Supplementary 1

Search result

Database, Platform and Coverage	Search Date	Number of references Retrieved
Cochrane library via OvidSP January 2013 Cochrane Central Register of Controlled Trials	January 3, 2013	3
MEDLINE(R) In-Process & Other Non-Indexed Citations and Ovid MEDLINE(R) via OVID	January 3, 2013	272
Embase Classic + Embase via OVID (limited to quality of life tools)	January 3, 2013	534
CINAHL via Ebscohost (medline records removed)	January 3, 2013	38
Clinicaltrials.gov (NIH web)	January 3, 2013	5
	Totals	852
	With duplicates removed	765

Search strategies for database searching

Pubmed

1. Spondylitis, Ankylosing
2. Spondylarthropathies
3. ankylosing or spondyl$[Title/Abstract]
4. bekhterev or bechterew[Title/Abstract]
5. or/1-4
6. methotrexate
7. Enthexate or mexate or Farmitrexate or Antifolan or Abitrexate or Folex or Ledertrexate or Methoblastin or Methohexate or Methotrate or Methylaminopterin or Mtx or Novatrex or Rheumatrex or amet?opterine or Met?opterine* or Emt?exate or Metotrexat*[Text Word]
8. or/7-8
9. Receptors, Tumor Necrosis Factor
10. Tumor Necrosis Factor-alpha
11. Antibodies, Monoclonal
12. anti-tumo?r necrosis factor$
13. anti-tnf
14. etanercept[Text Word]
15. enbrel[Text Word]
16. infliximab[Text Word]
17. remicade[Text Word]
18. adalimumab[Text Word]
19. humira[Text Word]
20. golimumab[Text Word]
21. simponi[Text Word]
22. certolizumab pegol[Text Word]
23. certolizumab or CDP870 or CDP 870 or Cimzia [Text Word]
24. or/9-23
25. randomized controlled trial[Publication Type]
26. controlled clinical trial[Publication Type]
27. randomized[Title/Abstract]
28. placebo[Title/Abstract]
29. drug therapy[MeSH Subheading].
30. randomly[Title/Abstract]
31. trial[Title/Abstract]
32. groups[Title/Abstract]
33. or/25-32
34. and/5,8,24,33
35. animals [mh] not humans [mh]
36. 34 not 35

Embase

1. ankylosing or spondylitis
2. (ankylos* or spondyl*).tw.
3. (bekhterev* or bechterew*).tw.
4. "Marie near/2 struempell*".tw.
5. 1 or 2 or 3 or 4
6. (Methotrexate or Enthexate or mexate or Farmitrexate or Antifolan or Abitrexate or Folex or Ledertrexate or Methoblastin or Methohexate or Methotrate or Methylaminopterin or Mtx or Novatrex or Rheumatrex or amet?opterine or Met?opterine* or Emt?exate or Metotrexat*).tw.
7. Receptors or 'Tumor Necrosis Factor'
8. 'Tumor Necrosis Factor-alpha'
9. Antibodies or Monoclonal
10. 'anti-tumo?r necrosis factor$'.tw.
11. anti-tnf.tw.
12. etanercept.tw.
13. enbrel.tw.
14. infliximab.tw.
15. remicade.tw.
16. adalimumab.tw.
17. humira.tw.
18. golimumab.tw.
19. Simponi.tw.
20. 'certolizumab pegol'.tw.
21. (certolizumab or CDP870 or 'CDP 870' or Cimzia).tw.
22. 7 or 8 or 9 or 10 or 11 or 12 or 13 or 14 or 15 or 16 or 17 or 18 or 19 or 20 or 21
23. (random* or placebo*).tw.
24. double* near/2 blind*.tw.
25. single* near/2 blind*.tw.
26. triple* near/2 blind*.tw.
27. treble* near/2 blind*.tw.
28. 'crossover procedure' .tw.
29. 'double blind procedure' .tw.
30. 'randomized controlled trial' .tw.
31. 'single blind procedure' .tw.
32. 23 or 24 or 25 or 26 or 27 or 28 or 29 or 30 or 31
33. 5 and 6 and 22 and 32 [<1946-2012]/py

CENTRAL

1. (ankylos$ or spondyl$).tw.
2. (bekhterev$ or bechterew$).tw.
3. (Marie adj struempell$).tw.
4. or/1-3
5. Methotrexate/
6. (Methotrexate or Enthexate or mexate or Farmitrexate or Antifolan or Abitrexate or Folex or Ledertrexate or Methoblastin or Methohexate or Methotrate or Methylaminopterin or Mtx or Novatrex or Rheumatrex or amet?opterine or A Met?opterine$ or Emt?exate or Metotrexat$).tw.
7. 5 and 6
8. Receptors, Tumor Necrosis Factor/
9. Tumor Necrosis Factor-alpha/
10. Antibodies, Monoclonal/
11. anti-tumo?r necrosis factor$.tw.
12. anti-tnf.tw.
13. etanercept.tw.
14. enbrel.tw.
15. infliximab.tw.
16. remicade.tw.
17. adalimumab.tw.
18. humira.tw.
19. golimumab.tw.
20. simponi.tw.
21. certolizumab pegol.tw.
22. (certolizumab or CDP870 or CDP 870 or Cimzia).tw.
23. or/7-22
24. 4 and 7 and 23

CINAHL

S49 S7 and S28 and S41
S48 S29 OR S30 OR S31 OR S32 or S33 or S34 or S35 or S36 or S37 or S38 or S39 or S40 or S41 or S42 or S43 or S44 or S45 or S46 or S47
S47 TI Cimzia OR AB Cimzia
S46 TI 'CDP 870' OR AB 'CDP 870'
S45 TI CDP870 OR AB CDP870
S44 TI certolizumab OR AB certolizumab
S43 TI certolizumab pegol OR AB certolizumab pegol
S42 TI simponi OR AB simponi
S41 TI golimumab OR AB golimumab
S40 TI humira OR AB humira
S39 TI adalimumab OR AB adalimumab
S38 TI remicade OR AB remicade
S37 TI infliximab OR AB infliximab
S36 TI enbrel OR AB enbrel
S35 TI etanercept OR AB etanercept
S34 TI anti-tnf OR AB anti-tnf
S33 TI anti-tumo?r necrosis factor$ OR AB anti-tumo?r necrosis factor$
S32 (MH "anti-tnf ")
S31 (MH "antibodies, monoclonal")
S30 (MH "tumor necrosis factor-alpha")
S29 (MH "receptors, tumor necrosis factor")
S28 S8 or S9 or S10 or S11 or S12 or S13 or S14 or S15 or S16 or S17 or S18 or S19 or S20 or S21 or S22 or S23 or S24 or S25 or S26 or S27
S27 TI Rheumatrex OR AB Rheumatrex
S26 TI Novatrex OR AB Novatrex
S25 TI Mtx OR AB Mtx
S24 TI Metotrexat* OR AB Metotrexat*
S23 TI Methylaminopterin OR AB Methylaminopterin
S22 TI Methotrate OR AB Methotrate
S21 TI Methohexate OR AB Methohexate
S20 TI Methoblastin OR AB Methoblastin
S19 TI Ledertrexate OR AB Ledertrexate
S18 TI Folex OR AB Folex
S17 TI Farmitrexate OR AB Farmitrexate
S16 TI Enthexate OR AB Enthexate
S15 TI Emt?exate OR AB Emt?exate
S14 TI Antifolan OR AB Antifolan
S13 TI A Met?opterine OR AB A Met?opterine
S12 TI Abitrexate OR AB Abitrexate
S11 TI mexate OR AB mexate
S10 TI amet?opterine OR AB amet?opterine

S9 TI Methotrexate OR AB Methotrexate
S8 (MH "Methotrexate")
S7 S1 or S2 or S3 or S4 or S5 or S6
S6 TI Marie struempell* OR AB Marie struempell*
S5 TI bechterew* OR AB bechterew*
S4 TI bekhterev* OR AB bekhterev*
S3 TI spondyl* OR AB spondyl*
S2 TI ankylos* OR AB ankylos*
S1 (MH "Spondylitis, Ankylosing")

Clinical Trials Registry Platform

ankylos* OR spondyl* OR bekhterev* OR bechterew* OR marie struempell* in Condition AND “methotrexate AND (tumor necrosis factor-alpha OR etanercept OR enbrel OR infliximab OR remicade OR adalimumab OR humira OR golimumab OR simponi OR certolizumab pegol OR certolizumab OR CDP870 OR CDP 870 OR Cimzia)” in Intervention

Supplementary 2

The Cochrane Collaboration's tool for assessing risk of bias

SEQUENCE GENERATION **Was the allocation sequence adequately generated? [Short form: *Adequate sequence generation*?]**	
Criteria for a judgement of 'YES' (i.e. low risk of bias).	The investigators describe a random component in the sequence generation process such as: • Referring to a random number table; • Using a computer random number generator; • Coin tossing; • Shuffling cards or envelopes; • Throwing dice; • Drawing of lots; • Minimization*. *Minimization may be implemented without a random element, and this is considered to be equivalent to being random.
Criteria for the judgement of 'NO' (i.e. high risk of bias).	The investigators describe a non-random component in the sequence generation process. Usually, the description would involve some systematic, non-random approach, for example: • Sequence generated by odd or even date of birth; • Sequence generated by some rule based on date (or day) of admission; • Sequence generated by some rule based on hospital or clinic record number. Other non-random approaches happen much less frequently than the systematic approaches mentioned above and tend to be obvious. They usually involve judgement or some method of non-random categorization of participants, for example: • Allocation by judgement of the clinician;

	• Allocation by preference of the participant; • Allocation based on the results of a laboratory test or a series of tests; • Allocation by availability of the intervention.
Criteria for the judgement of 'UNCLEAR' (uncertain risk of bias).	Insufficient information about the sequence generation process to permit judgement of 'Yes' or 'No

ALLOCATION CONCEALMENT **Was allocation adequately concealed? [Short form: *Allocation concealment*?]**	
Criteria for a judgement of 'YES' (i.e. low risk of bias).	Participants and investigators enrolling participants could not foresee assignment because one of the following, or an equivalent method, was used to conceal allocation: • Central allocation (including telephone, web-based, and pharmacy-controlled, randomization); • Sequentially numbered drug containers of identical appearance; • Sequentially numbered, opaque, sealed envelopes.
Criteria for the judgement of 'NO' (i.e. high risk of bias).	Participants or investigators enrolling participants could possibly foresee assignments and thus introduce selection bias, such as allocation based on: • Using an open random allocation schedule (e.g. a list of random numbers); • Assignment envelopes were used without appropriate safeguards (e.g. if envelopes were unsealed or non-opaque or not sequentially numbered); • Alternation or rotation; • Date of birth; • Case record number; • Any other explicitly unconcealed procedure.

Criteria for the judgement of 'UNCLEAR' (uncertain risk of bias).	Insufficient information to permit judgement of 'Yes' or 'No'. This is usually the case if the method of concealment is not described or not described in sufficient detail to allow a definite judgement – for example if the use of assignment envelopes is described, but it remains unclear whether envelopes were sequentially numbered, opaque and sealed.

BLINDING OF PARTICIPANTS, PERSONNEL AND OUTCOME ASSESSORS **Was knowledge of the allocated interventions adequately prevented during the study? [Short form: *Blinding*?]**	
Criteria for a judgement of 'YES' (i.e. low risk of bias).	Any one of the following: • No blinding, but the review authors judge that the outcome and the outcome measurement are not likely to be influenced by lack of blinding; • Blinding of participants and key study personnel ensured, and unlikely that the blinding could have been broken; • Either participants or some key study personnel were not blinded, but outcome assessment was blinded and the non-blinding of others unlikely to introduce bias.
Criteria for the judgement of 'NO' (i.e. high risk of bias).	Any one of the following: • No blinding or incomplete blinding, and the outcome or outcome measurement is likely to be influenced by lack of blinding; • Blinding of key study participants and personnel attempted, but likely that the blinding could have been broken; • Either participants or some key study personnel were not blinded, and the non-blinding of others likely to introduce bias.
Criteria for the judgement of 'UNCLEAR' (uncertain risk of bias).	Any one of the following: • Insufficient information to permit judgement of 'Yes' or 'No';

	• The study did not address this outcome.

INCOMPLETE OUTCOME DATA

Were incomplete outcome data adequately addressed? [Short form: *Incomplete outcome data addressed*?]

Criteria for a judgement of 'YES' (i.e. low risk of bias).	Any one of the following: • No missing outcome data; • Reasons for missing outcome data unlikely to be related to true outcome (for survival data, censoring unlikely to be introducing bias); • Missing outcome data balanced in numbers across intervention groups, with similar reasons for missing data across groups; • For dichotomous outcome data, the proportion of missing outcomes compared with observed event risk not enough to have a clinically relevant impact on the intervention effect estimate; • For continuous outcome data, plausible effect size (difference in means or standardized difference in means) among missing outcomes not enough to have a clinically relevant impact on observed effect size; • Missing data have been imputed using appropriate methods.
Criteria for the judgement of 'NO' (i.e. high risk of bias).	Any one of the following: • Reason for missing outcome data likely to be related to true outcome, with either imbalance in numbers or reasons for missing data across intervention groups; • For dichotomous outcome data, the proportion of missing outcomes compared with observed event risk enough to induce clinically relevant bias in intervention effect estimate; • For continuous outcome data, plausible effect size (difference in means or standardized difference in means) among missing outcomes enough to induce clinically relevant bias in observed effect size; • 'As-treated' analysis done with substantial departure of the intervention received from that

	assigned at randomization; • Potentially inappropriate application of simple imputation.
Criteria for the judgement of 'UNCLEAR' (uncertain risk of bias).	Any one of the following: • Insufficient reporting of attrition/exclusions to permit judgement of 'Yes' or 'No' (e.g. number randomized not stated, no reasons for missing data provided); • The study did not address this outcome.
SELECTIVE OUTCOME REPORTING	
Are reports of the study free of suggestion of selective outcome reporting? [Short form: *Free of selective reporting*?]	
Criteria for a judgement of 'YES' (i.e. low risk of bias).	Any of the following: • The study protocol is available and all of the study's pre-specified (primary and secondary) outcomes that are of interest in the review have been reported in the pre-specified way; • The study protocol is not available but it is clear that the published reports include all expected outcomes, including those that were pre-specified (convincing text of this nature may be uncommon).
Criteria for the judgement of 'NO' (i.e. high risk of bias).	Any one of the following: • Not all of the study's pre-specified primary outcomes have been reported; • One or more primary outcomes is reported using measurements, analysis methods or subsets of the data (e.g. subscales) that were not pre-specified; • One or more reported primary outcomes were not pre-specified (unless clear justification for their reporting is provided, such as an unexpected adverse effect); • One or more outcomes of interest in the review are reported incompletely so that they cannot be entered in a meta-analysis; • The study report fails to include results for a key outcome that would be expected to have

	been reported for such a study.
Criteria for the judgement of 'UNCLEAR' (uncertain risk of bias).	Insufficient information to permit judgement of 'Yes' or 'No'. It is likely that the majority of studies will fall into this category.
OTHER POTENTIAL THREATS TO VALIDITY **Was the study apparently free of other problems that could put it at a risk of bias? [Short form: *Free of other bias*?]**	
Criteria for a judgement of 'YES' (i.e. low risk of bias).	The study appears to be free of other sources of bias.
Criteria for the judgement of 'UNCLEAR' (uncertain risk of bias).	There may be a risk of bias, but there is either: • Insufficient information to assess whether an important risk of bias exists; or • Insufficient rationale or evidence that an identified problem will introduce bias.
Criteria for the judgement of 'NO' (i.e. high risk of bias)	There is at least one important risk of bias. For example, the study: • Had a potential source of bias related to the specific study design used; or • Stopped early due to some data-dependent process (including a formal-stopping rule); or • Had extreme baseline imbalance; or • Has been claimed to have been fraudulent; or • Had some other problem.