>Bibliographic reference</th><th>Tannenbaum,H., DeCoteau,W.E., Esdaile,J.M., A double blind multicenter trial comparing piroxicam and indomethacin in ankylosing spondylitis with long-term follow-up, Current Therapeutic Research - Clinical and Experimental, 36, 426-435, 1984</th></tr>
<tr><td></td><td>For both groups, the number of piroxicam or indomethacin capsules were increased or decreased in a parallel fashion whenever a change in dosage was required.
The paper states that in 75% of patients, no adjustments from the starting dosage of indomethacin (100mg) or piroxicam (20mg) were made. No further detail supplied.</td></tr>
<tr><td>Characteristics</td><td>Baseline characteristics
<table>
<tr><td></td><td>Piroxicam</td><td>indomethacin</td></tr>
<tr><td>Number</td><td>28</td><td>27</td></tr>
<tr><td>Age</td><td>35.6 (1.3)</td><td>34.0 (1.8)</td></tr>
<tr><td>Sex (m/f)</td><td>21/7</td><td>20/7</td></tr>
<tr><td>Disease duration (yrs)</td><td>8.8 (1.4)</td><td>9.7 (1.7)</td></tr>
<tr><td>Sacroiliitis on x-ray:</td><td></td><td></td></tr>
<tr><td>Grade 1</td><td>1</td><td>1</td></tr>
<tr><td>Grade 2</td><td>11</td><td>11</td></tr>
<tr><td>Grade 3</td><td>11</td><td>12</td></tr>
<tr><td>Grade 4</td><td>5</td><td>3</td></tr>
<tr><td>HLA-B27pos:neg</td><td>22:3</td><td>22:3</td></tr>
<tr><td>Not reported</td><td>3</td><td>2</td></tr>
</table></td></tr>
<tr><td>Results</td><td>All values expressed as mean (SEM)

Pain (VAS, using 17 point scale)
<table>
<tr><td></td><td colspan="2">Baseline</td><td colspan="2">Mean change</td></tr>
<tr><td></td><td>Piroxicam</td><td>Indomethacin</td><td>Piroxicam</td><td>Indomthacin</td></tr>
<tr><td>Patients self-assessment of pain</td><td>9.6 (0.6)</td><td>9.9 (0.7)</td><td>-6.3 (1.1)</td><td>-6.8 (0.8)</td></tr>
</table>

Withdrawals due to adverse events:
Piroxicam: 0
Indomethacin: 1</td></tr>
</table>

Bibliographic reference	Tannenbaum,H., DeCoteau,W.E., Esdaile,J.M., A double blind multicenter trial comparing piroxicam and indomethacin in ankylosing spondylitis with long-term follow-up, Current Therapeutic Research - Clinical and Experimental, 36, 426-435, 1984
	Withdrawals due to lack of efficacy: Piroxicam: 1 Indomethacin: 1
Overall Risk of Bias	Not stated whether ITT or how missing data dealt with.
Other information	Unblinded investigator dispensed the medications, scheduled visits and made any required dosage adjustments. A blinded investigator performed all clinical assessments, including assessment of pain. Compliance to the dosing regimen was measured at each visit by counting the returned medications. Student's t test used to compare differences between groups. Paired t test or Wilcoxon signed rank test used to compare data within group to determine significant change from baseline. Chi squared statistic and life table analysis used to analyse dropout pattern between the 2 groups.
Was the allocation sequence adequately generated?	UNCLEAR
Was allocation adequately concealed?	UNCLEAR
Was knowledge of the allocated intervention adequately prevented during the study?	UNCLEAR
Were incomplete outcome data adequately addressed?	UNCLEAR
Are reports of the study free of suggestion of selective outcome reporting?	UNCLEAR
Was the study apparently free of other problems that could put it at a high risk of bias?	UNCLEAR

Table 158: van der Heijde et al., 2005

Bibliographic reference	van der Heijde,Desiree, Baraf,Herbert S.B., Ramos-Remus,Cesar, Calin,Andrei, Weaver,Arthur L., Schiff,Michael, James,Margaret, Markind,Jan E., Reicin,Alise S., Melian,Agustin, Dougados,Maxime, Evaluation of the efficacy of etoricoxib in ankylosing spondylitis: results of a fifty-two-week, randomized, controlled study, Arthritis and rheumatism, 52, 1205-1215, 2005
Country/ies where the study was carried out	Europe, USA; 44 centres
Study type	Multicentre, double blind, parallel group. The first 6/52 was placebo controlled; from week 6-52 was an active comparator controlled study
Aim of the study	To assess the efficacy, safety and tolerability of etoricoxib for the treatment of AS.
Study dates	Not stated
Source of funding	Not stated
Sample size	n=387 (part 1). n=301 completed part 1. Of the 81 people who discontinued, 77 continued to part 2. n=374 (part 2), n=284 completed the study.
Inclusion criteria	Outpatients who fulfilled the modified New York criteria for AS. 18 years or older, diagnosis of AS made >6 months prior to study start, history of positive therapeutic benefit with NSAIDs, routine NSAID intake (use of NSAIDs for at least 25 of the previous 30 days prior to study enrolment), and at a therapeutic dose level for >30 days prior to study enrolment, use of approved non-study anti-rheumatic therapy at a stable dose for required time periods (MTX, SSZ for 3 months, other DMARDs for 6 months), satisfaction of flare criteria (>40mm on patients assessment of spine pain on 100mm VAS scale and increase of >30% compared with the pain rating at the screening visit) after the washout period for pre-study NSAIDs. Patients with chronic peripheral arthritis were eligible for inclusion in the study, if spine pain was the primary source of pain.
Exclusion criteria	Patients with concurrent rheumatic disease (e.g. SLE) that could confound the evaluation of efficacy, patients with acute peripheral articular disease (onset within 4 weeks prior to study or active peripheral arthritis), use of corticosteroid therapy within 1 month prior to the screening visit, use of analgesic medication within 3 days of study entry and through week 6 (acetaminophen was permitted prior to study entry), use of NSAID or selective COX-2 inhibitor, with the exception of low-dose aspirin (<100mg daily), which was allowed for cardiovascular prophylaxis.
Details	Part 1 - consisted of a 6 week, active comparator and placebo controlled treatment period. All patients who completed or discontinued part 1 (due to lack of efficacy of following at least 2 weeks of treatment during part 1) were given the opportunity to progress to part 2. Part 2 was a double blind, active comparator, 46 week period. Patients were randomly allocated to a treatment sequence using a computer generated random allocation schedule. Based on the original randomisation schedule, patients who received placebo during part 1 were reassigned 1:1:1 to etoricoxib 90mg, etoricoxib 10mg or naproxen 1g. Patients who received etoricoxib or naproxen during part 1 of the study continued to receive the same regimen for part 2 of the study.
Interventions	Etoricoxib 90mg daily Etoricoxib 120mg daily

<table>
<tr><td>Bibliographic reference</td><td>van der Heijde,Desiree, Baraf,Herbert S.B., Ramos-Remus,Cesar, Calin,Andrei, Weaver,Arthur L., Schiff,Michael, James,Margaret, Markind,Jan E., Reicin,Alise S., Melian,Agustin, Dougados,Maxime, Evaluation of the efficacy of etoricoxib in ankylosing spondylitis: results of a fifty-two-week, randomized, controlled study, Arthritis and rheumatism, 52, 1205-1215, 2005</td></tr>
<tr><td></td><td>Naproxen 500mg, twice daily
Placebo (part 1 only)
During part 1 patients received 3 bottles of study medication at randomisation and at weeks 2 and 4. Each bottle contained active medication or matching placebo. Patients also received acetaminophen (a rescue medication for breakthrough AS pain). During part 2, study medication was dispensed in blister cards, each containing active medication or matching placebo, for 7 days.</td></tr>
<tr><td>Characteristics</td><td>
<table>
<tr><td>Demographics</td><td>Placebo (n=93)</td><td>Etoricoxib 90mg (n=103)</td><td>Etoricoxib 120mg (n=92)</td><td>Naproxen 1g (n=99)</td><td>Total (n=387)</td></tr>
<tr><td>Female (%)</td><td>20.4</td><td>26.2</td><td>21.7</td><td>20.2</td><td>22.2</td></tr>
<tr><td>Age (mean, SD)</td><td>43.7 (12.1)</td><td>43.1 (12.1)</td><td>42.5 (12)</td><td>45 (11.4)</td><td>43.6 (11.9)</td></tr>
<tr><td>History of chronic peripheral arthritis (no, %)</td><td>37 (39.8)</td><td>41 (39.8)</td><td>36 (39.1)</td><td>41 (41.4)</td><td>155 (40.1)</td></tr>
<tr><td>History of corticosteroid use, no (%)</td><td>30 (32.3)</td><td>24 (23.3)</td><td>22 (23.9)</td><td>22 (22.2)</td><td>98 (25.3)</td></tr>
<tr><td>Concomitant DMARD use. no (%)</td><td>18 (19.4)</td><td>27 (26.2)</td><td>18 (19.6)</td><td>23 (23.2)</td><td>86 (22.2)</td></tr>
<tr><td>Baseline spine pain (100mm VAS), mean, (SD)</td><td>77.22 (15.24)</td><td>77.95 (13.94)</td><td>77.96 (14.16)</td><td>77.20 (16.45)</td><td>77.58 (14.92)</td></tr>
<tr><td>Patients global assessment of disease activity (100mm VAS), mean (SD)</td><td>64.26 (20.99)</td><td>63.19 (20.84)</td><td>64.29 (21.60)</td><td>64.65 (22.17)</td><td>64.08 (21.33)</td></tr>
<tr><td>BASFI (100mm VAS), mean, (SD)</td><td>54.12 (26.99)</td><td>56.89 (22.48)</td><td>55.23 (25.07)</td><td>54.09 (23.23)</td><td>55.11 (24.37)</td></tr>
</table>
</td></tr>
<tr><td>Results</td><td>Patients assessment of spine pain on VAS
<table>
<tr><td>End point</td><td>Placebo (n=93)</td><td>Etoricoxib 90mg (n=100)</td><td>Etoricoxib 120mg (n=90)</td><td>Naproxen 1000mg (n=97)</td></tr>
</table>
</td></tr>
</table>

<table>
<tr><th>Bibliographic reference</th><td>van der Heijde,Desiree, Baraf,Herbert S.B., Ramos-Remus,Cesar, Calin,Andrei, Weaver,Arthur L., Schiff,Michael, James,Margaret, Markind,Jan E., Reicin,Alise S., Melian,Agustin, Dougados,Maxime, Evaluation of the efficacy of etoricoxib in ankylosing spondylitis: results of a fifty-two-week, randomized, controlled study, Arthritis and rheumatism, 52, 1205-1215, 2005</td></tr>
<tr><td></td><td>
<table>
<tr><td>Patients assessment of spine pain on VAS (100mm)</td><td></td><td></td><td></td><td></td></tr>
<tr><td>6 weeks</td><td>-12.6 (2.3)</td><td>-41.5 (2.2)</td><td>-41.6 (2.4)</td><td>-33.7 (2.3)</td></tr>
<tr><td>1 year</td><td>-</td><td>-42.9 (2.2)</td><td>-43.7 (1.6)</td><td>-35.4 (2.3)</td></tr>
<tr><td>Patients global assessment of disease activity on VAS (100mm)</td><td></td><td></td><td></td><td></td></tr>
<tr><td>6 weeks</td><td>-3.4 (2.2)</td><td>-27.9 (2.1)</td><td>-26.6 (2.2)</td><td>-20.9 (2.1)</td></tr>
<tr><td>1 year</td><td>-</td><td>-29.5 (2.2)</td><td>-30.1(2.3)</td><td>-22.6 (2.2)</td></tr>
</table>

Discontinuations due to lack of efficacy
<table>
<tr><td></td><td>Placebo</td><td>90mg Etoricoxib</td><td>120mg Etoricoxib</td><td>1000mg Naproxen</td></tr>
<tr><td>6 weeks, n (%)</td><td>44 (47.3)</td><td>8 (7.8)</td><td>9 (9.8%)</td><td>20 (20.2)</td></tr>
<tr><td>1 year</td><td>-</td><td>10 (7.9)</td><td>12 (9.8)</td><td>22 (17.6)</td></tr>
</table>
Discontinuation due to adverse events
<table>
<tr><td></td><td>Placebo</td><td>90mg Etoricoxib</td><td>120mg etoricoxib</td><td>1000mg Naproxen</td></tr>
<tr><td>6 weeks</td><td>0</td><td>2 (1.9)</td><td>0</td><td>1 (1.0)</td></tr>
<tr><td>1 year</td><td>-</td><td>10 (7/9)</td><td>12 (9.8)</td><td>22 (17.6)</td></tr>
</table>
</td></tr>
<tr><td>Overall Risk of Bias</td><td>Allocation concealment not reported</td></tr>
<tr><td>Other information</td><td>Statistical analysis: modified intention to treat principle (i.e. inclusion of all patients in the analysis population for whom a baseline measurement and at least 1 post baseline measurement were available. Part 1 analysis undertaken on per protocol approach.
For part 1, the primary measures were a time weighted average of all measurements collected over the 6 week treatment period. The time weighted average changes from baseline and efficacy were analysed using ANOVA or ANCOVA, with treatment and presence/ absence of chronic peripheral arthritis as the main effects and baseline value as the covariate for end points measured at baseline.
Etoricoxib 120mg results reported here, but not included in final analysis as 120mg etoricoxib is not a licensed dose.</td></tr>
</table>

Bibliographic reference	van der Heijde,Desiree, Baraf,Herbert S.B., Ramos-Remus,Cesar, Calin,Andrei, Weaver,Arthur L., Schiff,Michael, James,Margaret, Markind,Jan E., Reicin,Alise S., Melian,Agustin, Dougados,Maxime, Evaluation of the efficacy of etoricoxib in ankylosing spondylitis: results of a fifty-two-week, randomized, controlled study, Arthritis and rheumatism, 52, 1205-1215, 2005
Was the allocation sequence adequately generated?	UNCLEAR
Was allocation adequately concealed?	UNCLEAR
Was knowledge of the allocated intervention adequately prevented during the study?	YES
Were incomplete outcome data adequately addressed?	YES
Are reports of the study free of suggestion of selective outcome reporting?	YES
Was the study apparently free of other problems that could put it at a high risk of bias?	YES

Table 159: Villa Alcazar et al., 1996

Bibliographic reference	Villa Alcazar,L.F., de Buergo,M., Rico Lenza,H., Montull Fruitos,E., Aceclofenac is as safe and effective as tenoxicam in the treatment of ankylosing spondylitis: a 3 month multicenter comparative trial. Spanish Study Group on Aceclofenac in Ankylosing Spondylitis, The Journal of rheumatology, 23, 1194-1199, 1996
Country/ies where the study was carried out	Spain, 16 centres involved in trial
Study type	Multicentre, double blind, parallel study

Bibliographic reference	**Villa Alcazar,L.F., de Buergo,M., Rico Lenza,H., Montull Fruitos,E., Aceclofenac is as safe and effective as tenoxicam in the treatment of ankylosing spondylitis: a 3 month multicenter comparative trial. Spanish Study Group on Aceclofenac in Ankylosing Spondylitis, The Journal of rheumatology, 23, 1194-1199, 1996**
Aim of the study	To compare efficacy and safety of NSAID aceclofenac 100mg bid orally with tenoxicam 20mg orally at bedtime in treatment of people with AS
Study dates	Not reported
Source of funding	Not reported
Sample size	n=273 (n=292 entered the washout period, n=19 withdrew because of insufficient control of symptoms or other reasons)
Inclusion criteria	Outpatients of both sexes, between 18-50 years of age, with defined clinical and radiological AS by New York criteria, eligible if at least 2 of the 3 following criteria were met: morning stiffness lasting 30 minutes or longer, pain requiring medication with NSAID and VAS pain of >40mm.
Exclusion criteria	People with other spondyloarthropathies or psoriasis, Paget's disease of the bone, gout, haemachromatosis and / or arthritis of any aetiology, patients with history of peptic ulcers of digestive haemorrhage caused by NSAID, patients with hypersensitivity to study drugs, patients with life expectancy of less than 2 years. Significant pulmonary, cardiac, cerebrovascular, hepatic or renal disease, pregnant women, nursing mothers, women of child bearing potential, anticoagulant therapy or other treatments that could interfere with the drugs under study, treatment with sulfasalazine, steroids or immunosuppressive drugs within the previous 3 months, concurrent pathologies or other circumstances that impeded the performance of trial controls.
Details	12 week trial. Suitable patients identified after a screening visit. Patients were withdrawn from all incompatible medication and thereafter started a washout period of 1 week, with the only drug allowed was paracetamol 500mg, up to 3 times daily to reduce pain. After the washout phase, patients were randomly assigned to receive Aceclofenac 100mg or tenoxicam. All medications were identical in appearance. Patients were evaluated after the washout period (baseline) days 15 and 30 and at months 2 and 3. Patients were recommended to take capsules after meals. Each medication unit was completed with emergency medication (paracetamol 500mg), presented in 3 bottles of 90 tablets, one bottle for each month of treatment.
Interventions	Aceclofenac (n=135) 100mg in morning and 100mg at bedtime. Tenoxicam (n=138)
Characteristics	Baseline characteristics: No significant differences observed between the groups regarding demographic and pre-trial AS severity data, clinical or analytical variables and frequency distribution. All patients were Caucasian. Parameter | Aceclofenac | Tenoxicam

<table>
<tr><th>Bibliographic reference</th><td>Villa Alcazar,L.F., de Buergo,M., Rico Lenza,H., Montull Fruitos,E., Aceclofenac is as safe and effective as tenoxicam in the treatment of ankylosing spondylitis: a 3 month multicenter comparative trial. Spanish Study Group on Aceclofenac in Ankylosing Spondylitis, The Journal of rheumatology, 23, 1194-1199, 1996</td></tr>
<tr><td></td><td>
<table>
<tr><td></td><td>n=135
mean, (SD) or N</td><td>n=138
mean, (SD) or N</td></tr>
<tr><td>Age (yrs)</td><td>37.4 (8.4)</td><td>37.1 (8.1)</td></tr>
<tr><td>Sex: m/f</td><td>112/23</td><td>106/32</td></tr>
<tr><td>Duration of disease (yrs)</td><td>6.3 (5.7)</td><td>5.4 (5.4)</td></tr>
</table>
</td></tr>
<tr><td>Results</td><td>Pain (VAS), mm
<table>
<tr><td></td><td>Aceclofenac (n=120)</td><td>Tenoxicam (n=115)</td></tr>
<tr><td>Baseline (mean scores)</td><td>57.9</td><td>58.1</td></tr>
<tr><td>Difference at end of therapy</td><td>-25.7*</td><td>-27.5*</td></tr>
<tr><td>% change from baseline</td><td>-44.5</td><td>-45.1</td></tr>
</table>
*Significance vs baseline p<0.01
Not clear whether Difference and % change outcomes were mean values.

Withdrawals due to adverse events
Aceclofenac (n=135): 3 (2%)
Tenoxicam (n=138): 2 (1%)
Withdrawals due to lack of efficacy of study drugs:
Aceclofenac (n=135): 8 (6%)
Tenoxicam (n=138): 7 (5%)</td></tr>
<tr><td>Other information</td><td>Sample size calculation based on outcome of morning stiffness, mean value of 50 mins with variance of 25 min after 3 months of treatment. Not clear what n required was.</td></tr>
<tr><td>Was the allocation sequence adequately generated?</td><td>UNCLEAR</td></tr>
<tr><td>Was allocation adequately concealed?</td><td>UNCLEAR</td></tr>
</table>

Bibliographic reference	Villa Alcazar,L.F., de Buergo,M., Rico Lenza,H., Montull Fruitos,E., Aceclofenac is as safe and effective as tenoxicam in the treatment of ankylosing spondylitis: a 3 month multicenter comparative trial. Spanish Study Group on Aceclofenac in Ankylosing Spondylitis, The Journal of rheumatology, 23, 1194-1199, 1996
Was knowledge of the allocated intervention adequately prevented during the study?	YES
Were incomplete outcome data adequately addressed?	UNCLEAR
Are reports of the study free of suggestion of selective outcome reporting?	NO
Was the study apparently free of other problems that could put it at a high risk of bias?	UNCLEAR

Table 160: Walker et al., 2016

Bibliographic reference	Walker,C., Essex,M.N., Li,C., Parl,P.W., Celecoxib versus diclofenac for the treatment of ankylosing spondylitis: 12-week randomized study in Norwegian patients, Journal of International Medical Research, 44(3), 483-95, 2016
Country/ies where the study was carried out	Norway, 16 centres involved in trial
Study type	Multicentre, double blind, parallel study
Aim of the study	To compare efficacy and safety of two different doses of celecoxib and diclofenac in the treatment of Norwegian patients with ankylosis spondylitis
Study dates	September 2002 to November 2004
Source of funding	Pfizer
Sample size	n=330
Inclusion criteria	Aged 18-75 with a diagnosis of ankylosis spondylitis (modified Ney York criteria) Active symptoms requiring daily treatment with NSAIDs during the 30 days prior to study entry
Exclusion criteria	Acute peripheral articular disease and/or ongoing extra-articular signs. Ulcerative colitis or Crohn's disease Endoscopy-confirmed gastroduodenal ulcer within the past year Gastrointestinal bleeding

<table>
<tr><th>Bibliographic reference</th><th>Walker,C., Essex,M.N., Li,C., Parl,P.W., Celecoxib versus diclofenac for the treatment of ankylosing spondylitis: 12-week randomized study in Norwegian patients, Journal of International Medical Research, 44(3), 483-95, 2016</th></tr>
<tr><td></td><td>Cardiac, renal or hepatic disease
Coagulation disorders
History of asthma
Known hypersensitivity to celecoxib, HSAIDs of sulphonamide medication</td></tr>
<tr><td>Details</td><td>12 week trial.
Suitable patients identified after a screening visit.
There was then a washout period before beginning the study drug</td></tr>
<tr><td>Interventions</td><td>200 mg of celecoxib once a day
400 mg of celecoxib once a day
50 mg of celecoxib three times a day</td></tr>
<tr><td>Characteristics</td><td>Mean age: 48 years
72% male
Mean time since diagnosis: 10.3 years
Other disease characteristics were similar across treatment groups (data not reported in paper)</td></tr>
<tr><td>Results</td><td>Pain (VAS), mm
<table>
<tr><td></td><td>Celecoxib 200mg</td><td>Celecoxib 400mg</td><td>Diclofenac</td></tr>
<tr><td>Baseline (mean scores)</td><td>61.3 (24.2)</td><td>57.9 (23.3)</td><td>62.0 (21.7)</td></tr>
<tr><td>Week 12</td><td>35.9 (26.3)</td><td>27.6 (23.4)</td><td>34.4 (25.7)</td></tr>
<tr><td>Change from baseline</td><td>-25.9 (2.5)</td><td>-33.1 (2.5)</td><td>-28.0 (2.4)</td></tr>
</table>

Withdrawals due to adverse events
Celecoxib 200mg: 12 (11.2%)
Celecoxib 400mg: 14 (13.0%)
Diclofenac: 15 (13.0%)</td></tr>
<tr><td>Was the allocation sequence adequately generated?</td><td>YES</td></tr>
<tr><td>Was allocation adequately concealed?</td><td>YES</td></tr>
<tr><td>Was knowledge of the allocated intervention</td><td>YES</td></tr>
</table>

Bibliographic reference	Walker,C., Essex,M.N., Li,C., Parl,P.W., Celecoxib versus diclofenac for the treatment of ankylosing spondylitis: 12-week randomized study in Norwegian patients, Journal of International Medical Research, 44(3), 483-95, 2016
adequately prevented during the study?	
Were incomplete outcome data adequately addressed?	UNCLEAR
Are reports of the study free of suggestion of selective outcome reporting?	YES
Was the study apparently free of other problems that could put it at a high risk of bias?	YES

E.3.5 Physical aids for spondyloarthritis

Review Question 18

What is the effectiveness of physical aids (for example, braces) compared with standard care for managing spondyloarthritis?

None

E.4 Surgical Interventions

Review Questions 34 and 35

- What factors predict clinical improvement after spinal surgery (including osteotomy and fusion) in people with axial inflammation?
- What factors predict clinical improvement after joint replacement surgery?

E.4.1 What factors predict clinical improvement after spinal surgery (including osteotomy and fusion) in people with axial inflammation?

No studies identified

E.4.2 What factors predict clinical improvement after joint replacement surgery?

Table 161: Lehtimaki et al, 2001

Bibliographic reference	Lehtimaki,M.Y., Lehto,M.U., Kautiainen,H., Lehtinen,K., Hamalainen,M.M., Charnley total hip arthroplasty in ankylosing spondylitis: survivorship analysis of 76 patients followed for 8-28 years, Acta Orthopaedica Scandinavica, 72, 233-236, 2001
Full citation	Lehtimaki,M.Y., Lehto,M.U., Kautiainen,H., Lehtinen,K., Hamalainen,M.M., Charnley total hip arthroplasty in ankylosing spondylitis: survivorship analysis of 76 patients followed for 8-28 years, Acta Orthopaedica Scandinavica, 72, 233-236, 2001
Ref Id	340117
Country/ies where the study was carried out	Finland
Study type	Case series; appears to be prospective, though this is not explicitly stated.
Aim of the study	To assess clinical outcome of Charnley total hip arthroplasty in ankylosing spondylitis.
Study dates	Operations performed between 1971 and 1991, with follow-up until the end of 1999.
Source of funding	Financial support was received from the Medical Research Fund of Tampere University Hospital, the Rheumatism Research Foundation and the Orthopedic and Traumatologic Research Fund.
Sample size	76 operations in 54 patients.
Diagnostic criteria	Not provided.
Inclusion criteria	Patients undergoing Charnley total hip arthroplasty for ankylosing spondylitis.
Exclusion criteria	Not provided.
Characteristics	

	Male (n = 37)	Female (n = 17)	All (n = 54)
Number of hips	54	22	76
Age (years), mean±SD	38±11	44±16	40±13
Weight (kg), mean±SD	64±10	57±12	62±11
Number on steroids	18	5	23
Number with amyloidosis	4	1	5
Preoperative bleeding (ml/kg/min), mean±SD	0.22±0.07	0.30±0.14	0.24±0.10
Duration of operation (mins), mean±SD	92±20	80±24	89±22

Consecutive recruitment?	Yes.
Surgical intervention	Total hip arthroplasty using Charnley's method.

<table>
<tr><th>Bibliographic reference</th><th>Lehtimaki,M.Y., Lehto,M.U., Kautiainen,H., Lehtinen,K., Hamalainen,M.M., Charnley total hip arthroplasty in ankylosing spondylitis: survivorship analysis of 76 patients followed for 8-28 years, Acta Orthopaedica Scandinavica, 72, 233-236, 2001</th></tr>
<tr><td></td><td>Cement was applied with the prevailing contemporary methods during the study period.
In the 1970s: surface preparation, removal of loose debris and control of bleeding with manual impaction of the cement.
In the 1980s: high-pressure pulse lavage, an intramedullary plug and a cement-gun to pressurise the cement in a retrograde fashion from the intramedullary plug.
In the 1990s: pressurisation of the acetabulum and a flanged cup introduced.
All Charnley stems were of the original nonmodular design, chosen for each individual patient to match the anatomical dimensions and femoral medullary cavity.
Trochanteric osteotomy was in use until 1985 and after that, the direct lateral approach.
All patients were operated on in the supine position.
Antibiotic prophylaxis was given for 3 days.
Postoperatively, they were encouraged to walk with protected weight bearing for 2 months, or for 6 months if bone grafts had been used.</td></tr>
<tr><td>Type and definition of surgical outcome(s)</td><td>Revision of the Charnley arthroplasty due to loosening of the prosthetic components.
Radiographic loosening was defined as migration of the component, fracture of the cement or the component, or a complete radiolucent line more than 2 mm in thickness.</td></tr>
<tr><td>Prognostic factors examined</td><td>Age, sex, weight, use of steroids and preoperative bleeding.</td></tr>
<tr><td>Analysis</td><td>Proportional hazard model</td></tr>
<tr><td>Reported data and analyses</td><td>
<table>
<tr><td>Variable</td><td>Hazard ratio (95% CI)</td><td>P value</td></tr>
<tr><td>Age (per year)</td><td>0.98 (0.95 to 1.01)</td><td>0.2</td></tr>
<tr><td>Sex (female)</td><td>1.70 (0.66 to 4.40)</td><td>0.3</td></tr>
<tr><td>Weight (per kg)</td><td>1.03 (0.99 to 1.07)</td><td>0.2</td></tr>
<tr><td>Steroids</td><td>1.23 (0.82 to 1.83)</td><td>0.3</td></tr>
<tr><td>Bleeding (>median)</td><td>0.85 (0.37 to 1.98)</td><td>0.7</td></tr>
</table>
</td></tr>
<tr><td>Reviewer calculations</td><td>None.</td></tr>
<tr><td>Sample sufficiently represents the population of interest with regard to key characteristics?</td><td>Yes.</td></tr>
</table>

Bibliographic reference	Lehtimaki,M.Y., Lehto,M.U., Kautiainen,H., Lehtinen,K., Hamalainen,M.M., Charnley total hip arthroplasty in ankylosing spondylitis: survivorship analysis of 76 patients followed for 8-28 years, Acta Orthopaedica Scandinavica, 72, 233-236, 2001
Loss to follow-up sufficiently unrelated to key characteristics?	Yes.
Prognostic factor adequately defined and measured?	Yes.
Outcome of interest adequately defined and measured?	Yes.
Important potential confounders appropriately accounted for?	Univariate analysis.
Statistical analysis appropriate?	Yes, although univariate only.

Table 162: Thilak et al, 2015

Bibliographic reference	Thilak, J., Pahakkal,J.J., Kim,T., Goodman,S.M., Lee,S., Salvati,E.A., Risk factors of heterotopic ossification following total hip arthroplasty in patient with ankylosing spondylitis, 30, 2307-7, 2015
Full citation	Thilak, J., Pahakkal,J.J., Kim,T., Goodman,S.M., Lee,S., Salvati,E.A., Risk factors of heterotopic ossification following total hip arthroplasty in patient with ankylosing spondylitis, 30, 2307-7, 2015
Country/ies where the study was carried out	South Korea
Study type	Retrospective case series.
Aim of the study	To investigate the risk factors of heterotopic ossification after total hip arthroplasty in ankylosing spondylitis
Study dates	February 2003 to January 2012.
Source of funding	No details provided.
Sample size	Initial inclusion: 47 hips in 20 patients
Diagnostic criteria	Modified New York diagnostic criteria
Inclusion criteria	Modified New York diagnostic criteria and under treatment by a rheumatologist. Primary total hip arthroplasty.
Exclusion criteria	Not provided.
Characteristics	Mean (range) follow-up = 54.8 months (32 to 129 months) Sex: 6 women, 18 men

<table>
<tr><th>Bibliographic reference</th><th>Thilak, J., Pahakkal,J.J., Kim,T., Goodman,S.M., Lee,S., Salvati,E.A., Risk factors of heterotopic ossification following total hip arthroplasty in patient with ankylosing spondylitis, 30, 2307-7, 2015</th></tr>
<tr><td></td><td>Mean (SD) age at entry into study = 36 years (8.75)
Mean (SD) duration of symptoms = 7.2 years (1.65)
Mean (SD) interval between surgeries = 9.7 months (10.30)
Mean (SD) duration of surgery = 107.7 minutes (15.24)</td></tr>
<tr><td>Consecutive recruitment?</td><td>Unclear</td></tr>
<tr><td>Surgical intervention</td><td>Total hip arthroplasty.
Modified Hardinge (30 hips) or posterior approach (17 hips)
All performed without trochanteric detachment, with perioperative parenteral antibiotics and thromboembolic prophylaxis with low molecular weight heparin given to all patients.</td></tr>
<tr><td>Type and definition of surgical outcome(s)</td><td>Heterotopic ossification</td></tr>
<tr><td>Prognostic factors examined</td><td>Patient-related factors: Age, duration of symptoms, preoperative hip ankyloses, occurrence of heterotopic ossification in previous total hip arthroplasty, preoperative ESR, preoperative CRP
Surgery-related factors: interval between both THAs, duration of surgery, type of anaesthesia, type of implant</td></tr>
<tr><td>Analysis</td><td>Stepwise logistic regression, performed separately on modifiable and non-modifiable risk factors.</td></tr>
<tr><td>Reported data and analyses</td><td>Non-modifiable risk factors:
<table>
<tr><td>Characteristics</td><td>No heterotopic ossification (n=40)</td><td>Heterotopic ossification (n=7)</td><td>OR (95%</td></tr>
<tr><td>Age (years)</td><td>36.6 (8.6)</td><td>31.4 (8.0)</td><td>0.90 (0.79</td></tr>
<tr><td>Duration of symptoms (years)</td><td>7.4 (1.6)</td><td>6.5 (1.9)</td><td>0.72 (0.39</td></tr>
<tr><td>Male</td><td>33</td><td>2</td><td></td></tr>
<tr><td>Female</td><td>7</td><td>5</td><td>11.79 (1.8</td></tr>
<tr><td>No Preoperative hip ankylosis</td><td>33</td><td>0</td><td></td></tr>
<tr><td>Preoperative hip ankylosis</td><td>7</td><td>7</td><td>67.00 (3.4</td></tr>
<tr><td>No heterotopic ossification in previous THA</td><td>19</td><td>0</td><td></td></tr>
<tr><td>Heterotopic ossification in previous THA</td><td>3</td><td>2</td><td>37.86 (1.0</td></tr>
</table>
Modifiable risk factors:</td></tr>
</table>

Bibliographic reference	Thilak, J., Pahakkal,J.J., Kim,T., Goodman,S.M., Lee,S., Salvati,E.A., Risk factors of heterotopic ossification following total hip arthroplasty in patient with ankylosing spondylitis, 30, 2307-7, 2015

Characteristics	No heterotopic ossification (n=40)	Heterotopic ossification (n=7)	OR (95% CI)
Preoperative ESR	29.8 (11.5)	46.0 (8.8)	1.12 (1.03, 1.21)
Preoperative CRP	7.6 (5.7)	17.1 (3.8)	1.27 (1.08, 1.48)
Interval between THAs (months)	6.6 (8.2)	15 (14.6)	1.06 (0.97, 1.18)
Duration of surgery (minutes)	105 (14.4)	123.1 (10.3)	1.12 (1.02, 1.23)
General anaesthesia	20	6	
Combined spinal epidural anaesthesia	20	1	0.17 (0.02, 1.51)
Uncemented implant	7	2	
Hybrid implant	14	3	0.75 (0.10, 5.58)
Cemented implant	14	2	0.50 (0.06, 4.33)

Sample sufficiently represents the population of interest with regard to key characteristics?	Yes, although information provided was limited
Loss to follow-up sufficiently unrelated to key characteristics?	Yes
Prognostic factor adequately defined and measured?	Unclear
Outcome of interest adequately defined and measured?	Yes
Important potential confounders appropriately accounted for?	Multivariate analysis used
Statistical analysis appropriate?	Yes, although diagnostic accuracy results are not presented

Table 163: Zhao et al, 2014

Bibliographic reference	Zhang,L., Yang,D., Yin,X., Zhou,Y., Risk factors for poor hip flexion after total hip arthroplasty for the treatment of ankylosing spondylitis a multivariate analysis, Clinical rheumatology, 33, 1295-1301, 2014
Country/ies where the study was carried out	China
Study type	Retrospective case series.
Aim of the study	To investigate the clinical and radiographic results of total hip arthroplasty for the treatment of ankylosing spondylitis, and to evaluate the effects of patient-, prosthesis design- and surgical technique-related risk factors on postoperative functional results.
Study dates	September 2001 to January 2009.
Source of funding	No details provided.
Sample size	Initial inclusion: 181 hips in 107 patients Available for follow-up (minimum 2 years): 167 hips in 100 patients
Diagnostic criteria	Not provided.
Inclusion criteria	Patients who underwent total hip arthroplasties performed to treat ankylosing spondylitis between September 2001 and January 2009. The indications for total hip arthroplasty included severe pain, limited motion and posture, and deformity.
Exclusion criteria	Not provided.
Characteristics	Mean (range) follow-up = 54.8 months (32 to 129 months) Sex: 19 women, 81 men Mean (range) age at onset of ankylosing spondylitis = 15.3 years (10 to 42 years) Mean (range) age at time of total hip arthroplasty = 36.4 years (17 to 69 years Mean (range) interval between onset of ankylosing spondylitis and surgery = 12.0 years (8.0 to 20.0 years) Mean (range) body mass index = 22.4 (13.7 to 34.1) No patient had any prior surgery on the involved hip.
Consecutive recruitment?	Yes.
Surgical intervention	Total hip arthroplasty. Prosthesis selection: all acetabular components used were cementless cups and were routinely implanted using the press-fit technique. A ceramic-on-ceramic bearing surface was used in 84 hips, a ceramic-on-polyethylene bearing surface on 54 hips, and cobalt-chrome heads on a polyethylene bearing surface in 29 hips. No patients received prophylaxis against heterotopic ossification.

Bibliographic reference	**Zhang,L., Yang,D., Yin,X., Zhou,Y., Risk factors for poor hip flexion after total hip arthroplasty for the treatment of ankylosing spondylitis a multivariate analysis, Clinical rheumatology, 33, 1295-1301, 2014**
Type and definition of surgical outcome(s)	Good hip flexion: >90° Poor hip flexion: <90°
Prognostic factors examined	Patient-related factors: sex, age at onset of ankylosing spondylitis, age at total hip arthroplasty, interval between onset and treatment, body mass index, degree of preoperative flexion contracture, degree of preoperative passive hip flexion, preoperative hip range of motion, acetabular protrusion, ankylosis, femoral neck-shaft angle, obturator foramen ratio, preoperative erythrocyte sedimentation rate, preoperative C-reactive protein level, and postoperative heterotopic ossification. Prosthesis-related factors: use of a 32-mm femoral head and use of an elevated liner.
Analysis	A univariate analysis was performed to assess whether each variable of interest was associated with poor hip flexion after total hip arthroplasty, using independent sample t tests or Mann-Whitney tests for continuous variables and chi-squared tests for dichotomous variables, respectively. A multivariate logistic regression model was then used to assess the risk factors identified as significant in the univariate analysis.
Reported data and analyses	Patient-related factors:

	Poor flexion group (n = 68)	Good flexion group (n = 99)	Univariate analysis P value	Multivariate analysis OR (95% CI)	Multivariate analysis P value
Female sex	13.2%	22.2%	0.142	-	-
Age at onset (mean±SD, years)	21.7± 8.2	21.6 ±8.1	0.528	-	-
Age at surgery (mean±SD, years)	37.9± 12.3	35.4 ±11.4	0.171	-	-
Interval between onset and surgery (mean, range)	12.0 (8.0 to 24.0)	12.0 (7.0 to 20.0)	0.135	-	-
Body mass index (mean±SD)	22.1 ±8.2	22.5± 4.6	0.528	-	-
Degree of preoperative flexion contracture (mean±SD)	21.9 ±18.9	14.7 ±17.2	0.011	0.976 (0.957 to 0.996)	0.018
Degree of preoperative passive hip flexion (mean±SD)	16.0± 26.4	27.6± 36.0	0.025	-	-

Bibliographic reference	Zhang,L., Yang,D., Yin,X., Zhou,Y., Risk factors for poor hip flexion after total hip arthroplasty for the treatment of ankylosing spondylitis a multivariate analysis, Clinical rheumatology, 33, 1295-1301, 2014

Preoperative range of motion (mean±SD)	23.3± 39.3	43.6 ±57.7	0.012	-	-
Acetabular protrusion	4.4%	12.1%	0.087	-	-
Ankylosis	64.7%	51.5%	0.091	-	-
Femoral neck-shaft angle	141.9 ±13.2	139.0± 16.2	0.211	-	-
Obturator foramen ratio	1.38± 0.26	1.30± 0.26	0.058	-	-
Preoperative erythrocyte sedimentation rate (mean±SD, mm/h)	29.9± 25.8	26.8± 21.3	0.395	-	-
Preoperative C-reactive protein level (mean±SD, mg/l)	31.0± 37.8	20.6 ±18.0	0.019	0.981 (0.968 to 0.994)	0.004
Postoperative heterotopic ossification	64.3%	35.7%	<0.001	0.237 (0.106 to 0.530)	<0.001

Prosthesis-related factors:

	Poor flexion group (n = 68)	Good flexion group (n = 99)	Univariate analysis P value	Multivariate analysis OR (95% CI)	Multivariate analysis P value
32-mm femoral head	25.4%	74.6%	0.001	3.902 (1.817 to 8.377)	<0.001
Elevated liner	49.4%	50.6%	0.023	-	-

Reviewer calculations	note: only performed for dichotomous prognostic factor data Reviewer calculations derived from data as follows: TP = n(FACTOR and good outcome) FP = n(FACTOR and poor outcome) FN = n(no FACTOR and good outcome)

Bibliographic reference	Zhang,L., Yang,D., Yin,X., Zhou,Y., Risk factors for poor hip flexion after total hip arthroplasty for the treatment of ankylosing spondylitis a multivariate analysis, Clinical rheumatology, 33, 1295-1301, 2014
	TN = n(no FACTOR and poor outcome) Female sex Poor flexion = 13.2% = 9 of 68 Good flexion = 22.2% = 22 of 99 Female sex as a predictor of good surgical outcome: TP = 22 FP = 9 FN = 77 TN = 59 Sensitivity (95% CI) = 22.2% (14.0 to 30.4%) Specificity (95% CI) = 86.8% (78.7 to 94.8%) Acetabular profusion Poor flexion = 4.4% = 3 of 68 Good flexion = 12.1% = 12 of 99 Acetabular profusion as a predictor of good surgical outcome: TP = 12 FP = 3 FN = 87 TN = 65 Sensitivity (95% CI) = 12.1% (5.7 to 18.6%) Specificity (95% CI) = 95.6% (90.7 to 100%) Ankylosis Poor flexion = 64.7% = 44 of 68 Good flexion = 51.5% = 51 of 99 Ankylosis as a predictor of good surgical outcome: TP = 51

Bibliographic reference	Zhang,L., Yang,D., Yin,X., Zhou,Y., Risk factors for poor hip flexion after total hip arthroplasty for the treatment of ankylosing spondylitis a multivariate analysis, Clinical rheumatology, 33, 1295-1301, 2014
	FP = 44 FN = 48 TN = 24 Sensitivity (95% CI) = 51.5% (41.7 to 61.4%) Specificity (95% CI) = 35.3% (23.9 to 46.7%) Heterotopic ossification Poor flexion = 64.3% = 44 of 68 Good flexion = 35.7% = 35 of 99 Heterotopic ossification as a predictor of good surgical outcome: TP = 35 FP = 44 FN = 64 TN = 24 Sensitivity (95% CI) = 35.4% (25.9 to 44.8%) Specificity (95% CI) = 35.3% (23.9 to 46.7%) Use of a 32-mm femoral head Poor flexion = Good flexion = Use of a 32-mm femoral head as a predictor of good surgical outcome: TP = 74 FP = 17 FN = 25 TN = 51 Sensitivity (95% CI) = 74.8% (66.2 to 83.3%) Specificity (95% CI) = 75.0% (64.7 to 85.3%) Use of an elevated liner Poor flexion = 49.4% = 36 of 68 Good flexion = 50.6% = 50 of 99 Use of an elevated liner as a predictor of good surgical outcome:

Bibliographic reference	Zhang,L., Yang,D., Yin,X., Zhou,Y., Risk factors for poor hip flexion after total hip arthroplasty for the treatment of ankylosing spondylitis a multivariate analysis, Clinical rheumatology, 33, 1295-1301, 2014
	TP = 50 FP = 36 FN = 49 TN = 32 Sensitivity (95% CI) = 50.5% (40.7 to 60.4%) Specificity (95% CI) = 47.1% (35.2 to 58.9%)
Sample sufficiently represents the population of interest with regard to key characteristics?	Unclear (limited information provided)
Loss to follow-up sufficiently unrelated to key characteristics?	Unclear
Prognostic factor adequately defined and measured?	Unclear
Outcome of interest adequately defined and measured?	Limited information provided
Important potential confounders appropriately accounted for?	Multivariate analysis used
Statistical analysis appropriate?	Yes, although data not reported as diagnostic test accuracy outcomes; this was calculated by the reviewer

Table 164: Zhao et al, 2014

Bibliographic reference	Zhao,J., Li,J., Zheng,W., Liu,D., Sun,X., Xu,W., Low body mass index and blood loss in primary total hip arthroplasty: Results from 236 consecutive ankylosing spondylitis patients, BioMed Research International, 2014, -, 2014
Country/ies where the study was carried out	China
Study type	Retrospective case series.

Bibliographic reference	**Zhao,J., Li,J., Zheng,W., Liu,D., Sun,X., Xu,W., Low body mass index and blood loss in primary total hip arthroplasty: Results from 236 consecutive ankylosing spondylitis patients, BioMed Research International, 2014, -, 2014**
Aim of the study	To evaluate the effect of low body mass index on blood loss during primary total hip arthroplasty in ankylosing spondylitis patients.
Study dates	December 2006 to June 2012.
Source of funding	No details provided.
Sample size	277 patients considered for inclusion. 236 patients were eligible for study inclusion (41 patients were excluded due to incomplete data (n = 10) or because they were undergoing bilateral procedures simultaneous to the total hip arthroplasty (n = 31)).
Diagnostic criteria	No details provided.
Inclusion criteria	Patients with ankylosing spondylitis undergoing total hip arthroplasty. The surgical indications were as follows: Bath Ankylosing Spondylitis Radiology Hip Index (BASRI-hip) ≥3, obvious impairment of hip function, and no surgical contraindications.
Exclusion criteria	Not provided.
Characteristics	

	Underweight group (n = 91)	Normal weight group (n = 145)	P value
Mean age±SD, years	36±8	37±8	0.485
Male:female	76:15	126:19	0.472
BMI	17.0±1.3	21.9±1.6	<0.001
Mean blood volume±SD, l	3.92±0.65	4.56±0.56	<0.001
Mean disease duration±SD, years	13±4	12±6	0.100
Mean Bath Ankylosing Spondylitis Disease Activity Index score±SD	5.2±0.8	5.3±0.8	0.334
Mean Bath Ankylosing Spondylitis Functional Index score±SD	5.5±0.7	5.0±0.8	<0.001
Bath Ankylosing Spondylitis Radiology Hip Index score 4:3	56:35	87:58	0.841
Osteoporosis:nonosteoporosis	15:91	10:145	0.020
Mean thromboplastin time±SD, seconds	13.1±0.6	13.1±0.8	0.876
Mean activated partial thromboplastin time±SD, second	36.8±2.9	36.9±3.3	0.808

Bibliographic reference	Zhao,J., Li,J., Zheng,W., Liu,D., Sun,X., Xu,W., Low body mass index and blood loss in primary total hip arthroplasty: Results from 236 consecutive ankylosing spondylitis patients, BioMed Research International, 2014, -, 2014			
	Mean preoperative hemoglobin±SD, g/l	127±16	128±15	0.227
	Mean preoperative hematocrit±SD, %	38±4	39±4	0.090
	Mean preoperative platelet count±SD, x109/l	252±62	248±59	0.527
	Mean preoperative albumin±SD, g/l	37±4	37±3	0.073
Consecutive recruitment?	Yes			
Surgical intervention	The operations were performed by the same surgery team; the surgical technique was standardized, and general anaesthesia was used for all patients. All procedures were carried out with the patients in the lateral position. The posterolateral approach and the same haemostasis techniques were used for all patients. To reduce postoperative blood loss, external wound compression was used without drainage for 48 hours after surgery. To prevent infection, cefuroxime sodium was routinely applied for 24 hours perioperatively. The postoperative venous thromboembolic prophylaxis included mechanical prophylaxis with thromboembolic disease stockings and was commenced immediately after surgery and continued for 5 weeks. NSAIDs were interrupted two weeks before surgery. The transfusion triggers were a haemoglobin concentration less than 80 g/L and a haematocrit below 25%. For patients > 60 years old, a haemoglobin concentration below 100 g/L was a transfusion trigger. Allogeneic blood transfusion was performed when it was required based on the triggers, and salvage of autologous blood was not used preoperatively.			
Type and definition of surgical outcome(s)	Blood loss: Perioperative total blood loss was estimated based on the Hb balance method. Intraoperative blood loss was determined by the assistant as the sum of gauze weighted plus the difference between the suction and irrigation volumes. The postoperative hidden blood loss was calculated as the difference between the total blood loss and the intraoperative blood loss. The ratio of blood loss and blood volume was used as the criterion for evaluating blood loss for individuals in this study. Wound healing Length of hospital stay			
Prognostic factors examined	Weight Body mass index was calculated based on the World Health Organization criteria. The patients were divided into two groups based on weight: the underweight group included 91 patients (BMI < 18.5 kg/m2)			

Bibliographic reference	Zhao,J., Li,J., Zheng,W., Liu,D., Sun,X., Xu,W., Low body mass index and blood loss in primary total hip arthroplasty: Results from 236 consecutive ankylosing spondylitis patients, BioMed Research International, 2014, -, 2014
	the normal weight group included 145 patients (18.5 kg/m2 < BMI < 25 kg/m2)
Analysis	Univariate analysis using Student's t-test and the chi-square test. Differences were considered statistically significant with P < 0.05.
Reported data and analyses	

	Underweight group (n = 91)	Normal weight group (n = 145)	P val
Mean operating time±SD, mins	60±11	61±8	0.984
Mean diameter of acetabular cup±SD, mm	52.0±2.2	52.4±2.0	0.092
Mean intrablood loss/blood volume±SD, %	10±1	10±2	0.277
Mean hidden blood loss/blood volume±SD, %	15±1	13±3	<0.00
Mean total blood loss/blood volume±SD, %	25±2	23±4	<0.00
Number to undergo transfusion	75	98	0.012
Mean length of external wound compression±SD, hours	35±7	43±6	<0.00
Number to experience poor healing of the incision	6	8	0.733
Number to experience early infection	0	0	-
Number to experience dislocation	0	0	-

Reviewer calculations	note: only performed for dichotomous prognostic factor data Reviewer calculations derived from data as follows: TP = n(no. underweight with poor outcome) FP = n(no. underweight with good outcome) FN = n(no. normal weight with poor outcome) TN = n(no. normal weight with good outcome) Number to undergo transfusion Underweight group = 75 of 91 Normal weight group = 98 of 145 Being underweight as a predictor of transfusion: TP = 75

Bibliographic reference	Zhao,J., Li,J., Zheng,W., Liu,D., Sun,X., Xu,W., Low body mass index and blood loss in primary total hip arthroplasty: Results from 236 consecutive ankylosing spondylitis patients, BioMed Research International, 2014, -, 2014
	FP = 16 FN = 98 TN = 47 Sensitivity (95% CI) = 43.4% (36.0 to 50.7%) Specificity (95% CI) = 74.6% (63.9 to 85.4%) Poor healing of incision Underweight group = 6 of 91 Normal weight group = 8 of 145 Being underweight as a predictor of poor healing of incision: TP = 6 FP = 85 FN = 8 TN = 137 Sensitivity (95% CI) = 42.9% (16.9 to 68.8%) Specificity (95% CI) = 61.7% (55.3 to 68.1%)
Sample sufficiently represents the population of interest with regard to key characteristics?	Unclear (limited information provided)
Loss to follow-up sufficiently unrelated to key characteristics?	Yes
Prognostic factor adequately defined and measured?	Yes
Outcome of interest adequately defined and measured?	Yes
Important potential confounders appropriately accounted for?	Univariate analysis only

Bibliographic reference	Zhao,J., Li,J., Zheng,W., Liu,D., Sun,X., Xu,W., Low body mass index and blood loss in primary total hip arthroplasty: Results from 236 consecutive ankylosing spondylitis patients, BioMed Research International, 2014, -, 2014
Statistical analysis appropriate?	Yes, although data not reported as diagnostic test accuracy outcomes; this was calculated by the reviewer

E.5 Organisation of care and long-term monitoring

E.5.1 Transition to adult services for young people with spondyloarthritis

Review questions 13

- How should transition from specialist paediatric services to specialist adult rheumatology services be managed for young people between the ages of 16 and 18?

None

E.5.2 Monitoring of pharmacological interventions used in spondyloarthritis

Review Question 22

- What is the usefulness of direct access to specialist care, compared with initial primary care access followed by specialist rheumatological care, in the management of flare episodes?

None

E.5.3 Care setting for management of flare episodes

Review Question 29

- What is the usefulness of direct access to specialist care, compared with initial primary care access followed by specialist rheumatological care, in the management of flare episodes?

None

E.5.4 Care setting for long-term management

Review Question 30

- What is the effectiveness of specialist-led long-term management of spondyloarthritis compared with primary-care-led long-term management?

None

E.5.5 Cross-speciality care

Review Question 31

- How should cross-speciality care for people with spondyloarthritis be organised?

None

E.5.6 Complications of spondyloarthritis

Review Question 32

- What are the long-term complications associated with spondyloarthritis?

Table 165: Summary of results from studies which reported either frequency of events or frequency of affected people in studies where people were assessed at more than one time point.

Author (year)	Study type	Population	n participants	Follow up period	Complication	Outcome measure
Ischemic heart disease						
Chou (2014)	Retrospective cohort	ankylosing spondylitis	25,048	maximum of 9 years	acute coronary syndrome	584 incident cases Incidence rate= 2.90 per 1000 person-years
Brophy (2012)	Retrospective cohort	ankylosing spondylitis	1686	15,620.6 person years	acute myocardial infarction	40 incident cases Incidence rate = 25.6 per 10,000 person years
Hung (2016)	Prospective cohort	ankylosing spondylitis	537	5 years	coronary heart disease	57 incident cases, (10.6%)
Haroon (2015)	Retrospective cohort	ankylosing spondylitis	21,473	166,920 person-years	vascular death (either from cardiovascular or cerebrovascular disease)	170 cases Mortality rate 1.018 per 1,000 person years
Edson-Heredia (2015)	Retrospective cohort	psoriatic arthritis	1,952	mean 3.0 years (SD 1.3)	acute myocardial infarction	incidence rate 0.15 per 100 persons (CI 0.14 to 0.16)
Aortic valve insufficiency						
Jantti (2002)	Prospective population-based study	psoriatic arthritis	19	8 years, 23 years	Aortic valve insufficiency	2 cases detected at 23 years (10.5%)

Author (year)	Study type	Population	n participants	Follow up period	Complication	Outcome measure
Kaarela (2009)(b)	Prospective population-based study	reactive arthritis	60 at baseline and 8 years; 50 at 20 years; 40 at 30/32 years	8 years, 20 years, 30/32 years(b)	Aortic valve insufficiency	1 patient died of aortic valve insufficiency at an unspecified time point.
Stroke/cerebrovascular events						
Brophy (2012)	Retrospective cohort	ankylosing spondylitis	1686	15,673.6 person years	CVD/stroke composite measure	37 incident cases Incidence rate = 23.6 per 10,000 person years
Hung (2016)	Prospective cohort	ankylosing spondylitis	537	5 years	cerebrovascular disease	49 cases (9.1%)
Keller (2014)	Retrospective cohort	ankylosing spondylitis	2,895	unclear. Measured from AS diagnosis till end of study for each subject	stroke	10.505 per 1,000 person years
Edson-Heredia (2015)	Retrospective cohort	psoriatic arthritis	1,952	mean 3.0 years (SD 1.3)	stroke	incidence rate 0.10 per 100 persons (CI 0.09 to 0.11)
Zoller (2012)	Prospective cohort	ankylosing spondylitis	2,416	up to 21 years	haemorrhagic stroke	6 cases within 1 year, 15 cases between 1-5 years, 7 cases between 5-10 years, 14 cases after 10 years
					ischaemic stroke	8 cases within 1 year, 44 cases between 1-5 years, 24 cases between 5-10 years, 35 cases after 10 years
		reactive arthritis	280	up to 21 years	haemorrhagic stroke	0 cases within 1 year, 1 cases between 1-5 years, 1 cases between 5-10 years, 0 cases after 10 years
					ischaemic stroke	0 cases within 1 year, 5 cases between 1-5 years, 6 cases between 5-10 years, 2 cases after 10 years
Uveitis/iritis						

Author (year)	Study type	Population	n participants	Follow up period	Complication	Outcome measure
Egeberg (2015)	Retrospective cohort	psoriatic arthritis	6,735	29,140.6 person years	uveitis	16 incident cases incidence rate of 5.40 per 10,000 person years (3.36 to 8.96)
Hart (1986)	Prospective cohort	reactive arthritis	111 approached, 98 available for follow up.	mean average disease duration 7.9 years	iritis	18 cases (18.4%)
Kaarela (2009)	Prospective population-based study	reactive arthritis	60 at baseline and 8 years; 50 at 20 years; 40 at 30/32 years	8 years, 20 years, 30/32 years(b)	Iritis	4 cases at baseline (6.7%), 6 new cases at 8 years (10%); 1 new case at 20 years (2%); 1 new case at 30/32 years (2.5%)
		ankylosing spondylitis	22 at 8 years; 9 at 20 years	8 years, 20 years	Iritis	2 cases before baseline, 4 patients with multiple episodes (44.4%)(c) [Assumed to be at the 20 year follow up but unclear]
Fracture						
Weinstein (1982)	Retrospective cohort	ankylosing spondylitis	105	6 years	acute spinal fracture	13 cases
Munoz-Ortego (2014)	Retrospective cohort	ankylosing spondylitis	6,474	6 years	clinical vertebral fractures	56 cases Incidence rate 2.12 per 1,000 years
Maillefert (2001)	Prospective longitudinal study	ankylosing spondylitis	54	6, 12, 18, 24 months (only 24 months reported)	Fracture	2 cases (3.7% at 24 months)
Kang (2014)	Prospective cohort	ankylosing spondylitis	298 at baseline, 287 at 2 year follow-up, 131 at 4	2 years, 4 years	Vertebral fracture	30 new VFs in 26 patients (10.8% at baseline, 4.7% at 2 years; 13.6% at 4 years)

Author (year)	Study type	Population	n participants	Follow up period	Complication	Outcome measure
			year follow –up			
Osteoporosis/osteopenia						
Maillefert (2001)	Prospective longitudinal study	ankylosing spondylitis	54	6, 12, 18, 24 months (only 24 months reported)	Osteoporosis, lumbar spine	8 cases (17% at 24 months)
					Osteoporosis, femoral neck	6 cases (11% at 24 months)
					Osteopenia, lumbar spine	19 cases (39% at 24 months)
					Osteopenia, femoral neck	21 cases (39% at 24 months)
Inflammatory bowel disease						
Edson-Heredia (2015)	Retrospective cohort	psoriatic arthritis	1,952	mean 3.0 years (SD 1.3)	Crohn's disease	incidence rate 0.02 per 100 persons (CI 0.01 to 0.02)
Mielants (1995)	Prospective cohort	spondyloarthritis	217	mean 5.7 years	inflammatory bowel disease	11 cases
Depression						
Shen (2016)	Retrospective cohort	ankylosing spondylitis	2331	median follow up of 5.99 years	depression	73 cases of depression (3.1% of cohort)
Edson-Heredia (2015)	Retrospective cohort	psoriatic arthritis	1,952	mean 3.0 years (SD 1.3)	depression	incidence rate 1.07 per 100 persons (CI 1.04 to 1.10)
Psoriasis/pustulosis palmoplantaris						
Theander (2014)	Prospective registry study	Psoriatic arthritis	197 with 5 years follow up data available (114 women, 83 men)	5 years	Psoriasis (skin), men	138 (both timepoints combined), (88.9% at baseline, 80.5% at 5 years)

Author (year)	Study type	Population	n participants	Follow up period	Complication	Outcome measure
					Psoriasis (skin), women	168 (both timepoints combined), (76.1% at baseline, 66.7% at 5 years)
					Psoriasis (nail), men	55 (both timepoints combined), (30.9% at baseline, 36.6% at 5 years)
					Psoriasis (nail), women	63 (both timepoints combined), (33.3% at baseline, 23.4% at 5 years)
					Pustulosis palmoplantaris, men	5 (both timepoints combined), (4.9% at baseline, at baseline, 1.2% at 5 years)
					Pustulosis palmoplantaris, women	5 (both timepoints combined), (16.8% at baseline, 7.2% at 5 years)
Jantti (2002)	Prospective population-based study	Psoriatic arthritis	19	8 years, 23 years	Psoriasis	10 cases detected at 23 years (52.6%)
Surgery						
Kaarela (2009)	Prospective population-based study	Reactive arthritis	60 at baseline and 8 years; 50 at 20 years; 40 at 30/32 years	8 years, 20 years, 30/32 years(b)	Surgery	1 case at baseline (1.7%), 1 new case at 8 years (1.7%); 2 new cases at 20 years (4%), 1 new case at 30/32 years (2.5%)
		Ankylosing spondylitis	22 at 8 years; 9 at 20 years	8 years, 20 years	Surgery	4 joint/tendon operations (44.4%) [Assumed to be at the 20 year follow up but unclear]

E.5.7 Complications of treatments for spondyloarthritis

Review Question 33

- What are the complications associated with treatments for spondyloarthritis?

Table 166: Summary of included studies for RQ33, complications of treatment, non-registry studies – unless otherwise specified, percentages are given as percentage of people in the study who had the event

Reference, diagnosis	Follow-up, number, country	Drugs involved	AEs reported included in review protocol	Outcomes
Baraliakos (2013) Ankylosing spondylitis	7 years N=26 Germany	Etanercept 2x25mg s.c./week	Uveitis	44% of people (7/16) developed uveitis during the 7 years of treatment. 10 dropped out: moving (2), lack of efficacy (2), heart discomfort, development of Crohn's disease, reactivation of Crohn's disease, heart discomfort, lung carcinoma, death (heart attack)
Bianchi (2006) Psoriatic arthritis	102 years N=34 Italy	Infliximab 5mg/kg at weeks 0, 2, 6, then every 8 weeks	Infections	No serious adverse events reported
Braun (2005) Ankylosing spondylitis	5 years N=52 Germany	Infliximab, IV, 5mg/kg, every 6wks	Infections	Infection: Common cold , 41% of AEs, Bronchitis, 11% of AEs Infection considered to represent a serious AE: Vaginal infection, N=1 Repeated upper RTI, N=1
Costa (2014) Psoriatic arthritis and untreated HCV infection	24 months N=15 Italy	Adalimumab 40mg s.c. every 2 weeks Etanercept 50mg s.c. every week	Hepatitis	No hepatitis reactivations No significant increase in viral load

Reference, diagnosis	Follow-up, number, country	Drugs involved	AEs reported included in review protocol	Outcomes
Davis (2005) and Davis (2008) Ankylosing spondylitis	192 weeks N=257 Canada, several European sites	Etanercept, 25mg x2/week for 72 weeks, after week 72 50mg x1/week (x2 25mg injections)	Infections, uveitis, depression, rash	Week 96: (only reported detail on AEs experienced by ≥5%) Infection: Serious infectious episodes, all resolved, N=5 (2%) Conjunctivitis, N=19 (7%) Rash, N=28 (11%) Depression, N=18 (7%) Uveitis, N=17 (6%) Week 192: Infections, N=187 (72.8), number of events 642 (upper respiratory tract 45% of infections, sinusitis 16%, flu 15%, bronchitis 11%) Serious infections, N=6 (2.3%), upper RTI, sinusitis, flu syndrome, bronchitis, TB Uveitis, 62 flares, 10 new incidences (30% had a history of uveitis) Depression, N=3 incidences
de Vlam (2015) Psoriatic arthritis	5.5 years N=301 Belgium (PROVE study)	Etanercept (dose not specified)	Infections, malignancy	5 cases of leukaemia (1.7%) 4 cases of malignancy (2 rectal cancer, 1 breast cancer, 1 lung adenocarcinoma) – 2 considered related to treatment 13 serious infections (4.3%) – 1 case of herpes zoster ophthalmic considered related to treatment
Deodhar (2015) Ankylosing spondylitis	5 years N=356 Multi-national (GO-RAISE)	Golimumab 50mg or 100mg every 4 weeks	Infections, malignancy	4 cases of pneumonia (1.1%) 4 cases of depression (1.1%) 1 case of pancreatic cancer (0.3%) 2 cases of non-melanoma skin cancer (0.6%) 21 cases of serious infection (5.9%)
Fouache (2009)	Retrospective cohort	Infliximab Etanercept Adalimumab	Uveitis	Uveitis: N=3 (with etanercept), frequency 1/100 patient years

Reference, diagnosis	Follow-up, number, country	Drugs involved	AEs reported included in review protocol	Outcomes
Ankylosing spondylitis Psoriatic arthritis	N=198, AS N=77, PsA France			
Gladman (2011) Psoriatic arthritis	24 months N=110 Canada	Etanercept, 50mg/week as x2 injections at separate sites or 2 injections on separate days	Infection, malignancy, skin rash	Infection: Nasopharyngitis, N=20 (18.2%) Upper RTI, N=15 (13.6%) Influenza-like illness, N=11 (10) Sinusitis, N=11 (10%) Viral pneumonia, streptococcal infection, abdominal abscess, appendicitis, all N=1 (0.9%) Malignancy, N=3 (2.7%) Lung neoplasm, malignant melanoma, malignant pleural effusion, all N=1 Skin rash, N=2 (1.8%)
Gossec (2006) Ankylosing spondylitis	2 years N=50 France	Infliximab, IV 5mg/kg 0,2 and 6weeks, infusions of 5mg/kg maintained as needed based on appearance of flare according to patient status (maximum frequency every 4weeks)	Malignancy, infection, dermatological manifestations	Infection: Bronchitis, 28% of AEs Upper RTI, 24% of AEs Dermatological manifestations, 24% of AEs (included pruritus, rash or fungal infections)
Heldman (2011) Ankylosing spondylitis	2 years N=103 6 European sites (including UK)	Infliximab every 6-8 weeks, 4-6mg/kg, so long as dosages between 3-10mg/kg and intervals of 4-12 weeks	Infections, malignancies, TB, uveitis	Infection, N=257 AEs (47.2% of AEs) Upper RTI, N=178 (69.3% of all infections) GI, N=29 (11.3% of all infections) Urogenital, N=17 (6.6% of all infections) Skin, N=18 (7.0% of all infections) Other, N=15 (5.8% of all infections)

Reference, diagnosis	Follow-up, number, country	Drugs involved	AEs reported included in review protocol	Outcomes
				Dermatological, N=41 AEs Uveitis, N=8 case in N=4 patients (only 1 new onset), 2.6/100 patient years Malignancy, N=0 TB, N=0 Opportunistic infections, N=0
Kavanaugh (2014) Psoriatic arthritis	252 weeks N=405 Multi-national (GO-REVEAL)	Golimumab, 50 or 100mg every 4 weeks	Infections, TB, malignancy	Infection: Serious infections N=15 (3.8%) 19 serious infections; 0.67 (0.34 to 1.20) per 100 patient years Opportunistic infections N=4, all 100mg group, (pulmonary TB and legionella pneumonia, histoplasmosis, eye toxoplasmosis, herpes zoster) Malignancy, N=21 Non-melanoma skin cancer N=10; 0.61 (0.29 to 1.12) per 100 patient years Other N=10 (breast N=2, small cell lung N=2, prostate N=1, oesophageal N=1, colon N=3, bladder N=2)
Kavanaugh (2015) Psoriatic arthritis	88 weeks N=615 Multi-national	Ustekinumab 45mg or 90mg at week 0 and 4, then every 12 weeks	Infections, cardiovascular, malignancy	11 cases of serious infection (1.8%) 7 major adverse cardiovascular events (1.2%) – 1 stroke, 1 ischaemic stroke, 5 myocardial infarctions 4 malignancies (0.7%) – 1 B-cell lymphoma, 1 basal cell carcinoma, 1 renal cell carcinoma, 1 squamous cell carcinoma
Mease (2016) Psoriatic arthritis	96 weeks N=409 Multi-national (RAPID-PsA trial)	Certolizumab 200 mg every 2 weeks or 400mg every 4 weeks	Infections, malignancy	16 serious infections (4.1%) – Pneumonia, HIV, erysipelas, UTI 4 malignancies (1.0%) – 2 breast cancer, 1 lymphoma, 1 cervix carcinoma

Reference, diagnosis	Follow-up, number, country	Drugs involved	AEs reported included in review protocol	Outcomes
Park (2016) Ankylosing spondylitis	54 weeks N=250 Multinational (PLANETAS study)	Infliximab or CT-P13 biosimilar 5mg/kg at week 0, 2, 6, then every 8 weeks	Infections	3 cases of TB (1.2%) 4 cases of herpes virus infection (1.6%)
Sengupta (2015) Ankylosing spondylitis	3 years N=25 India	Infliximab on demand – average dose of 3.28mg/kg when BASDAI≥4 (every 28.9 weeks)	TB	1 case of extrapulmonary TB (4%)
Sieper (2015) Axial spondyloarthritis	96 weeks N=315 Multi-national (RAPID-axSPA trial)	Certolizumab 200 mg every 2 weeks or 400mg every 4 weeks	Infections	12 serious infections (3.8%) 1 case of active TB (0.3%)
Song (2014) Axial spondyloarthritis	3 years 61 people Germany (ESTHER study)	Etanercept (dose not specified)	Infections	No serious adverse events reported
Tong (2015) Ankylosing spondylitis	2 years 172 people China	Etanercept, infliximab (dose not specified)	Infections	13 cases of pneumonia (7.6%) 6 cases of TB (3.5%)

Reference, diagnosis	Follow-up, number, country	Drugs involved	AEs reported included in review protocol	Outcomes
van der Heijde (2009) Ankylosing spondylitis	2 years N=311 RCT in 43 sites, Europe, USA	Adalimumab , s/c 40mg every other week, in the extension study 24mg every other week for up to 4.5 years; those with inadequate response 40mg every week	Infections, rash, uveitis, malignancies, TB, demyelinating disease	Infection: Nasopharyngitis, N=80 (25.7%) Upper RTI, N=53 (17%) Sinusitis, N=30 (9.6%) Influenza, N=23 (7.4%) Viral infection, N=19 (6.1%) Serious infections; N=6 (1.9%), N=3 considered possibly/probably related to study drug (N=1 each of cellulitis, pneumonia, rectal abscess) Rash, N=17 (5.5%) Uveitis, N=12 (3.9%) – N=3 new onset, N=12 flares (N=94/311 who had at least 1 dose of adalimumab had a history of uveitis) Malignancy, N=4 (1.3%), 0.7 per 100 patient/years (N=1 for each of basal-cell carcinoma, malignant melanoma, non-Hodgkin's lymphoma, squamous cell carcinoma of the skin – non-Hodgkin's considered possibly related to study drug) TB, N=0 Demyelinating disease, N=0
Westhovens (2014) Spondyloarthritis	4 years N=231 Belgium	Etanercept (51%), infliximab (38%), adalimumab (9%) and golimumab (2%)	Malignancy	6 cases of malignancy (2.6%) – 3 breast cancer, 1 bladder cancer, 1 malignant mesothelioma, 1 basocellular carcinoma of the skin

Table 167: Summary of included studies for RQ33, registry studies – unless otherwise specified, percentages are given as percentage of people in the study who had the event

<table>
<tr><th>Reference, diagnosis</th><th>Follow-up, number, country</th><th>Drugs involved</th><th>AEs reported included in review protocol</th><th>Outcomes</th></tr>
<tr>
<td>Carmona (2006)

Ankylosing spondylitis
Psoriatic arthritis
Undifferentiated spondyloarthritis</td>
<td>BIOBADSER registry

N=657, AS
N=570, PsA
N=187, undifferentiated
Spain</td>
<td>Arthritis duration, mean±SD;
AS, 12±8
PsA, 9±7
Undifferentiated, 8±7

Infliximab, etanercept, adalimumab

2000-2005</td>
<td>Infection, neoplastic, ophthalmologic, neurological</td>
<td>Infection;
<table>
<tr><th colspan="2">Infliximab (1915 patient years)</th><th colspan="2">Etanercept (507 patient years)</th><th colspan="2">Adalimumab (5.7 patie years)</th></tr>
<tr><th>Cases</th><th>Incidence rate (95%CI)</th><th>Cases</th><th>Incidence rate (95%CI)</th><th>Cases</th><th>Incidence rate (95%CI)</th></tr>
<tr><td>102</td><td>5.87 (4.83 to 7.13)</td><td>5</td><td>1.01 (0.42 to 2.43)</td><td>1</td><td>18.90 (2.66 to 134.14)</td></tr>
</table>
Neoplastic;
<table>
<tr><th colspan="2">Infliximab (1915 patient years)</th><th colspan="2">Etanercept (507 patient years)</th><th colspan="2">Adalimumab (5.7 pati years)</th></tr>
<tr><th>Cases</th><th>Incidence rate (95%CI)</th><th>Cases</th><th>Incidence rate (95%CI)</th><th>Cases</th><th>Incidence rate (95%CI)</th></tr>
<tr><td>6</td><td>0.35 (0.16 to 0.77)</td><td>1</td><td>0.20 (0.03 to 1.4)</td><td>0</td><td>-</td></tr>
</table>
Ophthalmologic;
<table>
<tr><th colspan="2">Infliximab (1915 patient years)</th><th colspan="2">Etanercept (507 patient years)</th><th colspan="2">Adalimumab (5.7 patie years)</th></tr>
<tr><th>Cases</th><th>Incidence rate (95%CI)</th><th>Cases</th><th>Incidence rate (95%CI)</th><th>Cases</th><th>Incidence rate (95%CI)</th></tr>
<tr><td>4</td><td>0.23 (0.09 to 0.61)</td><td>0</td><td>-</td><td>0</td><td>-</td></tr>
</table>
Neurological;
<table>
<tr><th>Infliximab (1915 patient years)</th><th>Etanercept (507 patient years)</th><th>Adalimumab (5.7 patie years)</th></tr>
</table>
</td>
</tr>
</table>

<table>
<tr><th>Reference, diagnosis</th><th>Follow-up, number, country</th><th>Drugs involved</th><th>AEs reported included in review protocol</th><th>Outcomes</th></tr>
<tr><td></td><td></td><td></td><td></td><td>
<table>
<tr><td>Cases</td><td>Incidence rate (95%CI)</td><td>Cases</td><td>Incidence rate (95%CI)</td><td>Cases</td><td>Incidence rate (95%CI)</td></tr>
<tr><td>5</td><td>0.29 (0.12 to 0.69)</td><td>1</td><td>0.20 (0.03 to 1.43)</td><td>0</td><td>-</td></tr>
</table>
</td></tr>
<tr><td>Haynes (2013)

Ankylosing spondylitis
Psoriatic arthritis</td><td>Registry data, 4 sources

N=783, AS (N=703 comparator drug)
N=1036, PsA (N=1462 comparator drug)
USA</td><td>Arthritis duration not reported

Infliximab, adalimumab, etanercept

1998-2007</td><td>Cancer</td><td>Incidence rates per 100 person-years;
Any lymphoma (drug and comparator groups), 0
Any lymphoma or leukaemia (drug and comparator groups), 0
Any solid cancer:
PsA; drug 0.77 (N=8), comparator 0.81 (N=7), HR 0.88 (95%CI 0.39 to 1.98)
AS; drug 0.44 (<5), comparator 0.44 (<5), HR 0.15 (95%CI 0.03 to 0.76)
Non-melanoma skin cancer:
PsA; drug 0.29 (<5), comparator 0.34 (<5), HR 2.65 (95%CI 0.33 to 21.07)
AS; drug 0.15 (<5), comparator 0.73 (<5), HR 0.57 (95%CI 0.13 to 2.58)</td></tr>
<tr><td>Hellgren (2014)

Ankylosing spondyloarthritis
Psoriatic arthritis</td><td>National registry data

N=8,707, AS
N=19,283, PsA
Sweden</td><td>Arthritis duration not reported

TNFi treated (≥1 period of therapy)

1998-2007</td><td>Lymphoma</td><td>Lymphoma
<table>
<tr><td></td><td>No. of lymphomas, AS (person time)</td><td>Crude incidence (95%CI) per 100,000person years</td><td>No. of lymphomas, PsA (person time)</td><td>Crude incidence (95%CI) per 100,000person years</td></tr>
<tr><td>Overall</td><td>11 (39640)</td><td>28 (14 to 50)</td><td>37 (83468)</td><td>44 (31 to 61)</td></tr>
<tr><td>TNFi treated</td><td>2 (7028)</td><td>28 (3 to 102)</td><td>5 (9600)</td><td>52 (17 to 122</td></tr>
<tr><td>Non-TNFi treated</td><td>9 (32882)</td><td>27 (12 to 52)</td><td>32 (74230)</td><td>43 (29 to 61)</td></tr>
</table>
(person time = days of follow-up)</td></tr>
<tr><td>Jung (2015)

Ankylosing spondylitis</td><td>10 years (average)

N=4,260

South Korea</td><td>Etanercept, infliximab or adalimumab (dose not specified)</td><td>TB</td><td>45 cases of TB in AS (1.1%)
1 case of TB in PsA (0.9%)
IRR for AS and PsA lower than for RA and IBD
IRR for Etanercept lower than for adalimumab and infliximab</td></tr>
</table>

<table>
<tr><th>Reference, diagnosis</th><th>Follow-up, number, country</th><th>Drugs involved</th><th>AEs reported included in review protocol</th><th>Outcomes</th></tr>
<tr><td>Kim (2014)

Ankylosing spondylitis</td><td>7 years (average)

N=336

South Korea</td><td>Etanercept (40%), adalimumab (37%), infliximab (19%), golimumab (3%) and certolizumab (0%)</td><td>TB</td><td>7 cases of TB in AS (2.1%)
7 cases of TB in RA (3.2%) – equivalent registry</td></tr>
<tr><td>Kristensen (2015)

Ankylosing spondylitis
Spondyloarthritis</td><td>1.5 years (average)

N=21,872

Sweden</td><td>Etoricoxib, celecoxib, nonselective NSAIDs, no treatment</td><td>Cardiovascular, renal</td><td>
<table>
<tr><th>Event</th><th>NS NSAIDs</th><th>Etoricoxib</th><th>Celecoxib</th><th>Non-expose</th></tr>
<tr><td>Atherosclerotic CV event</td><td>Ref</td><td>0.6 (0.2, 1.7)</td><td>0.5 (0.2, 1.6)</td><td>0.9 (0.5,1.4)</td></tr>
<tr><td>Atherosclerotic cerebrovascular</td><td>Ref</td><td>1.3 (0.4, 4.3)</td><td>1.6 (0.5, 4.9)</td><td>1.3 (0.8, 2.3</td></tr>
<tr><td>Severe hypertension</td><td>Ref</td><td>0.8 (0.5, 1.4)</td><td>0.9 (0.5, 1.6)</td><td>1.0 (0.7, 1.3</td></tr>
<tr><td>Congestive heart failure</td><td>Ref</td><td>0.9 (0.3, 3.5)</td><td>0.5 (0.1, 3.0)</td><td>2.0 (1.3, 3.2</td></tr>
<tr><td>GI (perforation, ulcer, bleeding)</td><td>Ref</td><td>1.3 (0.6, 2.7)</td><td>0.8 (0.3, 2.2)</td><td>0.5 (0.3, 0.7</td></tr>
<tr><td>Renal insufficiency</td><td>Ref</td><td>1.2 (0.3, 5.6)</td><td>N/A</td><td>1.2 (0.7, 2.4</td></tr>
</table>
</td></tr>
<tr><td>Pena-Sagredo (2009)

Spondyloarthropathies</td><td>BIOBADSER registry

N=1525</td><td>Arthritis duration not reported

Biologic therapies

2001-2006</td><td>Salmonella</td><td>N=3/17 cases, incidence rate 0.7 (95%CI; 0.2 to 2.3)</td></tr>
<tr><td>Saad (2010)

Psoriatic arthritis</td><td>Registry BSRBR

N=596

UK</td><td>Arthritis duration mean 12.4 (SD 8.7)</td><td>Infections, TB, neoplasms, nervous system disorders</td><td>Infections, N=53 (all anti-TNF), 11.2 (10.3 to 12.1) per 1000 person years, adjusted IRR (control group as reference) 0.7 (0.5 to 1.1)
TB, N=0
Serious opportunistic infection, N=1 (herpes simplex, infliximab group)</td></tr>
</table>

Reference, diagnosis	Follow-up, number, country	Drugs involved	AEs reported included in review protocol	Outcomes
		Etanercept, s/c, 25mg x2/week or 50mg x1/week Adalimumab, s/c 40mg, every 2weeks Infliximab, IV, 5mg/kg, 0,2,6 and 8wees, then every 8weeks (recommended given with methotrexate) 2002-2006		Neoplasms, N=14 (2.3%), incidence rate 18.1 (95%CI, 15.9 to 20.5)/1000 person years (incidence rate ration 1.0 (0.5 to 2.2)
Wallis (2015) Axial spondyloarthritis	3.89 years (average) N=440 Canada	Anti-TNFs, DMARDs, glucocorticoids	Infections	ORs for infection DMARDs 1.76 (1.12, 2.76) Glucocorticoids 1.10 (0.54, 2.26) Biologics 1.25 (0.90, 1.73) “The rate of serious infections in this axial SpA cohort is lower when compared with rheumatoid arthritis”
Zisman (2016) Psoriatic arthritis	12 years (average) N=3,128 Israel	Anti-TNFs, DMARDS	Infections	HRs for herpes zoster infection DMARDs 1.11 (0.76, 1.62) Anti-TNFs 1.28 (0.69, 2.40) DMARDs + anti-TNFs 2.37 (1.32, 4.22)

E.6 Information for people with spondyloarthritis

E.6.1 Information for people with spondyloarthritis

Review Question 27

- What information on treatment, long-term complications and self-management do young people and adults with spondyloarthritis find useful?

Table 168: Cooksey et al., 2012

Bibliographic reference	Cooksey,R., Brophy,S., Husain,M.J., Irvine,E., Davies,H., Siebert,S., The information needs of people living with ankylosing spondylitis: a questionnaire survey, BMC Musculoskeletal Disorders, 13, 243-, 2012
Country/ies where the study was carried out	UK
Study type	Questionnaire survey
Aim of the study	To provide the participants with information about AS and to examine the information needs and preferences of people with AS by exploring participant access, usage and opinion of available sources of AS information.
Study dates	Not reported
Source of funding	Medical Research Council (Patient Research Cohort Initiative)
Sample size	Questionnaires were completed by 211 out of 418 participants.
Inclusion criteria	People with AS who were resident in Wales were recruited to the PAS (population-based AS study) cohort through their general practitioner (GP), rheumatologist, membership of the National Ankylosing Spondylitis Society (NASS), or through physiotherapy.
Exclusion criteria	Not reported
Diagnostic criteria	Not reported
Characteristics	Male - n/N (%): 171/211 (81.0) Age in years - mean (SD): 57 (13)

<table>
<tr><th>Bibliographic reference</th><th>Cooksey,R., Brophy,S., Husain,M.J., Irvine,E., Davies,H., Siebert,S., The information needs of people living with ankylosing spondylitis: a questionnaire survey, BMC Musculoskeletal Disorders, 13, 243-, 2012</th></tr>
<tr><td></td><td>Duration of disease in years - mean (SD): 23 (14)
Member of support group: Not reported</td></tr>
<tr><td>Details</td><td>Participants asked to complete a postal or online questionnaire about information needs, developed by a team of researchers and a rheumatologist at Swansea University. Participants were reminded by post or via email to complete the questionnaire, up to a total of two times in an attempt to improve participation rates. The questionnaire consisted of open and close-ended questions.
Scores for the questionnaire items were calculated as means and standard deviations. The responses to open ended questionnaire items were explored for patterned responses and emerging themes using thematic analysis.</td></tr>
<tr><td>Interventions</td><td>Not applicable</td></tr>
<tr><td>Missing data handling/loss to follow up</td><td>Questionnaires were completed by 211 out of 418 participants</td></tr>
<tr><td>Results</td><td>Quantitative:
Internet:
<table>
<tr><td></td><td>n/N (%)</td></tr>
<tr><td>Used the internet for information about AS</td><td>103/211 (49)</td></tr>
<tr><td>(Of those) frequency of online AS information searching reported as “every 6 months or less”</td><td>60/211 (58)</td></tr>
<tr><td>Used the internet for information about AS (age 20-39)</td><td>17/22 (77)</td></tr>
<tr><td>Used the internet for information about AS (age 60+)</td><td>40/112 (36)</td></tr>
<tr><td>Found the currently available online AS information as ‘helpful’</td><td>90/114 (79)</td></tr>
<tr><td>Would like to see provided on the internet: - summaries of the latest research and medications</td><td>95/155 (61)</td></tr>
<tr><td>Would like to see provided on the internet: - the opportunity to ask a doctor questions</td><td>66/155 (43)</td></tr>
<tr><td>Would like to see provided on the internet: - AS networking</td><td>39/155 (25)</td></tr>
</table>
Written information:</td></tr>
</table>

Bibliographic reference	Cooksey,R., Brophy,S., Husain,M.J., Irvine,E., Davies,H., Siebert,S., The information needs of people living with ankylosing spondylitis: a questionnaire survey, BMC Musculoskeletal Disorders, 13, 243-, 2012

	n/N (%)
Reported obtaining written information on AS	105/211 (50)
Info obtained from: hospital clinics	70/211 (33)
Info obtained from: national charities	39/211 (18)
Info obtained from: GP surgeries	25/211 (12)
Info obtained from: libraries	7/211 (3)
Info obtained from: books or other places	5/211 (2)
Would like to receive a regular or occasional newsletter about AS	157/166 (95)
Would like to see (in AS newsletters): - summaries of the latest AS research	138/211 (65)
Would like to see (in AS newsletters): - stories and experiences from other AS patients	90/211 (43)
Would like to see (in AS newsletters): - an opportunity to ask a doctor about questions	74/211 (35)
Would like to see (in AS newsletters): - information about local events	56/211 (27)

Non-written information sources:

Source of non-written or non-electronic information:	n/N (%)
Rheumatologist	117/209 (56)
GP	77/209 (37)
Nursing and physiotherapy team	68/209 (35)
Friends and family	41/209 (20)

Qualitative:

Other information that people would like to see on the internet included help-lines, practical information about dealing with AS and a facility whereby patients could contact the rheumatology clinic they attend, although the numbers reporting these were small.

Bibliographic reference	Cooksey,R., Brophy,S., Husain,M.J., Irvine,E., Davies,H., Siebert,S., The information needs of people living with ankylosing spondylitis: a questionnaire survey, BMC Musculoskeletal Disorders, 13, 243-, 2012
	Participants appear to favour practical information, medication information and self-help guidance over purely factual information about the disease course itself and would like to see such information contained in AS newsletters. Participants felt that information on the disease itself was readily available and reading it would not change their outcome and as such, was of limited help to them. Thematic analyses revealed that older participants more frequently reported that they were happy with the level of AS information available and that they did not want any more information. All age groups expressed the view that GP knowledge and support, access to specialist healthcare professionals and services, AS groups or advice from others and updates of current news and research could be improved. When asked about how AS information and support could be improved, the most commonly reported recommendation was for improved access to AS specialists and services. Many participants stated that they were happy with the current level of AS information available to them. However, participants would like to see improved GP knowledge and support and improved public awareness about AS. Quotes from comments made by respondents in the Information Needs Questionnaire: Reasons for not accessing AS information online: Don't need further information: “I do not need to know any further information as I am already informed.” (Male, aged 70) “I think that there is enough information via leaflets, AS sites and health sites.” (Female, aged 43) “. . .I do not need to keep reading things. I know I have a stiff back but do not need to keep reading about things.” (Male, aged 51) Don't want further information: “Having AS is bad enough, I don’t want to read about it!” (Male, aged 62) “Don’t always feel like [using internet for AS information].” (Female, aged 50) “all doom and gloom”. (Male, aged 32) Don’t trust the information “It is difficult to know which sites to trust” (Male, aged 37)“ “Possible safety implications [discourage me from accessing AS information online]”. (Female, aged 65) Dislike Internet “I don’t use the internet or a computer as I think it is the biggest backward set mankind has ever made.” (Male, aged 62)

Bibliographic reference	Cooksey,R., Brophy,S., Husain,M.J., Irvine,E., Davies,H., Siebert,S., The information needs of people living with ankylosing spondylitis: a questionnaire survey, BMC Musculoskeletal Disorders, 13, 243-, 2012
	"A load of rubbish on it." (Male, aged 64) Time constraints "I have an 18 month old that keep me busy – no time." (Female, aged 38) "Can be time consuming – too much info." (Male, aged 51) Don't think to look for information "Don't always think about looking as I have had AS for so long." (Female, aged 50) "[Looking up AS online] Does not occur to me generally." (Female, aged 71) Prefer information from professional "I prefer to talk to a professional, face to face." (Male, aged 55) "I feel supported by my rheumatologist and have never felt the need to turn to anyone else. . ." (Female, aged 65) Confusing information, do not understand "Difficult to understand [information]." (Male, aged 63) "Not understanding properly what [information] I need." (Female, aged 40) Suggestions for improving information and support: Improved access to professionals/services "More available access to AS professionals - I see physio once a year if I am lucky." (Female, aged 44) "A more efficient means of accessing medical help. I have waited for up to 18 months to see a consultant." (Male, aged 66) "The main issue is access to specialists. GPs often seem to know little about conditions such as AS and my consultants AS clinic (which is very good) only takes place every 3–6 months. There is a need to be able to discuss issues arising from flare-ups while they are occurring - not weeks or months later," (Male, aged 37). Happy with current level of AS Information "I am happy now with the information I receive. However when I was really bad it was very hard to get to the people I needed to see." (Female, 49) "Satisfied with the information and support that I have received." (Female, 62) "As of the moment I am more than happy with the excellent level of support received from the rheumatology department at my local hospital - A veritable breath of fresh air, thank you." (Male, 55) Improved GP knowledge and support "GP knows little about AS. GPs should be better informed and show interest at least." (Male, aged 60) "Doctors that listen to you when you tell them that you get back pain so painful it gives me breathing problems." (Male, aged 29) "I don't always find GPs very knowledgeable about AS and sometimes they are quite dismissive of the condition." (Female, aged 29) AS groups or advice from others

Bibliographic reference	Cooksey,R., Brophy,S., Husain,M.J., Irvine,E., Davies,H., Siebert,S., The information needs of people living with ankylosing spondylitis: a questionnaire survey, BMC Musculoskeletal Disorders, 13, 243-, 2012
	"Swapping stories and self-help, get AS sufferers to socialise with each other." (Male, aged 34) "A helpline for people to contact for help e.g. for backup about the disease in relation to sickness claims and advice on drugs." (Male, aged 47) Information on cause and treatment "Generally greater information on the cause of AS and the known treatments available. Plus what new treatments are coming onto the market or will be available in the near future." (Male, aged 46) More written information "I would buy from book shops but I have never seen any books on AS." (Male, aged 50) "I think the leaflets on AS should be displayed in GP surgeries or Hospitals. There are ones on Arthritis but nothing for AS." (Male, aged 77) More electronic information "Better (more comprehensive) internet facility." (Male, aged 41) "Regular emails to provide recent findings and other peoples experiences," (Male, aged 36). Updates to current news/research "Updates regarding new treatments or therapies." (Male, aged 66) "Regular feedback from health professionals as to research and different treatments available." (Male, aged 46) Better public awareness "Not many people understand AS so if information was presented in simple language more people could have a better understanding of what people with AS suffer." (Female, aged 61) "I think it would be a good idea to make people aware of AS through the media, perhaps then people would not shrug off an aching back for weeks on end before getting checked out. . ." (Male, aged 61) "More understanding from everyone, just even if people were more aware as with other inflammatory diseases." (Male, aged 29)
1.1 Is a qualitative approach appropriate?	Appropriate
1.2 Is the study clear in what it seeks to do?	Clear
2.1 How defensible/rigorous is the research design/methodology?	Not sure
3.1 How well was the data collection carried out?	Appropriate

Bibliographic reference	Cooksey,R., Brophy,S., Husain,M.J., Irvine,E., Davies,H., Siebert,S., The information needs of people living with ankylosing spondylitis: a questionnaire survey, BMC Musculoskeletal Disorders, 13, 243-, 2012
4.1 Is the context clearly described?	Clear
4.2 Were the methods reliable?	Reliable
5.1 Are the data 'rich'?	Rich
5.2 Is the analysis reliable?	Reliable
5.3 Are the findings convincing?	Convincing
5.4 Are the conclusions adequate?	Adequate
6.1 Was the study approved by an ethics committee?	Yes
6.2 Is the role of the researcher clearly described?	Not sure / not reported
Overall Risk of Bias	Overall risk of bias seems low. However, the researchers noted that "the sample was not representative of the whole PAS cohort as younger individuals participated less." Additionally, although the survey was administered by post or online, there is no indication as to what proportion of the respondents completed it via each method. There was also fairly low response rate (50%), but there was an effort to contact non-responders.
Other information	n/a

Table 169: Dragoi et al., 2013

Bibliographic reference	Dragoi,R.G., Ndosi,M., Sadlonova,M., Hill,J., Duer,M., Graninger,W., Smolen,J., Stamm,T.A., Patient education, disease activity and physical function: can we be more targeted? A cross sectional study among people with rheumatoid arthritis, psoriatic arthritis and hand osteoarthritis, Arthritis Research & Therapy, 15, R156-, 2013
Country/ies where the study was carried out	Austria
Study type	Survey

Bibliographic reference	**Dragoi,R.G., Ndosi,M., Sadlonova,M., Hill,J., Duer,M., Graninger,W., Smolen,J., Stamm,T.A., Patient education, disease activity and physical function: can we be more targeted? A cross sectional study among people with rheumatoid arthritis, psoriatic arthritis and hand osteoarthritis, Arthritis Research & Therapy, 15, R156-, 2013**
Aim of the study	To develop an educational needs assessment tool, explore the educational needs of patients with rheumatoid arthritis, psoriatic arthritis and hand arthritis and to search relationships between educational needs, gender, age and disease activity and functional ability.
Study dates	Not reported
Source of funding	European League Against Rheumatism
Sample size	Psoriatic arthritis N = 125
Inclusion criteria	Patients with psoriatic arthritis diagnosed according to criteria described by Moll and Wright, and by McGonagle et al.
Exclusion criteria	Comorbidity with a rheumatic or neuromotor disease, inability to understand language or study procedures and unwillingness to participate.
Diagnostic criteria	Patients with psoriatic arthritis diagnosed according to criteria described by Moll and Wright, and by McGonacle et al.
Characteristics	Male - n/N (%): 56/123 (45) Age in years - mean (SD): 51 (10.5) Duration of disease in years - mean (SD): 11 (10.9) Member of supported group: Not reported
Details	An existing educational needs assessment tool (ENAT; self-report questionnaire) was adapted into German following established cross-cultural adaptation processes. It was then assessed for validity and reliability. The validated tool was then used in a cross-sectional survey to assess the relationship between educational needs, disease activity and function. Patients were asked to complete the tool at a routine visit to the rheumatology outpatient clinic. The questionnaire included 39 items grouped into 7 domains (e.g. managing pain, movement, feelings etc.), each item was rated on a Likert scale of 1 (not important at all) to 4 (extremely important).
Interventions	Not applicable
Missing data handling/loss to follow up	Not reported
Results	Reported education needs Domain (score range) | Mean (SD) Managing Pain (0-24) | 14.29 (6.69) Movement (0-20) | 9.79 (5.67)

Bibliographic reference	Dragoi,R.G., Ndosi,M., Sadlonova,M., Hill,J., Duer,M., Graninger,W., Smolen,J., Stamm,T.A., Patient education, disease activity and physical function: can we be more targeted? A cross sectional study among people with rheumatoid arthritis, psoriatic arthritis and hand osteoarthritis, Arthritis Research & Therapy, 15, R156-, 2013
	<table><tr><td>Feelings (0-16)</td><td>8.68 (4.73)</td></tr><tr><td>Arthritis Process (0-28)</td><td>19.44 (6.89)</td></tr><tr><td>Treatments (0-28)</td><td>15.90 (7.59)</td></tr><tr><td>Self-help Measures (0-24)</td><td>15.76 (5.90)</td></tr><tr><td>Support systems (0-16)</td><td>6.83 (4.40)</td></tr></table> These data could suggest a high need for information on arthritis process and self-help measures, a moderate need for information on managing pain, treatments and feelings and a lower need for information on movement and support systems. Varying educational needs were measured across gender, age, disease duration and educational background: Female patients scored significantly higher than males on movement and feelings Older patients scored significantly higher than younger patients in the pain domain Patients with basic education scored significantly higher than those with higher educational background overall, especially on movement and arthritis process
1.1 Is a qualitative approach appropriate?	Appropriate
1.2 Is the study clear in what it seeks to do?	Clear
2.1 How defensible/rigorous is the research design/methodology?	Defensible
3.1 How well was the data collection carried out?	Appropriate
4.1 Is the context clearly described?	Clear
4.2 Were the methods reliable?	Not sure
5.1 Are the data 'rich'?	Not sure / not reported
5.2 Is the analysis reliable?	Not sure / not reported

Bibliographic reference	Dragoi,R.G., Ndosi,M., Sadlonova,M., Hill,J., Duer,M., Graninger,W., Smolen,J., Stamm,T.A., Patient education, disease activity and physical function: can we be more targeted? A cross sectional study among people with rheumatoid arthritis, psoriatic arthritis and hand osteoarthritis, Arthritis Research & Therapy, 15, R156-, 2013
5.3 Are the findings convincing?	Not sure
5.4 Are the conclusions adequate?	Adequate
6.1 Was the study approved by an ethics committee?	Yes
6.2 Is the role of the researcher clearly described?	Not sure / not reported
Overall Risk of Bias	Data are for Austrian population, may not be entirely generalisable to the UK. Educational needs could be greater than those in the UK, as "the Austrian health care system does not routinely offer a structured form of education to patients with rheumatic diseases".
Other information	n/a

Table 170: Giacomelli et al., 2015

Bibliographic reference	Giacomelli,R., Gorla,R., Trotta,F., Tirri,R., Grassi,W., Bazzichi,L., Galeazzi,M., Matucci-Cerinic,M., Scarpa,R., Cantini,F., Gerli,R., Lapadula,G., Sinigaglia,L., Ferraccioli,G., Olivieri,I., Ruscitti,P., Sarzi-Puttini,P., Quality of life and unmet needs in patients with inflammatory arthropathies: results from the multicentre, observational RAPSODIA study, Rheumatology, 54, 792-797, 2015
Country/ies where the study was carried out	Italy
Study type	Questionnaire survey
Aim of the study	To evaluate the quality of life and unmet needs in patients with rheumatoid arthritis. psoriatic arthritis and ankylosing spondylitis in Italy. To assess: information delivery to patients; patient involvement in medical decisions; unmet healthcare needs and how these relate to health status.
Study dates	Not reported
Source of funding	Schering-Plough (Merck & Co.)
Sample size	Psoriatic arthritis N = 214, Ankylosing spondylitis

<table>
<tr><th>Bibliographic reference</th><th>Giacomelli,R., Gorla,R., Trotta,F., Tirri,R., Grassi,W., Bazzichi,L., Galeazzi,M., Matucci-Cerinic,M., Scarpa,R., Cantini,F., Gerli,R., Lapadula,G., Sinigaglia,L., Ferraccioli,G., Olivieri,I., Ruscitti,P., Sarzi-Puttini,P., Quality of life and unmet needs in patients with inflammatory arthropathies: results from the multicentre, observational RAPSODIA study, Rheumatology, 54, 792-797, 2015</th></tr>
<tr><td></td><td>N = 200</td></tr>
<tr><td>Inclusion criteria</td><td>> 18 years of age,
diagnosis of psoriatic arthritis or ankylosing spondylitis based on standard criteria,
receiving rheumatology care for previous 2 years
able to read and understand Italian.</td></tr>
<tr><td>Exclusion criteria</td><td>Not reported</td></tr>
<tr><td>Diagnostic criteria</td><td>Standard criteria and detail not reported</td></tr>
<tr><td>Characteristics</td><td>Entire sample
Male -n/N (%): 312/743 (42)
Age in years: Not reported but 493 aged more than 45 years
Duration of disease: Not reported
Member of support group: Not reported</td></tr>
<tr><td>Details</td><td>Patients were asked to complete, anonymously and independently, a specifically developed questionnaire during their scheduled rheumatology consultation. There were 60 questions in 14 domains, including those related to information.</td></tr>
<tr><td>Interventions</td><td>Not applicable</td></tr>
<tr><td>Missing data handling/loss to follow up</td><td>Not reported</td></tr>
<tr><td>Results</td><td>
<table>
<tr><td></td><td>n/N (%)</td></tr>
<tr><td>GPs explained their disease in understandable terms.</td><td>728/743 (98)</td></tr>
<tr><td>patients needed more information on diagnosis, medication, exercises and how to improve performance of daily activities</td><td>446/743 (60)</td></tr>
<tr><td>Satisfied with information on treatment</td><td>275/743 (37)</td></tr>
<tr><td>reported good involvement in process</td><td>379/743 (51)</td></tr>
</table>
</td></tr>
</table>

Bibliographic reference	**Giacomelli,R., Gorla,R., Trotta,F., Tirri,R., Grassi,W., Bazzichi,L., Galeazzi,M., Matucci-Cerinic,M., Scarpa,R., Cantini,F., Gerli,R., Lapadula,G., Sinigaglia,L., Ferraccioli,G., Olivieri,I., Ruscitti,P., Sarzi-Puttini,P., Quality of life and unmet needs in patients with inflammatory arthropathies: results from the multicentre, observational RAPSODIA study, Rheumatology, 54, 792-797, 2015**
	reported receiving adequate information on biologics and participated in therapy decision: 265/519 (
1.1 Is a qualitative approach appropriate?	Appropriate
1.2 Is the study clear in what it seeks to do?	Clear
2.1 How defensible/rigorous is the research design/methodology?	Not sure
3.1 How well was the data collection carried out?	Appropriate
4.1 Is the context clearly described?	Unclear
4.2 Were the methods reliable?	Not sure
5.1 Are the data 'rich'?	Poor
5.2 Is the analysis reliable?	Unreliable
5.3 Are the findings convincing?	Not convincing
5.4 Are the conclusions adequate?	Not sure
6.1 Was the study approved by an ethics committee?	Yes
6.2 Is the role of the researcher clearly described?	Not clear
Overall Risk of Bias	High risk of bias: very little of raw data is presented.
Other information	

Table 171: Leung et al., 2009

Bibliographic reference	Leung,Y.Y., Tam,L.S., Lee,K.W., Leung,M.H., Kun,E.W., Li,E.K., Involvement, satisfaction and unmet health care needs in patients with psoriatic arthritis, Rheumatology, 48, 53-56, 2009
Country/ies where the study was carried out	Hong Kong
Study type	Questionnaire survey
Aim of the study	To examine the involvement in care, participation in medical decisions, satisfaction of health care and unmet needs in patients with psoriatic arthritis. To explore factors related to involvement and satisfaction with care.
Study dates	Not reported
Source of funding	Not reported
Sample size	N = 105
Inclusion criteria	aged >18 yrs diagnosed with psoriatic arthritis
Exclusion criteria	Not reported
Diagnostic criteria	Psoriatic arthritis diagnosed using the CASPAR criteria
Characteristics	Male - n/N (%): 52/105 (49.5) Age in years - mean (SD): 50.3 (12.2) Duration of disease in years - mean (SD): 9.8 (6.9)
Details	Patients were requested and consented to self-administer questionnaires on demographic data, QoL, adequacy of perceived care, participation in medical decision, satisfaction with health care and specific health care needs.
Interventions	Not applicable
Missing data handling/loss to follow up	Not reported
Results	Proportion of patients expressing unmet needs

Unmet need	n/N %
Wish to participate in medical decision	69/105 (65)
Need for information of disease	72/105 (68)
Need for advice on exercise	77/105 (73)
Need for counselling	31/105 (29)
Need for social support	44/105 (41)

Bibliographic reference	Leung,Y.Y., Tam,L.S., Lee,K.W., Leung,M.H., Kun,E.W., Li,E.K., Involvement, satisfaction and unmet health care needs in patients with psoriatic arthritis, Rheumatology, 48, 53-56, 2009
	Use of alternative medicine: 35/105 (33) Proportion of patients interested to join various social programs: Unmet need: n/N (%) Educational talk: 53/105 (50) Rehabilitation programme: 52/105 (50) Patient self-help group: 34/105 (32) Personal counselling: 23/105 (22) Social gathering: 33/105 (31)
1.1 Is a qualitative approach appropriate?	Appropriate
1.2 Is the study clear in what it seeks to do?	Clear
2.1 How defensible/rigorous is the research design/methodology?	Defensible
3.1 How well was the data collection carried out?	Appropriate
4.1 Is the context clearly described?	Clear
4.2 Were the methods reliable?	Reliable
5.1 Are the data 'rich'?	Not sure / not reported
5.2 Is the analysis reliable?	Reliable
5.3 Are the findings convincing?	Convincing
5.4 Are the conclusions adequate?	Adequate

Bibliographic reference	Leung,Y.Y., Tam,L.S., Lee,K.W., Leung,M.H., Kun,E.W., Li,E.K., Involvement, satisfaction and unmet health care needs in patients with psoriatic arthritis, Rheumatology, 48, 53-56, 2009
6.1 Was the study approved by an ethics committee?	Yes
6.2 Is the role of the researcher clearly described?	Not sure / not reported
Overall Risk of Bias	Data from population in Hong Kong may not be entirely generalisable to UK population.
Other information	n/a

E.6.2 Information and education for flare management in spondyloarthritis

Review Question 28

- What is the effectiveness of information and education in the management of flare episodes?

None