Table 1: Detailed risk of bias assessment: domains "random sequence generation" to "blinding of outcome assessment"

Study ID	ROB assessment used from other Cochrane review?	Random sequence generation (selection bias)	Random sequence generation: Support for decision	Allocation concealment (selection bias)	Allocation concealment: Support for decision	Blinding of participants and personnel (performance bias): Radiographic outcomes	Blinding of participants and personnel (performance bias): Non-radiographic outcomes	Blinding of participants and personnel: Support for decision	Blinding of outcome assessment (detection bias): Radiographic outcomes	Blinding of outcome assessment (detection bias): Non-radiographic outcomes	Blinding of outcome assessment: Support for decision
AVERT 2015	N	Low	Quote:"Centralised randomization system"	Low	Quote:"Centralised randomization system"	Not applicable	Unclear	Comment: Double-blind, without additional details.	Not applicable	Unclear	Comment: Double-blind, without additional details.
Iwahashi 2014	N	Unclear	Comment: Randomized without additional details	Unclear	Comment: Randomized without additional details	Not applicable	Unclear	Comment: Double-blind without additional details	Not applicable	Unclear	Comment: Double-blind without additional details
ASSET 2013	N	Low	Quote:"Randomisation was by central allocation of a unique number in order of qualification for treatment. "	Low	Quote:"Randomisation was by central allocation of a unique number in order of qualification for treatment. "	Not applicable	Unclear	Quote: "Clinicians and patients were blinded;"	Not applicable	Unclear	Quote: "Clinicians and patients were blinded"
Takeuchi 2013a	N	Unclear	Comment: Randomized without additional details	Unclear	Comment: Randomized without additional details	Not applicable	Unclear	Comment: Double-blind without additional details	Not applicable	Unclear	Comment: Double-blind without additional details
Matsubara 2012	N	Unclear	Comment: Randomized without additional details	Unclear	Comment: Randomized without additional details	Not applicable	Unclear	Comment: No description of placebo formulation	Not applicable	Unclear	Comment: Double-blind without additional details
ACQUIRE 2011	N	Unclear	Comment: Randomized without additional details	Unclear	Comment: Randomized without additional details	Not applicable	Low	Quote: "A double-dummy design was used to maintain blinding...Patients and study site personnel remained blinded with regard to treatment assignments"	Not applicable	Low	Quote: "A double-dummy design was used to maintain blind-ing...Patients and study site personnel remained blinded with regard to treatment assignments"
Shim 2010	N	Unclear	Comment: Randomized without additional details	Unclear	Comment: Randomized without additional details	Not applicable	Unclear	Comment: No description of placebo formulation	Not applicable	Unclear	Comment: Double-blind without additional details
AGREE 2009	(Singh 2011)	Unclear	Comment: Randomized without additional details	Unclear	Comment: Randomized without additional details	Low	Low	Comment: Double-blind with placebo and statement that patients, sites and radiographic sites remained blinded	Low	Low	Comment: Double-blind with placebo and statement that patients, sites and radiographic sites remained blinded throughout treatment

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								throughout treatment			
AIM 2006	(Singh 2011)	Unclear	Comment :No discussion on how sequence was gererated	Low	See Cochrane	Low	Unclear	Comment: Double-blind, but without additional details	Low	Low	Comment: Both physicians and x-ray readers blinded. Clearly described
Kremer 2005	(Singh 2011)	Unclear	See Cochrane	Low	Comment: Central randomization	Not applicable	Unclear	Comment: Double-blind without additional details	Not applicable	Unclear	Comment: Double-blind without additional details
RA-BEAM 2015	N	Unclear	Comment: Randomized without additional details	Unclear	Comment: Randomized without additional details	Not applicable	Unclear	Comment: Double-blind, without additional details.	Not applicable	Unclear	Comment: Double-blind, without additional details.
Weinblatt 2015	N	Unclear	Comment: Randomized without additional details	Unclear	Comment: Randomized without additional details	Not applicable	Unclear	Comment: Double-blind, without additional details.	Not applicable	Unclear	Comment: Double-blind, without additional details.
HOPEFUL-I 2014	N	Unclear	Comment: Randomized without additional details	Unclear	Comment: Randomized without additional details	Low	Unclear	Comment: Double-blind without additional details	Low	Unclear	Comment: Double-blind without additional detailsfor clinical outcomes; x-ray readers blinded
OPERA 2014	N	Low	Quote: "Patients were randomised in blocks of four from a central, computer-generated list of study numbers."	Low	Quote: "Patients were randomised in blocks of four from a central, computer-generated list of study numbers."	Not applicable	Low	Quote: "Blinding was maintained throughout the study period"	Not applicable	Low	Quote: "Blinding was maintained throughout the study period"
HITHARD 2013	N	Unclear	Comment: Randomized without additional details	Unclear	Comment: Randomized without additional details	Low	Unclear	Comment: Double-blind without additional details	Low	Unclear	Comment: Double-blind with no details; x-ray readers blinded
OPTIMA 2013	N	Low	Comment: IVRS	Low	Quote: "Patients were centrally randomized"	Unclear	Unclear	Comment: Double-blind (in introduction) with no details	Unclear	Unclear	Comment: Double-blind (in introduction) with no details
AUGUST-II 2011	N	Low	Comment: IVRS	Low	Quote: "Central randomization"	Not applicable	High	Comment: ADA arm open-label	Not applicable	High	Comment: ADA arm open-label
Chen 2011	N	Unclear	Comment: Randomized without additional details	Unclear	Comment: Randomized without additional details	Not applicable	Unclear	Comment: Double-blind, without additional details.	Not applicable	Unclear	Comment: Double-blind without additional details
Chen 2009	(Singh 2011)	Unclear	See Cochrane	Unclear	See Cochrane	Not applicable	Unclear	Comment: Double-blind without additional details	Not applicable	Unclear	Comment: Double-blind without additional details
GUEPARD 2009	N	Unclear	Quote: "randomized (per centre)"	Unclear	Quote: "randomized (per centre)"	Unclear	High	Comment: Unblinded	Low	High	Comment: Unblinded except for x-ray readers

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Huang 2009	N	Unclear	Comment: Randomized without additional details	Unclear	Comment: Randomized without additional details	Not applicable	Unclear	Comment: Double-blind, without additional details.	Not applicable	Unclear	Comment: Double-blind without additional details
Bejarano 2008	N	Low	Quote: "computer-generated randomization schedule"	Low	Comment: "randomization schedule developed centrally by the study sponsor."	Not applicable	Low	Comment: Very well described; blinding of patients with matching placebos	Not applicable	Low	Comment: Very well described
Kim 2007	(Singh 2011)	Unclear	See Cochrane	Unclear	See Cochrane	Not applicable	Unclear	See Cochrane	Not applicable	Unclear	See Cochrane
PREMIER 2006	(Singh 2011)	Unclear	See Cochrane	Unclear	See Cochrane	Low	Unclear	Comment: Double-blind without additional details	Low	Unclear	Comment: Double-blind without additional details
DE019 2004	(Singh 2011)	Unclear	See Cochrane	Unclear	See Cochrane	Low	Unclear	Comment: Double-blind without additional details	Low	Unclear	Comment: Double-blind without additional details
ARMADA 2003	(Singh 2011)	Unclear	See Cochrane	Unclear	See Cochrane	Not applicable	Unclear	Comment: Double-blind without additional details	Not applicable	Unclear	Comment: Double-blind without additional details
C-EARLY 2015	N	Unclear	Comment: Randomized without additional details	Unclear	Comment: Randomized without additional details	Low	Unclear	Comment: Double-blind, without additional details.	Unclear	Unclear	Comment: Double-blind, without additional details.
C-OPERA 2014	N	Unclear	Comment: Randomized without additional details	Unclear	Comment: Randomized without additional details	Not applicable	Unclear	Comment: Double-blind without additional details	Not applicable	Unclear	Comment: Double-blind without additional details
JRAPID 2014	N	Low	Quote: "The random allocation sequence was generated using uniform random numbers from SAS¨ RANUNI function"	Low	Quote: "The study drug allocation center was responsible for preparation and storage of the randomization table, study drug allocation, and confirmation of indistinguishability of study drugs, while the registration center was responsible for assignment of study drug numbers to patients."	Low	Low	Comment: Double-blind with matching placebos	Low	Unclear	Comment: Radiograph readers blinded, otherwise unlcear
Choy 2012	N	Low	Quote:"rando- mized on a 1:1 basis via an interactive voice-response system"	Low	Quote:"rando-mized on a 1:1 basis via an interactive voice-	Not applicable	Low	Quote: "To preserve the blind to clin-ical research	Not applicable	Low	Quote: "To preserve the blind to clin- ical research staff, the

					response system"			staff, the study site pharmacist labelled clin- ical supplies (study medication syringes), and a sorbitol placebo was used to match the viscosity of CZP"			study site pharmacist labelled clin- ical supplies (study medication syringes), and a sorbitol placebo was used to match the viscosity of CZP"
Kang 2012	N	Unclear	Comment: Randomized without additional details	Unclear	Comment: Randomized without additional details	Not applicable	Unclear	Comment: Double-blind without additional details	Not applicable	Unclear	Comment: Double-blind without additional details
RAPID-II 2009	(Singh 2011)	Unclear	See Cochrane	Unclear	See Cochrane	Low	Unclear	Comment: Double-blind without additional details	Low	Unclear	Comment: Double-blind with no details for clinical outcomes; x-ray readers blinded
RAPID-I 2008	N	Unclear	Comment: Randomized without additional details	Unclear	Comment: Randomized without additional details	Low	Unclear	Comment: Double-blind without additional details	Low	Unclear	Comment: Double-blind with no details for clinical outcomes; x-ray readers blinded
EMPIRE 2014	N	Low	Quote:"Patients were randomised (1:1) according to a computer- generated list in blocks of four"	Low	Quote:"Patients were randomised (1:1) according to a computer-generated list in blocks of four"	Low	Low	Quote: "Clinicians, nurses, local pharmacists, patients and assessors were blinded to treat- ment allocation throughout the study." "or visually identical placebo (sterile lyophilised powder of similar appearance to ETN)"	Low	Low	Quote: "Clinicians, nurses, local pharmacists, patients and assessors were blinded to treat- ment allocation throughout the study." "or visually identical placebo (sterile lyophilised powder of similar appearance to ETN)"
Takeuchi 2013b	N	Low	Quote: "The allocation of eligible subjects to the treatment groups was performed through the computerized randomization"	Unclear	Comment: No mention of central allocation	Low	Unclear	Comment: Double-blind without additional details	Low	Unclear	Comment: Double-blind without additional detailsfor clinical outcomes; x-ray readers blinded
Huang 2012	N	Unclear	Comment: "Randomly divided" without additional details	High	Comment: No mention of central allocation; "randomly divided into groups"	Not applicable	High	Comment: Placebo given, but no mention of blinding	Not applicable	High	Comment: Placebo given, but no mention of blinding
ESCAPE 2010	N	Low	Comment: IVRS	Low	Comment: Performed centrally through IVRS	Not applicable	High	Comment: ETN arm open-label	Not applicable	High	Comment: ETN arm open-label

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COMET 2008	(Singh 2011)	Low	See Cochrane	Low	See Cochrane	Low	Low	See Cochrane	Low	Low	See Cochrane
Marcora 2006	N	Low	Quote: "computer-generated list of random numbers"	High	Quote: "Both the patients and the clinician responsible for their management (GM) were aware of treatment allocation". Comment: Unclear whether this relates to knowing the sequence of allocation vs. the treatment assigned, but no discussion of this raises concern for high bias	Not applicable	High	Comment: Not blinded	Not applicable	High	Comment: Not blinded
Lan 2004	(Singh 2011)	Unclear	See Cochrane	Unclear	See Cochrane	Not applicable	Unclear	See Cochrane	Not applicable	Unclear	See Cochrane
TEMPO 2004	(Singh 2011)	Unclear	See Cochrane	Low	See Cochrane	Low	Low	Comment: Blinded; Identical appearing placebos	Low	Low	Comment: Blinded; Identical appearing placebos
ERA 2000	(Singh 2011)	Unclear	See Cochrane	Unclear	See Cochrane	Low	Unclear	Comment: Double-blind without additional details; x-ray readers blinded	Low	Unclear	Comment: Double-blind without additional details; x-ray readers blinded
Weinblatt 1999	(Singh 2011)	Unclear	See Cochrane	Unclear	See Cochrane	Not applicable	Low	See Cochrane	Not applicable	Unclear	See Cochrane
GOBEFORE 2013	(Singh 2010)	Low	See Cochrane	Low	See Cochrane	Low	Low	See Cochrane	Low	Low	Quote: "An independent assessor at each study center, who had no access to patient records and no other role in the study, performed the joint assessments." Comment: Readers also blinded (see Genovese 2012)
GOFURTHER 2013	N	Low	Comment: Performed centrally through IVRS	Low	Comment: Performed centrally through IVRS	Unclear	Low	Comment: Placebo described. EE patients also received PBO	Unclear	Unclear	Comment: "Double-blind" but no mention of which assessors were blinded
NCT01248780 2013	N	Unclear	Comment: Randomized without additional details	Unclear	Comment: Randomized without additional details	Not applicable	Unclear	Comment: Double-blind without additional details	Not applicable	Unclear	Comment: Double-blind without additional details
GOFORTH 2012	N	Unclear	Quote: "Eligible patients were randomly (1:1:1)	Unclear	Quote: "Eligible patients were randomly (1:1:1)	Low	Unclear	Comment: Double-blind without	Low	Unclear	Comment: Double-blind without additional

			assigned"		assigned"			additional details			details
GOFORWARD 2009	(Singh 2010)	Unclear	Comment:No details on how randomization sequence was generated	Low	See Cochrane	Low	Low	See Cochrane	Low	Unclear	Comment: Joint assessors blinded, but unsure about treating physicians.
Kay 2008	N	Unclear	Comment: Randomized without additional details	Unclear	Comment: Randomized without additional details	Not applicable	Low	Quote: "Patients who received golimumab every 4 weeks received placebo injections at the alternate visits to maintain blinding...Patients in the golimumab groups remained blinded to their dose assignment through the end of the study"	Not applicable	Unclear	Comment: Double-blind without additional details
MacIsaac 2014	N	Unclear	Comment: Randomized without additional details	Unclear	Comment: Randomized without additional details	Not applicable	Unclear	Comment: Double-blind, without additional details.	Not applicable	Unclear	Comment: Double-blind, without additional details.
Kim 2013	N	Unclear	Comment: Randomized without additional details	Unclear	Comment: Randomized without additional details	Not applicable	Unclear	Comment: Double-blind with placebos, but no description of pbo formulations	Not applicable	Low	Quote: "The investigators, independent joint assessors and patients were blinded to the treatment assignments"
Li 2013	N	Unclear	Comment: Randomized without additional details	Unclear	Comment: Randomized without additional details	Not applicable	Unclear	Comment: Double-blind without additional details	Not applicable	Unclear	Comment: Double-blind without additional details
Tam 2012	N	Unclear	Comment: Randomized without additional details	Unclear	Comment: Randomized without additional details	Not applicable	High	Comment: Not blinded	Not applicable	High	Comment: Not blinded
Xia 2011	N	High	Comment: Confirmed with authors by e-mail that study was randomized, but no mention in paper	High	Comment: No details on randomization procedure/allocation concealment	Not applicable	High	Comment: No mention of blinding, no placebo given	Not applicable	High	Comment: No mention of blinding, no placebo given
Durez 2007	(Singh 2011)	Unclear	See Cochrane	Unclear	See Cochrane	Not applicable	High	Comment: See Cochrane	Not applicable	Low	Comment: See Cochrane
Abe 2006	N	Unclear	Comment: Randomized without additional details	Unclear	Comment: Randomized without additional details	Not applicable	Unclear	Comment: Double-blind without additional details	Not applicable	Unclear	Comment: Double-blind without additional details

START 2006	(Singh 2011)	Low	Quote: "Patients were assigned to the treatment groups using adaptive allocation, with stratification according to the investigational site and concomitant oral corticosteroid use" Comment: Assume computer generated as adaptive design	Unclear	Quote: "Patients were assigned to the treatment groups using adaptive allocation, with stratification according to the investigational site and concomitant oral corticosteroid use" Comment: No mention of central allocation	Not applicable	Low	Quote: "Patients, investigators, and other study personnel, except for pharmacists, were blinded to the study treatment assignments." Comment: Matching placebos also used.	Not applicable	Low	Quote: "Patients, investigators, and other study personnel, except for pharmacists, were blinded to the study treatment assignments." Comment: Matching placebos also used.
Zhang 2006	N	Unclear	Comment: Randomized without additional details	Unclear	Comment: Randomized without additional details	Not applicable	Unclear	Comment: Double-blind without additional details	Not applicable	Unclear	Comment: Double-blind without additional details
BEST 2005	N	Unclear	Comment: Randomized without additional details	Low	Comment:Well-described. Central allocation with closed envelopes	Unclear	High	Comment: Patients not blinded	Low	Unclear	Comment: Nurse assessors but not rheumatologists blinded; x-ray readers blinded
Quinn 2005	N	Low	Quote:"Patients were assigned to a treatment group using an adaptive stratified randomization technique" Comment: Assume this is computer generated	Unclear	Comment: No mention of central allocation	Low	Unclear	Comment: Double-blind without additional details	Low	Unclear	Comment: Double-blind without additional details. X-ray reader blinded
ASPIRE 2004	(Singh 2011)	Low	See Cochrane	Low	See Cochrane	Low	Low	Comment: Double-blind with matching placebo	Low	Unclear	Comment: Joint assessors and x-ray readers blinded, unclear if physicians blinded
ATTRACT 2000	N	Unclear	Comment: Randomized without additional details	Low	Comment: Central randomization	Low	Low	Quote: "The investigators and patients were blinded to the treatment assignments. An independent assessor, unaware of the patient assignment or other clinical response indices and not involved in the administration of the infusions, assessed the joint scores." Comment: Matching placebos used	Low	Low	Quote: "he investigators and patients were blinded to the treatment assignments. An independent assessor, unaware of the patient assignment or other clinical response indices and not involved in the administration of the infusions, assessed the joint scores." Comment: Matching placebos used
IMAGE 2012	N	Low	Comment: IVRS	Low	Quote: "At randomisation,	Low	Low	Quote: "The sponsor,	Low	Low	Comment: All blinded, including

					patients were assigned unique medication and randomisation numbers via the IVRS"			investigators and patients were blinded to treat- ment allocation until week 52" Comment: Placebo infusions given			x-ray readers
SERENE 2010	N	Unclear	Comment: Randomized without additional details	Unclear	Comment: Randomized without additional details	Not applicable	Unclear	Comment: Double-blind without additional details	Not applicable	Unclear	Comment: Double-blind without additional details
DANCER 2006	(Singh 2011)	Unclear	See Cochrane	Unclear	See Cochrane	Not applicable	Unclear	Comment: See Cochrane	Not applicable	Unclear	Comment: See Cochrane
Edwards 2004	(Singh 2011)	Unclear	See Cochrane	Unclear	See Cochrane	Not applicable	Unclear	Quote: "Investigators and patients remained blinded to the assigned study medications." Comment: No description of PBO formulations	Not applicable	Low	Quote: "Investigators and patients remained blinded to the assigned study medications."
SURPRISE 2016	N	Unclear	Comment: Randomized without additional details	Unclear	Comment: Centralised randomization	Unclear	High	Comment: Open-label	High	High	Comment: Open-label
MEASURE 2015	N	Low	Comment: IVRS	Low	Comment: IVRS	Not applicable	Low	Quote: "blinded (pateint and treating team)"; matching placebos	Not applicable	Low	Quote: "blinded (pateint and treating team)"; matching placebos
TOMERA 2014	N	Unclear	Comment: Randomized without additional details	Unclear	Comment: Randomized without additional details	Not applicable	Unclear	Comment: Double-blind without additional details	Not applicable	Unclear	Comment: Double-blind without additional details
ACT-RAY 2013	N	Unclear	Comment: Randomized without additional details	Unclear	Comment: Randomized without additional details	Low	Low	Quote:"All patients received identical capsules of either placebo (switch strategy arm) or methotrexate 2.5 mg (add-on strategy arm), with the number of capsules at study entry being consistent with prestudy dos- age"	Low	Unclear	Comment: Double-blind without additional details except x-ray readers (blinded)
FUNCTIO N 2013	N	Unclear	Comment: Randomized without additional details	Unclear	Comment: Randomized without additional	Low	Unclear	Comment: Double-blind without	Low	Unclear	Comment: Double-blind without additional

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					details			additional details			details; x-ray readers blinded
LITHE 2011	N	Unclear	Comment: Randomized without additional details	Unclear	Comment: Randomized without additional details	Low	Unclear	Comment: Double-blind without additional details	Low	Unclear	Comment: X-ray reading well blinded, details of other blinding unclear. No discussion of formulation of PBO
AMBITION 2010	N	Unclear	Comment: Randomized without additional details	Unclear	Comment: Randomized without additional details	Not applicable	Unclear	Comment: Double-blind without additional details	Not applicable	Low	Quote: "Patients were assessed for efficacy and safety using a dual assessor approach to ensure blinded evaluation for efficacy; a trained joint assessor, with no access to patient data, performed each SJC and TJC."
SATORI 2009	(Singh 2011)	Unclear	Comment: Randomized without additional details	Low	Comment: Central randomization	Not applicable	Unclear	Comment: Double-blind without additional details	Not applicable	Unclear	Comment: Double-blind without additional details
OPTION 2008	(Singh 2011)	Low	Quote: "interactive voice response system"	Low	Quote: "Randomisation was done centrally"	Not applicable	Unclear	Comment: Double-blind without additional details	Not applicable	Low	Quote: "To maintain the double-blind status, a dual assessor approach for efficacy and safety assessments was used."
CHARISMA 2006	(Singh 2011)	Low	See Cochrane	Low	See Cochrane	Not applicable	Low	Comment: See Cochrane	Not applicable	Low	Comment: See Cochrane
Conaghan 2015	N	Unclear	Comment: Randomized without additional details	Unclear	Comment: Randomized without additional details	Low	Unclear	Comment: Double-blind, without additional details.	Unclear	Unclear	Comment: Double-blind, without additional details.
ORALSCAN 2013	N	Low	Comment: IVRS	Low	Comment: IVRS	Low	Unclear	Comment: Double-blind without additional details	Low	Unclear	Comment: X-ray readers blinded; blinding of outcome assessors not described
Kremer 2012	N	Unclear	Comment: Randomized without additional details	Unclear	Comment: Randomized without additional details	Not applicable	Unclear	Comment: Double-blind without additional details	Not applicable	Unclear	Comment: Double-blind without additional details
Tanaka 2011	N	Unclear	Comment: Randomization procedure not described	Unclear	Comment: Allocation concealment not described	Not applicable	Unclear	Comment: Double-blind without additional details	Not applicable	Unclear	Comment: Double-blind without additional details
AMPLE 2014	N	Unclear	Comment: Randomized without additional details	Unclear	Comment: Randomized without additional details	Unclear	High	Comment: Patients not blinded	Low	Unclear	Comment Assessors blinded, but patients not, so unblinding could

											occur
ORALSTD 2012	N	Low	Quote: "By means of an interactive voice-response system, were randomly assigned, in a 4:4:4:1:1 ratio"	Low	Comment: Used IVRS. Detailed info in protocol	Not applicable	Low	Quote: "The study medication will be labeled in such a manner that the patient and study staff will be unable to determine from the dispensed packaging to which treatment arm the patient is assigned."	Not applicable	Low	Comment: From protocol - investigator blinded
ATTEST 2008	(Singh 2011)	Unclear	See Cochrane	Unclear	See Cochrane	Not applicable	Low	See Cochrane	Not applicable	Low	See Cochrane
Cuomo 2006	N	High	Comment: Only mention of randomization is in the abstract and results, not discussed in methods.	High	Comment: Only mention of randomization is in the abstract and results, not discussed in methods.	Not applicable	High	Comment: No mention of blinding	Not applicable	High	Comment: No mention of blinding
RACAT 2013	N	Low	Quote: From protocol "The Boston VA Cooperative Studies Program Coordinating Center (CSPCC) will develop the randomization scheme and, with the assistance of a web-based randomization system"	Low	Quote: From protocol "The participating center will access the web-based randomization system to verify eligibility for randomization."	Low	Low	Comment: Double-blinded with identical PBO used	Low	Low	Comment: Double-blinded with identical PBO used; x-ray readers blinded
Joo 2012	N	Unclear	Comment: Randomized without additional details	Unclear	Comment: Randomized without additional details	Not applicable	High	Comment: Open label	Not applicable	High	Comment: Open label
SWEFOT 2012	N	Low	Quote: "Randomisation was done with a computer-generated random list of assignments communicated by the Swefot coordinator to the investigator."	Low	Quote: "The statistician who generated the randomisation sequence was not otherwise involved in the trial." Comment: Further details also in appendix	Unclear	High	Comment: Unblinded, except for x-ray readers	Low	High	Comment: Unblinded, except for x-ray readers
TEAR 2012	N	Low	Quote: "Treat- ment was allocated via a computerized data entry system at a 2:1 ratio for etanercept versus triple therapy, using a standard permuted block approach, by site,	Low	Quote:"The data entry system masked both participants and investi- gators to the study medication arm"	Low	Low	Quote:"medicat ion kits were assigned to participants by using a blinded drug distribu- tion system. Investigators and participants	Low	Low	Quote:"Investigato rs and participants remained blinded to the treatment assignment until the end of year 2. Matching placebos were used throughout the

			with block sizes of 6 or 12."					remained blinded to the treatment assignment until the end of year 2. Matching placebos were used throughout the trial, including during the step-up period, when all participants were dispensed a step-up kit even if he or she was already receiving immediate therapy"			trial, including during the step-up period, when all participants were dispensed a step-up kit even if he or she was already receiving immediate therapy". X-ray"The readers scored all of the films grouped per patient but blinded for time sequence and clinical data."
Willkens 1992	(Katchamart 2010)	Unclear	Comment: Not described	Low	See Cochrane	Not applicable	Low	Comment: Double-blind with matching placebos	Not applicable	Unclear	Comment: Double-blind with no additional details
CARDERA 2008	N	Unclear	Comment: Not described	Low	Comment: Well described	Low	Low	Quote: "The study was fully blinded with matching placebos for oral glucocorticoids and ciclosporin."	Low	Low	Quote: "The study was fully blinded with matching placebos for oral glucocorticoids and ciclosporin."
CIMESTRA 2006	(Katchamart 2010)	Low	See Cochrane	Low	See Cochrane	Low	Low	Comment: Double-blind with matching placebos	Low	Low	Quote: "Joints were evaluated and injections were given by an independent, blinded, and trained assessor"
Sarzi-Puttini 2005	N	Unclear	Comment: Randomized without additional details	Unclear	Comment: Randomized without additional details	Unclear	High	Comment: Open-label	Low	High	Comment: Open-label, but x-ray readers blinded
Gerards 2003	N	Low	Quote: "Randomisation was performed by a computer generated list"	Unclear	Comment: Not described	Low	Low	Quote: "The placebo was produced by the pharmacy of the VU Medical Centre and was packed and made indistinguishable from MTX at that centre"	Low	Unclear	Comment: X-ray readers blinded; double-blind, but unclear which assessors were blinded
Marchesoni 2003	(Katchamart 2010)	Unclear	See Cochrane	Low	See Cochrane	Unclear	High	Comment: Patients not blinded	Unclear	Unclear	Comment: "single-blind" (clinical investigator); uncertain if this is outcome assessors or not

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Giacomelli 2002	N	Unclear	Comment: Randomized without additional details	Unclear	Comment: Randomized without additional details	Not applicable	High	Comment: Open-label	Not applicable	High	Comment: Open-label
Machein 2002	N	Unclear	Comment: Randomized without additional details	Unclear	Comment: Randomized without additional details	Not applicable	Unclear	Comment: Double-blind without additional details	Not applicable	Unclear	Comment: Double-blind without additional details
Kim 2000	N	Unclear	Comment: Randomized without additional details	Unclear	Comment: Randomized without additional details	Not applicable	Low	Comment: Double-blind with placebo that were "identical in taste and shape"	Not applicable	Unclear	Comment: Double-blind withour additional details
Tugwell 1995	(Katchamart 2010)	Unclear	See Cochrane	Unclear	Quote: "A separate randomization schedule was generated at each center."	Not applicable	Low	See Cochrane	Not applicable	Low	See Cochrane
Singh 2012	N	Unclear	Comment: Randomized without additional details	High	Comment: No mention of central randomization. Single centre investigator-initiated study published only as abstract; signficant probability that was not concealed	Not applicable	High	Comment: No mention of blinding, assume open-label	Not applicable	High	Comment: No mention of blinding, assume open-label
Shashikumar 2010	N	Low	Comment: Used online software (referenced)	Unclear	Comment: No details provided	Not applicable	High	Comment: Unblinded	Not applicable	High	Comment: Unblinded
Ghosh 2008	N	High	Quote: "Divided into 2 groups randomly, irrespective ofÉ" Comment: No mention of how this was performed, also some baseline imbalances suggest problems with randomization	High	Comment: Unlikely to have been concealed based on wording of their randomization procedure (see sequence generation)	Not applicable	High	Comment: Open-label	Not applicable	High	Comment: Open-label
Mottaghi 2005	N	High	Quote: "Systematically allocated" (although states randomly divided in abstract)	High	Quote: "Systematically allocated" (although states randomly divided in abstract)	Not applicable	High	Comment: Open label	Not applicable	High	Comment: Open label
Zhang 2004	N	Unclear	Comment: Patients separated based on random number table	Unclear	Comment: Patients separated based on random number table; no mention of central randomization	Not applicable	High	Comment: Open-label	Not applicable	High	Comment: Open-label
Ferraz 1994	(Katchamart 2010)	Low	See Cochrane	Unclear	Comment: Allocation concealment not described	Not applicable	Low	See Cochrane	Not applicable	Low	See Cochrane
Trnavsky 1993	N	Unclear	Comment: Randomized without additional details	Unclear	Comment: Randomized without additional details	Low	Low	Comment: Double-blind with matching placebos	Low	Unclear	Comment: Double-blind without additional details for clinical

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											outcomes; x-ray readers blinded
METGO 2005	N	Low	Quote: "was generated with a random number table with variable-sized blocks"	Low	Quote: "Center inves- tigators received unique randomization codes in sequentially numbered sealed opaque envelopes."	Not applicable	Low	Quote: "The multidose (10 ml of 50 mg/ml) vials of IM gold (aurothioglucose) and placebo were in bottles impenetrable to light. The gold or placebo was administered using graduated 1-ml amber-colored glass syringes "	Not applicable	Low	Quote: "A blinded assessor other than the center investigator or study nurse, who was kept uninformed of patient treatment and treatment response, assessed the key variables for the primary outcome as well as grip strength and morning stiffness at the 0-, 12-, 24-, 36-, and 48-week visits and at one premature withdrawal visit, if necessary. The assessor had no contact with study participants at other visits."
CareRA 2015	N	Unclear	Comment: Randomized without additional details	Unclear	Comment: Randomized without additional details	Not applicable	High	Comment: Open-label	Not applicable	High	Comment: Open-label
Mehrotra 2006	N	Unclear	Comment: "Randomly divided" only comment on randomization	Unclear	Comment: "Randomly divided" only comment on randomization	Unclear	High	Comment: No mention of blinding	High	High	Comment: No mention of blinding
Kremer 2002	N	Low	Quote: "Randomization was done by using the Aventis stan- dard random-code generator"	Low	Quote: "The randomization code used was concealed from investigators and patients throughout the study."	Not applicable	Low	Comment: Double-blind with matching placebos	Not applicable	Low	Comment: Double-blind and "All ACR assessments were performed by the investigators, and the same assessor performed all analyses throughout the study whenever possible to increase the reliability of the assess- ment." Therefore, unblinding unlikely to have occured
MASCOT 2007	(Katchamart 2010)	Low	See Cochrane	Low	See Cochrane	Low	Unclear	Comment: Double-blind without additional details	Low	Unclear	Comment: Double-blind without additional details; X-ray
Tascioglu 2003	(Katchamart 2010)	Unclear	See Cochrane	Unclear	Comment: Randomized without additional	Not applicable	High	Comment: Open label	Not applicable	High	Comment: Open label

					details						
Islam 2000	(Katchamart 2010)	Unclear	See Cochrane	Unclear	See Cochrane	Not applicable	High	Comment: Open label	Not applicable	High	Comment: Open label
Dougados 1999	(Katchamart 2010)	Unclear	See Cochrane	Unclear	See Cochrane	Low	Unclear	Comment: Double blind, no description of whether placebo matched active drug	Low	Unclear	Comment: Double-blind with no additional details
Haagsma 1997	(Katchamart 2010)	Unclear	Comment: Does not describe how randomization sequence was generated	Unclear	Comment: Randomized without additional details	Not applicable	Low	Comment: Double-blind with matching placebos	Not applicable	Unclear	Comment: Double-blind with no additional details
Haagsma 1994	(Katchamart 2010)	Unclear	Comment: Does not describe how randomization sequence was generated	Unclear	Comment: Randomized without additional details	Not applicable	High	Comment: Open-label	Not applicable	High	Comment: Open-label
tREACH 2013	N	Low	Quote: "Patients were randomised...by an independent call-centre during working hours".	Low	Quote: "Patients were randomised...by an independent call-centre during working hours".	Not applicable	High	Comment: Single blinded	Not applicable	Unclear	Comment: Nurse assessors, but not physicians blinded
Gubar 2008	N	Unclear	Comment: Cards indicating the type of therapy were randomly selected indpenedently from investigators; method of generating cards not specified	Unclear	Comment: Cards indicating the type of therapy were randomly selected indpenedently from investigators; not clear if envelopes were opaque	Not applicable	High	Comment: Open label	Not applicable	High	Comment: Open label
Odell 2002	N	Low	Quote: "equal numbers of cards with each group assignment were mixed, drawn, and placed in sequentially numbered envelopes that were opened as the patients were enrolled"	Low	Quote:"The ran-domization and distribution of medication was handled centrally"	Not applicable	Low	Quote: "The placebos were supplied by the pharmaceutical companies and were identical to the active medications"	Not applicable	Low	Quote: "by their physicians, who were unaware of the treatment assignment"
Odell 1996	(Katchamart 2010)	Low	See Cochrane	Low	See Cochrane	Not applicable	Low	See Cochrane	Not applicable	Low	See Cochrane
Sigidin Ya 1994	N	Unclear	Comment: Randomized without additional details	Unclear	Comment: Randomized without additional details	Unclear	High	Comment: Open label	High	High	Comment: Open label
Westedt 1994	N	Unclear	Quote: "Envelopes containing the randomization lists were prepared in advance" Comment: Unclear how list was generated	Unclear	Quote: "Envelopes containing the randomization lists were prepared in advance" Comment: No mention of whether this process occurred independently of	Not applicable	High	Comment: Open-label	Not applicable	High	Comment: Open-label

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					investigators						
Jeurissen 1991	N	Unclear	Comment: Randomized without additional details	Unclear	Comment: Randomized without additional details	Low	Low	Comment: Double-blind with matching placebos	Low	Unclear	Comment: Double-blind with matching placebos; Quote: "Medical treatment and clinical evaluation of all patients was performed by the same rheumatologist"
Arnold 1990	N	Unclear	Comment: Randomized without additional details	Unclear	Comment: Randomized without additional details	Not applicable	High	Comment: Open label	Not applicable	High	Comment: Open label
Hamdy 1987	N	Low	Quote: "by a predetermined computer code"	Unclear	Comment: Not described	Low	Low	Comment: Double-blind with double-dummy design	Low	Unclear	Quote: "The same blinded physician was the assessorÉ" Comment: Blinding of x-ray reader not described
Singh 2000	N	Unclear	Comment: Randomized without additional details	Unclear	Comment: Randomized without additional details	Not applicable	High	Comment: Open-label	Not applicable	High	Comment: Open-label
Drosos 1998	N	Low	Quote:"randomization tables"	High	Comment: Sequential patients assigned "code numbers", then randomized using random number table; high likelihood that subsequent patients could bhave been predicted	Unclear	High	Comment: Open-label	Unclear	High	Comment: Open-label
Alam 2012	N	High	Quote:"É first patients were selected by lottery method into methotrexate group then rest of the patients was included alternately into HCQ and MTX"	High	Comment: No concelament; quasi-randomized	Not applicable	High	Comment: Open-label	Not applicable	High	Comment: Open-label
Van Jaarsveld 2000	N	Low	Quote: "All randomization was done by drawing sealed envelopes from blocks of 100"	Low	Quote: "All randomization was done by drawing sealed envelopes from blocks of 100"	Not applicable	High	Comment: Open-label	Not applicable	High	Comment: Open-label
Hamilton 2001	N	Unclear	Comment: Randomized without additional details	Unclear	Comment: Randomized without additional details	Not applicable	High	Comment: Open-label	Not applicable	High	Comment: Open-label
Rau 1997	N	Unclear	Comment: Randomized without additional details	Unclear	Comment: Randomized without additional details	Not applicable	Low	Comment: Double-blind with matching placebos	Not applicable	Low	Comment: Well described

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Rau 1991	N	Unclear	Comment: Randomized, but no details provided	Unclear	Comment: Randomized, but no details provided	Low	Low	Comment: Blinded with matching medications	Unclear	Low	Comment: Blinded outcome assessors, but not discussed if x-ray readers were blinded
Morassut 1989	N	Low	Quote: "by a predetermined computer code"	Unclear	Comment: Not described	Not applicable	Unclear	Comment: Double-blind without additional details	Not applicable	Low	Quote: "Éby the same blinded assessor"
Suarez-Almazor 1988	N	Unclear	Comment: Randomized without additional details	Unclear	Comment: Randomized without additional details	Not applicable	Unclear	Comment: Double-blind without additional details	Not applicable	Unclear	Comment: Double-blind without additional details
Elmuntaser 2014	N	Unclear	Comment: Randomized without additional details	Unclear	Comment: Randomized without additional details	Not applicable	High	Comment: Open-label	Not applicable	High	Comment: Open-label
Fedorenko 2012	N	Unclear	Comment: Randomized without additional details	Unclear	Comment: Randomized without additional details	Not applicable	High	Comment: No mention of blinding	Not applicable	High	Comment: No mention of blinding
Jaimes-Hernandez 2012	N	Low	Quote: "Table of random numbers"	Low	Quote: "Éwithout the intervention of the reviewers"	Not applicable	Low	Comment: Matching placebos used	Not applicable	Unclear	Comment: "Researchers blinded" but no other details
Lisbona 2012	N	Unclear	Comment: Randomized without additional details	Unclear	Comment: Randomized without additional details	Not applicable	High	Comment: No mention of blinding; not placebo controlled	Not applicable	High	Comment: No mention of blinding; not placebo controlled
Ishaq 2011	N	Unclear	Comment: Randomized without additional details	Unclear	Comment: Randomized without additional details	Not applicable	Unclear	Comment: "double-blind" but few details provided; was double-dummy design, but no mention of PBO formulation	Not applicable	Unclear	Comment: "double-blind" but few details provided; was double-dummy design, but no mention of PBO formulation
Fiehn 2007	N	Low	Quote: "ÉOpening a closed envelop in the study centre at the University of Heidelberg with a 50% chance of being stratified"	Low	Quote: "ÉOpening a closed envelop in the study centre at the University of Heidelberg with a 50% chance of being stratified"	Not applicable	High	Comment: Open-label	Not applicable	High	Comment: Open-label
Bao 2003	N	High	Comment: Randomized without additional details - imbalance in numbers between groups with no mention of different randomization ratio (i.e.- 3:2) used	Unclear	Comment: Not described	Not applicable	Low	Quote: "The color, size tase and package of leflunomide were identical with those of its placebo, so that neither physician not patient could distinguish them. MTX and its corresponding placebo were	Not applicable	Unclear	Quote: "The color, size tase and package of leflunomide were identical with those of its placebo, so that neither physician not patient could distinguish them. MTX and its corresponding placebo were similarly disguised."

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								similarly disguised."			Comment: Did not discuss which assessors blinded
Lau 2002	N	Unclear	Comment: Randomized without additional details	Unclear	Comment: Randomized without additional details	Not applicable	Unclear	Comment: Double-blind without additional details	Not applicable	Unclear	Comment: Double-blind without additional details
Reece 2002	N	Unclear	Comment: Randomized without additional details	Unclear	Comment: Randomized without additional details	Not applicable	Unclear	Comment: Double-blind without additional details	Not applicable	Unclear	Comment: Double-blind without additional details
Shuai 2002	N	Unclear	Comment: Randomized without additional details	Unclear	Comment: Randomized without additional details	Not applicable	Unclear	Comment: Double-blind without additional details	Not applicable	Unclear	Comment: Double-blind without additional details
Hu 2001	N	High	Comment: States randomized, but different numbers between groups and no mention of differential randomization	Unclear	Comment: No details	Not applicable	Low	Comment: Single-blind with placebo tablets	Not applicable	High	Comment: Single-blind only
Lao 2001	N	Unclear	Comment: Randomized without additional details	Unclear	Comment: Randomized without additional details	Not applicable	Unclear	Comment: Double-blind without additional details	Not applicable	Unclear	Comment: Double-blind without additional details
Bao 2000	N	Unclear	Comment: Randomized without additional details	Unclear	Comment: Randomized without additional details	Not applicable	Unclear	Comment: Double-blind without additional details	Not applicable	Unclear	Comment: Double-blind without additional details
Emery 2000	N	Unclear	Comment: Randomized without additional details	Unclear	Comment: Randomized without additional details	Low	Unclear	Comment: Double-blind without additional details	Low	Unclear	Comment: X-ray readers blinded; no details on blinding of other outcome assessors
Kraan 2000	N	Unclear	Comment: Randomized without additional details	Unclear	Comment: Randomized without additional details	Not applicable	Unclear	Comment: Double-blind without additional details	Not applicable	Unclear	Comment: Double-blind without additional details
ULTRA 1999	N	Low	Quote: "Éused a computerized adaptive algorithmÉ"	Low	Comment: Centralized allocation	Low	Low	Comment: Double-blind, with placebos	Unclear	Unclear	Comment: Double-blind, but no details about blinding of outcome assessors including clinical and x-ray outcomes
Ferraccioli 2002	N	Unclear	Comment: Randomized without additional details	Unclear	Comment: Randomized without additional details	Not applicable	High	Comment: Open-label	Not applicable	High	Comment: Open-label
Salaffi 1995	N	Low	Quote:"By a predetermined computer code"	Unclear	Comment: Not described	Not applicable	High	Comment: Open-label	Not applicable	High	Comment: Open-label
Ahmed 2010	N	Unclear	Quote: "randomly assigned (according	High	Quote: "randomly assigned	Not applicable	High	Comment: Open-label	Not applicable	High	Comment: Open-label

			to random table)"		(according to random table)" Comment: Single-author study, so would have access to randomization sequence						
Braun 2008	N	Low	Quote: "Permuted block randomization stratified by study center" Comment: Does not discuss how sequence generated (although likely computer generated)	Unclear	Comment: Not described	Not applicable	Unclear	Comment: Double-blind, double-dummy, but syringe not identical	Not applicable	Unclear	Comment: Double-blind, double-dummy, but syringe not identical
Pinheiro 1993	N	Unclear	Comment: Randomized without additional details	Unclear	Comment: Randomized without additional details	Not applicable	Low	Comment: Well described; DB with identical PBOs	Not applicable	Low	Comment: Well described; DB with identical PBOs
Furst 1989	N	Unclear	Comment: Randomized without additional details	Unclear	Comment: Randomized without additional details	Not applicable	Low	Comment: Well described; DB with identical PBOs	Not applicable	Low	Comment: Well described; DB with identical PBOs
Anderson 1985	N	Low	Quote: "Randomly assigned by random number tables"	Unclear	Comment: No details provided	Not applicable	Unclear	Comment: Double-blind without additional details; no discussion of whether PBO formulation was identical	Not applicable	Unclear	Comment: Double-blind without additional details; no discussion of whether PBO formulation was identical
Weinblatt 1985	N	Unclear	Comment: Randomized without additional details	Unclear	Comment: Randomized without additional details	Not applicable	Unclear	Comment: Double-blind without additional details	Not applicable	Unclear	Comment: Double-blind without additional details
Williams 1985	N	Unclear	Comment: "Randomly assigned"; no details regarding sequence generation	Low	Comment: Central randomization	Not applicable	Unclear	Comment: Double-blind without additional details	Not applicable	Unclear	Comment: Double-blind without additional details

Table 2: Detailed risk of bias assessment: domains "incomplete outcome data" to "overall"

Study ID	Incomplete outcome data (attrition bias): All other outcomes	Incomplete outcome data (attrition bias): Radiographic outcomes	Incomplete outcome data (attrition bias): Withdrawals	Incomplete outcome data: Support for decision	Selective reporting (reporting bias)	Selective reporting: Support for decision	Other bias	Other bias: Support for decision	Overall: Radiographic outcomes	Overall: Withdrawals	Overall: All other outcomes	Overall: Support for decision
AVERT 2015	Unclear	Not applicable	Low	Comment: ~10-20% WD across arms, not completely balanced, NRI used	Low	Comment: All protocol outcomes reported	Low	Comment: No other ROB identified	Not applicable	Low	Low	Comment: Well designed and reported, some missing data but no major imbalance
Iwahashi 2014	Low	Not applicable	Low	Comment: Very low WD rates, not an EE design, well reported	Low	Comment: All protocol outcomes reported	Low	Comment: No other ROB identified	Not applicable	Low	Low	Comment: Double-blind, low drop-out
ASSET 2013	Low	Not applicable	Low	Comment: Very low drop-out	Low	Comment: All protocol outcomes reported	Low	Comment: No other ROB identified	Not applicable	Low	Low	Comment: Well-reported, low drop-out rates
Takeuchi 2013a	Low	Not applicable	Low	Comment: Very low drop-out	Unclear	Comment: Protocol not available	Low	Comment: No other ROB identified	Not applicable	Low	Low	Comment: Well designed and reported study
Matsubara 2012	Low	Not applicable	Low	Comment: Very low WD rate	Unclear	Comment: All protocol outcomes reported, but full trial not yet published	Low	Comment: No other ROB identified	Not applicable	Unclear	Unclear	Comment: Well reported on clintrials site with low drop-out, but full article not yet published
ACQUIRE 2011	Low	Not applicable	Low	Comment: <10% WD, balanced	Low	Comment: All protocol outcomes reported	Low	Comment: No other ROB identified	Not applicable	Low	Low	Comment: Well-reported, low drop-out rates
Shim 2010	Low	Not applicable	Low	Comment: Low WD rate	High	Comment: Unpublished. Outcomes on clinicaltrials.gov	Low	Comment: No other ROB identified	Not applicable	Unclear	Unclear	Comment: Well reported on clintrials site with low drop-out, but full article not yet published
AGREE 2009	Low	Low	Low	Comment: ~10% drop-out, balanced, no early escape. X-ray drop-outs well reported and relatively low with balance across groups	Low	Comment: All protocol outcomes reported	Low	Comment: No other ROB identified	Low	Low	Low	Comment: Well-reported, low drop-out rates
AIM 2006	Unclear	Unclear	Low	Comment: 26% WD PBO versus 11% ABAT; 92% x-rays complete. Also - 14 patients excluded from one site because of non-adherence issues. Multiple sensitivity analyses performed around imputation decisions with robust results	Unclear	Comment: A larger number of secondary outcomes in protocol, not all reported. All major primary outcomes and typical outcomes reported	Low	Comment: No other ROB identified	Unclear	Low	Unclear	Comment: Well designed and reported study. Concern over loss to follow-up (particularly the 14 patients excluded from one site), but results robust to sensitivity analyses
Kremer 2005	High	Not applicable	Low	Comment: Drop-out high and imbalanced. Also unusual imputation; WD inefficacy counted as non-responders, but WD for other reasons used LOCF	Unclear	Comment: Protocol not available	Low	Comment: No other ROB identified	Not applicable	Low	Unclear	Comment: Double-blind, but relatively high drop-out rate with imbalance between groups and questionnable method of imputation. Some study details not well reported.
RA-BEAM 2015	Unclear	NA	Unclear	Comment: >90% completion rate, but 26% rescue rate in PBO arm	Unclear	Comment: Only published as abstract	Low	Comment: No other ROB identified	Not applicable	Low	Low	Comment: Published only as abstract, some study details unclear
Weinblatt 2015	Low	Not applicable	Low	Comment: Low WD rate	Unclear	Comment: Outcomes not specified on ct.gov	Low	Comment: No other ROB identified	Not applicable	Low	Low	Comment: Double-blind, double dummy with low WD rate

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HOPEFUL-I 2014	Unclear	Unclear	Unclear	Comment: ~20% WD rate, but also EE design with 28/163 in PBO arm receiving rescue therapy	Low	Comment: All protocol outcomes reported	Low	Comment: No other ROB identified	Unclear	Unclear	Unclear	Comment: Main ROB is WD rate and EE design
OPERA 2014	Unclear	Not applicable	Unclear	Comment: WD reported at study end, not at 3 months when non-responders switched treatment (strategy trial)	Unclear	Comment: Protocol does not report planned outcomes	Low	Comment: No other ROB identified	Not applicable	Unclear	Unclear	Comment: Main issue for this review is the switch to triple therapy allowed (strategy trial)
HITHARD 2013	Low	Unclear	Low	Comment: Low WD at 24 weeks (end-trial WD much higher)	Low	Comment: All protocol outcomes reported	Low	Comment: No other ROB identified	Low	Low	Low	Comment: Some study details not well reported; but overall low drop-out rate. Also using 24 week outcomes of 48 week trial
OPTIMA 2013	Low	Low	Low	Comment: 10% drop-out, balanced, most had x-rays available	Low	Comment: All protocol outcomes reported	Low	Comment: No other ROB identified	Low	Low	Low	Comment: Some study details missing, but low WD and double-blind
AUGUST-II 2011	Unclear	Not applicable	Low	Comment: 10-15% WD rate	Unclear	Comment: Protocol available, but does not specify outcomes in detail	Low	Comment: No other ROB identified	Not applicable	Unclear	Unclear	Comment: ADA arm open-label
Chen 2011	Unclear	Not applicable	Unclear	Comment: Missing data and drop-outs not reported	Unclear	Comment: Protocol not available	Low	Comment: No other ROB identified	Not applicable	Unclear	Unclear	Comment: Lack of study details, particularly no discussion of WD, but DB PBO controlled
Chen 2009	Unclear	Not applicable	Unclear	Comment: Missing data and overall WD not reported (WDAE reported)	Unclear	Comment: Protocol not available	Low	Comment: No other ROB identified	Not applicable	Unclear	Unclear	Comment: Blinded, but study details not well reported.
GUEPARD 2009	Low	Low	Low	Comment: Low WD rate and balanced at trial end (strategy trial); outcomes for review taken at 12 weeks where wd not reported.	Unclear	Comment: Protocol not available	Unclear	Comment: Recruitment numbers did not match sample size	Unclear	High	High	Comment: Unblinded (except for x-ray readers), randomization not well described - done at each center
Huang 2009	Low	Not applicable	Low	Comment: Very low WD rate to 12 weeks	Low	Comment: All protocol outcomes reported	Low	Comment: No other ROB identified	Not applicable	Unclear	Unclear	Comment: Some lack of study details, but DB, pbo-controlled with low drop-out
Bejarano 2008	High	Not applicable	Low	Comment: High drop-out, differential between arms, but WD well reported.	Unclear	Comment: Protocol not available	Low	Comment: No other ROB identified	Not applicable	Low	Unclear	Comment: Well designed, described study, but high WD rate in PBO arm
Kim 2007	Unclear	Not applicable	Unclear	Comment:Low WD, relatively low EE rates, but with imbalance. >60% of PBO patients completed Rx on assigned Rx.	Unclear	Comment: Protocol not available	Low	Comment: No other ROB identified	Not applicable	Unclear	Unclear	Comment: Lack of study details. EE design, although EE relatively low
PREMIER 2006	High	High	Low	Comment: 40% WD rate in PBO arm, 25% in treatment arm.	Unclear	See Cochrane	Low	Comment: No other ROB identified	Unclear	Low	Unclear	Comment: Main ROB is high drop-out rate
DE019 2004	High	High	High	Comment: 70-80% completion rates, but also had 33% patients in PBO get rescue treatment versus very few in Rx arms	Unclear	Comment: Protocol not available	Low	Comment: No other ROB identified	Unclear	Unclear	Unclear	Comment: Double blind, study details not well reported, relatively high WD/rescue rate
ARMADA 2003	High	Not applicable	Unclear	Comment: Rescue design with a large number of patients requiring rescue therapy (56% in highest arm). Also WD not reported by arm	Unclear	Comment: Protocol not available	Low	Comment: No other ROB identified	Not applicable	Unclear	Unclear	Comment: Main ROB is WD rate given early escape design

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C-EARLY 2015	High	High	Low	Comment: High WD rate in PBO arm ~50%	Low	Comment: All protocol outcomes reported	Low	Comment: No other ROB identified	Unclear	Low	Unclear	Comment: Main issue is incomplete data
C-OPERA 2014	Unclear	Not applicable	Not applicable	Comment: WD not reported	Unclear	Comment: Published only as abstract.No outcomes on protocol	Low	Comment: No other ROB identified	Unclear	Not applicable	Unclear	Comment: Double blind, but only published as abstract and lack of many study details
JRAPID 2014	High	High	Unclear	Comment: High rate of drop-out when WD combined with EE (25/77 PBO and 66/82 active completed Rx)	Unclear	Comment: Protocol available, but does not specify outcomes	Low	Comment: No other ROB identified	High	Unclear	High	Comment: Well designed and reported, but high and imbalance in patients entering EE
Choy 2012	High	Not applicable	Low	Comment: High rates of WD at 6 months with imbalance between groups (54% PBO, 78%TCZ)	Unclear	Comment: Protocol not clear on what outcomes, also 6 month data of a 2-year study	Low	Comment: No other ROB identified	Not applicable	Low	High	Comment: Main source of bias is very high WD rates with imbalance between groups. Imputation by mixed methods (NRI for dichotomous, but LOCF for joint counts and continuous)
Kang 2012	High	Not applicable	High	Comment: High and differential rate of WD (50% in PBO group completed Rx). EE design and EE not reported	High	Comment: Protocol not available and published only as abstract	Low	Comment: No other ROB identified	Not applicable	High	High	Comment: Published only as abstract, High and differential rate of WD and EE not reported
RAPID-II 2009	High	High	Unclear	Comment: Very high WD rate when EE patients in included in all arms with imbalance. PBO group WD+EE>80%	Unclear	Comment: Protocol available, but does not specify outcomes	Low	Comment: No other ROB identified	High	Unclear	High	Comment: Very high withdrawal/EE rate with imbalance
RAPID-I 2008	High	High	Unclear	Comment: Very high WD rate when EE patients in included in all arms with imbalance. PBO group: 43/199 completed Rx on assigned therapy	Unclear	Comment: Protocol available, but does not specify outcomes	Low	Comment: No other ROB identified	High	Unclear	High	Comment: Very high withdrawal/EE rate with imbalance
EMPIRE 2014	Unclear	Unclear	Low	Comment: WD ~20%, balanced. WD well reported	Low	Comment: All protocol outcomes reported	Unclear	Comment: Allowed discontinuation of therapy after week 32	Unclear	Low	Unclear	Comment: Well described, moderate WD rate
Takeuchi 2013b	Unclear	Unclear	Low	Comment: ~20% WD, relatively balanced with standard imputation techniques	Low	Comment: All protocol outcomes reported	Low	Comment: No other ROB identified	Unclear	Low	Unclear	Comment: Moderate WD rate, otherwise DB and reasonably well reported
Huang 2012	Unclear	Not applicable	Not applicable	Comment: WD not reported	Unclear	Comment: No protocol available; study done for primarily a basic science outcome with clinical outcomes secondary; therfore, may not expect typical outcomes	Low	Comment: No other ROB identified	Not applicable	Not applicable	High	Comment: Concerns over randomization sequence and blinding; also poorly reported
ESCAPE 2010	Low	Not applicable	Low	Comment: Relatively low WD rate, balanced between PBO and ETN arms.	Unclear	Comment: Protocol available, but does not specify outcomes	Low	Comment: No other ROB identified	Not applicable	Unclear	Unclear	Comment: Main ROB is open-label ETN arm in setting of an experimental drug
COMET 2008	High	High	Low	Comment: Withdrawal rates 20%/30%, unbalanced with LOCF used for	Unclear	Comment: Study reports more outcomes than listed	Low	Comment: No other ROB identified	Unclear	Low	Unclear	Comment: Well-designed, but high WD rate, with difference

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				imputation. For the primary outcome, results were compared to an observed Rx analysis with similar findings		in protocol; protocol must not be complete						between arms.
Marcora 2006	Low	Not applicable	Low	Comment: Very low WD rate, balanced. Did not do true ITT analysis, but only 2/0 patients WD	Unclear	Comment: Protocol not available	Low	Comment: No other ROB identified	Not applicable	High	High	Comment: Not blinded and concern over allocation concealment, did not do ITT analysis
Lan 2004	Low	Not applicable	Low	See Cochrane	Unclear	Comment: Protocol not available	Low	Comment: No other ROB identified	Not applicable	Unclear	Unclear	Comment: Main ROB is poor reporting of study details
TEMPO 2004	High	High	Low	Comment: 30% WD in MTX arm; 16% in combination arm. LOCF used for imputation (not NRI)	Unclear	Comment: Protocol not available	Low	Comment: No other ROB identified	Unclear	Low	Unclear	Comment: Drop-out rate main source of bias. Used LCOF for imputation of dichotomous outcomes, which differs from NRI used for most trials
ERA 2000	Low	Low	Low	Comment: >90% follow-up, 15 additional patients (total) had missing x-rays; balanced across groups. Missing x-rays imputed using linear extrapolation, but expected impact of this is minimal	Unclear	Comment:Protocol not available	Low	Comment: No other ROB identified	Low	Low	Low	Comment: Lack of some study details, but blinded with a low drop-out rate
Weinblatt 1999	Unclear	Not applicable	Low	Comment: Moderate WD rate with some imbalance (97%/80%); NRI for missing dichotomous and LOCF for missing continuous	Unclear	Comment: Protocol not available	Low	Comment: No other ROB identified	Not applicable	Low	Unclear	Comment: Moderate WD rates; study details reasonably well reported with some gaps
GOBEFORE 2013	High	High	Unclear	Comment: >30% WD rate, EE design, although EE relatively low. 51% of patients in PBO arm completed Rx on azssigned Rx	Unclear	Comment: No outcomes specified on CT.gov protocol	Low	Comment: No other ROB identified	Unclear	Unclear	Unclear	Comment: Main ROB is missing outcome data.
GOFURTHER 2013	Unclear	Unclear	Unclear	Comment: Low WD rate apart from EE, EE imputed by LOCF for dichotomous outcomes	Unclear	Comment: x-ray outcomes on clintrials website but not reported	Unclear	Comment: Allowed early escape, but did not analyze outcomes at trial end through NRI	Unclear	Unclear	Unclear	Comment: Main ROB is EE design; imputed using LOCF only for PBO arm (treatment arm not imputed). Missing description of x-ray outcomes
NCT01248780 2013	Unclear	Not applicable	Unclear	Comment: EE design, EE patients not reported	High	Comment: Published only as trial register	Low	Comment: No other ROB identified	Not applicable	Unclear	Unclear	Comment: Double-blind, but lack of reporting of study details and no mention of how many patients required EE
GOFORTH 2012	High	High	Unclear	Comment: >30% EE in PBO arm at 24 weeks. Components of ACR imputed if missing using LOCF (clinical outcomes); missing x-ray values imputed (see appendix) but unclear how much missing data	Unclear	Comment: Protocol not available	Low	Comment: No other ROB identified	Unclear	Unclear	Unclear	Comment: Moderate EE in PBO arm (64% of patients in PBO arm completed on assigned Rx). Processes of allocation, selection and randomization also not well described.
GOFORWARD 2009	High	High	Unclear	Comment: Low WD rate, but high EE rate (>30%), imbalance in EE across	Unclear	See Cochrane	Low	Comment: No other ROB identified	Unclear	Unclear	Unclear	Comment: Main ROB is imputation of missing data and early escape

Hazlewood GS, Barnabe C, Tomlinson G, Marshall D, Devoe DJA, Bombardier C. Methotrexate monotherapy and methotrexate combination therapy with traditional and biologic disease modifying anti-rheumatic drugs for rheumatoid arthritis: A network meta-analysis. Cochrane Database of Systematic Reviews 2016, Issue 5. Art. No.: CD010227. DOI: 10.1002/14651858.CD010227.

				arms. Missing x-ray data unclear								design. Details of other trials aspects not well specified.
Kay 2008	Unclear	Not applicable	Low	Comment: 10-20% drop out at week 16	Unclear	Comment: More outcomes in paper than listed in protocol	Unclear	Comment: Allowed early escape, but did not analyze outcomes at trial end through NRI	Not applicable	Unclear	Unclear	Comment: Missing some study details, but double blind.
MacIsaac 2014	Low	Not applicable	Low	Comment: No drop-out	Low	Comment: All protocol outcomes reported	Low	Comment: No other ROB identified	Not applicable	Low	Low	Comment: No issues
Kim 2013	Unclear	Not applicable	Low	Comment: ~20% WD rate, balanced, but not well reported (only total WD reported)	Unclear	Comment: No outcomes specified on trial register	Low	Comment: No other ROB identified	Not applicable	Unclear	Unclear	Comment: Double-blind, 20%WD rate (not well reported)
Li 2013	Unclear	Not applicable	Unclear	Comment: Very low WD rate, but EE design and EE not reported	Unclear	Comment: Full-text not yet available	Low	Comment: No other ROB identified	Not applicable	Unclear	Unclear	Comment: Double-blind and low WD rate, but lack of study details and EE design with no reporting of EE
Tam 2012	Low	Not applicable	Low	Comment: Low WD rate	Unclear	Comment: Protocol not available	Low	Comment: No other ROB identified	Not applicable	High	High	Comment: Not blinded and poor reporting of study details
Xia 2011	Unclear	Not applicable	Not applicable	Comment: Missing data/withdrawals not reported	Unclear	Comment: No protocol	Low	Comment: No other ROB identified	Not applicable	Not applicable	High	Comment: Poorly reported study; main ROB is uncertainty around randomization and lack of blinding
Durez 2007	Low	Not applicable	Low	Comment: Low drop-out	Unclear	Comment: Protocol not available	Low	Comment: No other ROB identified	Not applicable	Unclear	Unclear	Comment: Patients not blinded
Abe 2006	Low	Not applicable	Low	Comment: Low WD rate	Unclear	Comment: Protocol not available	Low	Comment: No other ROB identified	Not applicable	Low	Low	Comment: Lack of study details, but double-blind and low drop-out
START 2006	Low	Not applicable	Low	Comment: <10% drop-out to month 6 and balanced	Unclear	Comment: Protocol not available	Low	Comment: No other ROB identified	Not applicable	Low	Low	Comment: Well designed, reported and low drop-out
Zhang 2006	Unclear	Not applicable	Unclear	Comment: 10-20% drop-out. WD not well reported	Unclear	Comment: Protocol not available	Low	Comment: No other ROB identified	Not applicable	Unclear	Unclear	Comment: Many details not reported
BEST 2005	Low	Unclear	Low	Comment: Very low withdrawal rate	Unclear	Comment: Protocol not available	Low	Comment: No other ROB identified	Unclear	Unclear	Unclear	Comment: Well designed, low drop-out but patients unblinded
Quinn 2005	Low	Low	Low	Comment: Low drop-out	Unclear	Comment: Protocol not available	Low	Comment: No other ROB identified	Low	Low	Low	Comment: Double-blind, low drop-out
ASPIRE 2004	Unclear	Unclear	Unclear	Comment: 10-20% drop-out, relatively balanced. Some patients excluded from efficacy analysis; not true ITT	Unclear	Comment: Protocol not available	Low	Comment: No other ROB identified	Unclear	Unclear	Unclear	Comment: Well designed and reported. Some missing data and not true ITT. Data imputation methods for all variables not well described
ATTRACT 2000	High	High	Low	Comment: 50%WD rate in PBO arm with unclear methods of imputation	Unclear	Comment: Protocol not available	Low	Comment: No other ROB identified	Unclear	Low	Unclear	Comment: Main ROB is high and differential drop-out with unclear methods of imputation
IMAGE 2012	Unclear	Unclear	Unclear	Comment:Withdrawal rates to one year 80% and not well reported; non-	Unclear	Comment: Not all secondary outcomes reported	Low	Comment: No other ROB identified	Unclear	Low	Unclear	Comment: Double-blind,Moderate drop-out rate, imputation method

				responder imputation for ACR responses (appropriate); linear interpolation for x-ray data								for x-rays unclear
SERENE 2010	Unclear	Not applicable	Unclear	Comment: Low drop-out but num patients requiring rescue treatment prior to week 24 not reported.	Unclear	Comment: Protocol not available	Low	Comment: No other ROB identified	Not applicable	Unclear	Unclear	Comment: Double-blind, low drop-out, but study details unclear and num of rescue patients prior to week 24 not reported
DANCER 2006	High	Not applicable	Low	Comment: 35% drop out in PBO arm, imbalanced. Appropriate imputation (NRI for dichotomous)	Unclear	Comment: Protocol not available	Low	Comment: No other ROB identified	Not applicable	Unclear	Unclear	Comment: Some study details missing and high drop out in PBO arm
Edwards 2004	Low	Not applicable	Low	Comment: Low drop-out	Unclear	Comment: Protocol not available	Low	Comment: No other ROB identified	Not applicable	Low	Low	Comment: Well designed, reported and low drop-out
SURPRISE 2016	Unclear	Unclear	Unclear	Comment: 78% completed, balanced between arms	Low	Comment: All protocol outcomes reported (on clintrials website)	Low	Comment: No other ROB identified	High	High	High	Comment: Open-label, relatively high WD rate
MEASURE 2015	Unclear	Not applicable	Unclear	Comment: Very low WD, but high EE rates (~30%)	Low	Comment: All protocol outcomes reported	Low	Comment: No other ROB identified	Not applicable	Unclear	Unclear	Comment: DB, low WD rate, but high EE rate, with imbalance
TOMERA 2014	Unclear	Not applicable	Not applicable	Comment: WD not reported	Unclear	Comment: Protocol not avialable	Low	Comment: No other ROB identified	Not applicable	Not applicable	Unclear	Comment: Lack of reporting of study details and no discussion of drop-outs
ACT-RAY 2013	Low	Unclear	Low	Comment: Low WD rates, but missing x-ray data unclear	Unclear	Comment: Protocol not clear on what outcomes, also 6 month data of a 2-year study	Low	Comment: No other ROB identified	Low	Low	Low	Comment: Overall low ROB as randomized DB with low WD rate
FUNCTION 2013	High	High	Unclear	Comment: 30% WD over 2 years; escape patients not reported (trial only reported as abstract and CT register so far)	Unclear	Comment: Full-text not yet published; available as CT register though	Low	Comment: No other ROB identified	Unclear	Unclear	Unclear	Comment: Double-blind RCT, reported on CT.gov, but full-text (including results of early escape) not yet reported.
LITHE 2011	High	High	Unclear	Comment:WD rate overall ~15%, but very high rates of escape in PBO arm (>50%), imbalance.	Low	Comment: All usual outcomes and all outcomes in protocol reported	Low	Comment: No other ROB identified	High	Unclear	High	Comment: Main ROB is very high rate of EE in PBO arm (~33% completed Rx on assigned Rx in PBO arm)
AMBITION 2010	Unclear	Not applicable	Unclear	Comment: Low WD rate and EE rate, but no discussion of what EE treatment was and how imputation was performed	Unclear	Comment: Protocol available, but does not specify outcomes	Low	Comment: No other ROB identified	Not applicable	Unclear	Unclear	Comment: Main ROB is lack of study details regarding impuation of missing data/handling of early escape patients. Also unclear if other DMARDs were used
SATORI 2009	High	Not applicable	Low	Comment: 48% vs 11% WD rate in PBO versus treatment arm; LOCF used for imputation	Unclear	Comment: Protocol available, but does not specify outcomes	Low	Comment: No other ROB identified	Not applicable	Unclear	High	Comment: Very high WD rate
OPTION 2008	Unclear	Not applicable	Unclear	Comment: Low WD rate, but higher rate of rescue therapy (124/204 PBO patients completed Rx on assigned therapy)	Unclear	Comment: Protocol available, but does not specify outcomes	Low	Comment: No other ROB identified	Not applicable	Unclear	Unclear	Comment: Main ROB is early escape design.
CHARISMA 2006	High	Not applicable	Low	Comment: 20%+WD rate, minor imbalances across	Unclear	Comment: protocol not avialable	Low	Comment: No other ROB	Not applicable	Low	Unclear	Comment: WD rate main source of potential bias

				arms, with MTX and TCZ monotherapy arms having the highest rates				identified				
Conaghan 2015	Unclear	Unclear	Low	Comment: 20-30% WD, with some imbalance; WD well reported	Low	Comment: All protocol outcomes reported	Low	Comment: No other ROB identified	Unclear	Low	Unclear	Comment: Somw imbalance of WD, but overall no major concerns
ORALSCAN 2013	High	High	Unclear	Comment: High rates of EE with imbalance (31% in PBO group completed on assigned Rx); appropriate imputation	Low	Comment: All protocol outcomes reported (some on clintrials.gov)	Low	Comment: No other ROB identified	High	Unclear	High	Comment: Main ROB is EE design + WD rate with imbalance
Kremer 2012	High	Not applicable	Unclear	Comment: Moderately high EE rates, results reported as observed and NRI/LOCF imputation. 52% of patients in PBO arm completed on assigned Rx	Low	Comment: All protocol outcomes reported	Low	Comment: No other ROB identified	Not applicable	Unclear	Unclear	Comment: Main ROB is EE design.
Tanaka 2011	Unclear	Not applicable	Low	Comment: Proportion missing not reported; LOCF imputation with NRI as sensitivity analysis	Unclear	Comment: Not all secondary outcomes reported	Low	Comment: No other ROB identified	Not applicable	Unclear	Unclear	Comment: Lack of details in study design, but double-blinded
AMPLE 2014	Unclear	Unclear	Low	Comment:20-25% drop-out, balanced; NRI, LOCF and linear extrapolation for dichotomous/continuous/xray outcomes	Unclear	Comment: Protocol available, but does not specify outcomes in detail	Low	Comment: No other ROB identified	Unclear	Unclear	Unclear	Comment: Main ROB is patients not blinded
ORALSTD 2012	High	Not applicable	Unclear	Comment: Low WD rate to 6 months, but EE design that was only allowed for PBO arm; 52% of PBO patients completed Rx to 6 months on assigned Rx	Unclear	Comment: Not all secondary outcomes reported	Low	Comment: No other ROB identified	Not applicable	Unclear	Unclear	Comment: Main ROB is the rescue design with rescue only allowed in placebo arm - pre-rescue data will have low ROB (but short duration)
ATTEST 2008	Low	Not applicable	Low	Comment: <10% WD ate in all arms	Low	Comment: All protocol outcomes reported (some on clintrials.gov)	Low	Comment: No other ROB identified	Not applicable	Low	Low	Comment: Well designed and reported double-blind RCT with low drop-out
Cuomo 2006	Unclear	Not applicable	Unclear	Comment: Not reported	Unclear	Comment: No protocol available	Unclear	Comment: Methods very poorly described	Not applicable	High	High	Comment: Very poorly reported; question whether was truly randomized or not
RACAT 2013	Low	Low	Low	Comment: To week 24, low rates of WD, balanced between groups and no data imputation used. Few missing x-rays.	Low	Comment: Initial protocol specified a different primary outcome (Acheivement of LDAS), but this was changed due to low enrollement(to a continuous measure to gain statistical power. This should have little impact on the findings though.	Low	Comment: No other ROB identified	Low	Low	Low	Comment: Very well designed and reported study with minimal missing data
Joo 2012	Unclear	Not applicable	Unclear	Comment: WD rate in LEF group not discussed	High	Comment: No protocol available and published only as abstract	Low	Comment: No other ROB identified	Not applicable	High	High	Comment: Open-label and only published as abstract
SWEFOT 2012	High	High	Low	Comment: Large rates of WD 56/130; 38/128 with imbalance between arms (understandable given long	Unclear	Comment: Not all secondary outcomes reported	Low	Comment: No other ROB identified	Unclear	Unclear	High	Comment: Main ROB are open-label design (except x-ray readers) and WD rates.

Hazlewood GS, Barnabe C, Tomlinson G, Marshall D, Devoe DJA, Bombardier C. Methotrexate monotherapy and methotrexate combination therapy with traditional and biologic disease modifying anti-rheumatic drugs for rheumatoid arthritis: A network meta-analysis. Cochrane Database of Systematic Reviews 2016, Issue 5. Art. No.: CD010227. DOI: 10.1002/14651858.CD010227.

				f/u) but appropriate methods of imputation for all variabvles								
TEAR 2012	High	High	Low	Comment: High rates of withdrawals, but appropriate imputation (multiple analyses presented; observed and imputed)	Unclear	Comment: Protocol not available	Low	Comment: No other ROB identified	Low	Low	Low	Comment: Only potential bias is withdrawal rates, but these imputed appropriately and reasonable with 2 year study
Willkens 1992	High	Not applicable	Low	Comment: 26% vs 38% drop-out. Imputed by assigning treatment failures scores associated with "maximum deterioration"	Unclear	Comment: Protocol not available	Low	Comment: No other ROB identified	Not applicable	Low	Unclear	Comment: Main ROB is drop-out rate and non-traditional means of imputation
CARDERA 2008	High	High	Low	Comment: >20% WD rate, all data imputed with LOCF	Unclear	Comment: Protocol available but not outcomes specified	Low	Comment: No other ROB identified	Unclear	Low	Unclear	Comment: Moderate WD rate, otherwise well designed and reported
CIMESTRA 2006	Unclear	Unclear	Low	Comment: 86% Completion, balanced between groups. Imputed using NRI and LOCF	Unclear	Comment: Protocol not available	Unclear	Comment: Baseline CS imbalance	Unclear	Unclear	Unclear	Comment: Well designed issue, only concern is imbalance in steroid use between arms
Sarzi-Puttini 2005	Unclear	Unclear	Low	Comment: Drop out rate 15-17 %, balanced; missing data not well reported.	Unclear	Comment: Protocol not available	Low	Comment: No other ROB identified	Unclear	Unclear	Unclear	Comment: Open label; otherwise well designed
Gerards 2003	High	High	High	Comment:Close to 50% WD rate. EE design, but escape therapy was another DMARD and was applied equally to intervention arms	Unclear	Comment: Protocol not available	Low	Comment: No other ROB identified	Unclear	Unclear	Unclear	Comment: Main ROB is WD rate (close to 50%), but otherwise well designed and reported study
Marchesoni 2003	Low	Low	Low	Comment: Low WD rate, LOCF for imputation	Unclear	Comment: Protocol not available	Low	Comment: No other ROB identified	Unclear	Unclear	Unclear	Comment: Patients, and possibly outcome assessors not blinded
Giacomelli 2002	Unclear	Not applicable	Unclear	Comment: Low WD rate to Day 60; WD not reported past then	Unclear	Comment: Protocol not available	High	Comment: Poorly reported; time-point of outcomes not clear	Not applicable	High	High	Comment: Not blinded and poorly reported
Machein 2002	Unclear	Not applicable	Unclear	Comment: Missing data not reported	High	Comment :Published as letter to the editor; Protocol not available	Low	Comment: No other ROB identified	Not applicable	Unclear	Unclear	Comment: Published only as letter to the editor; many study details not well reported, but double-blind placebo controlled
Kim 2000	Low	Not applicable	Low	Comment: Low WD rate	Unclear	Comment: Protocol not available	Low	Comment: No other ROB identified	Not applicable	Unclear	Unclear	Comment: Study details not well reported
Tugwell 1995	Unclear	Not applicable	Unclear	Comment: Drop-out rate 25%/16%; LOCF for imputation	Unclear	Comment: Protocol not available	Low	Comment: No other ROB identified	Not applicable	Unclear	Unclear	Comment: Some study details unclear, moderate WD rate with LOCF imputation
Singh 2012	Unclear	Not applicable	Not applicable	Comment: WD not reported	High	Comment: Published only as abstract, not registered	Low	Comment: No other ROB identified	Not applicable	Not applicable	High	Comment: Open-label, concerns over randomization, published only as abstract and poorly reported
Shashikumar 2010	Unclear	Not applicable	Unclear	Comment: Low WD rates, but handling of missing data not reported	High	Comment: Primary outcome (EULAR response) not reported	Low	Comment: No other ROB identified	Not applicable	High	High	Comment: Unblinded and poorly reported

Ghosh 2008	Unclear	Not applicable	Not applicable	Comment: WD not reported	High	Comment: Unusual outcome reporting; likely not pre-sepcified	Low	Comment: No other ROB identified	Not applicable	Not applicable	High	Comment: Open-label, quesitons over randomization and poorly reported
Mottaghi 2005	Unclear	Not applicable	Not applicable	Comment: WD not reported	Unclear	Comment: No protocol available	Low	Comment: No other ROB identified	Not applicable	Not applicable	High	Comment: Questionnable randomization, unblinded and poorly reported
Zhang 2004	Low	Not applicable	Low	Comment: Low WD rate	High	Comment: Protocol not available; some unusual ways of reporting outcomes (used lowest of pt and physician global)	High	Comment: Selection bias: Patients that were judged to have good compliance were selected from the overall sample.	Not applicable	High	High	Comment: Open-label, some concern over concealment of randomization and postential selection bias
Ferraz 1994	Unclear	Not applicable	Low	Comment: 17% drop-out rate; balanced. No imputation (only continuous outcomes reported)	Unclear	Comment: No protocol available	Low	Comment: No other ROB identified	Not applicable	Low	Low	Comment: Double-blind, relatively low drop-out
Trnavsky 1993	Unclear	Unclear	Not applicable	Comment: WD not reported	Unclear	Comment: No protocol available	Low	Comment: No other ROB identified	Unclear	Not applicable	Unclear	Comment: Lack of study details, particularly no discussion of withdrawals. Also, prior DMARD use not reported
METGO 2005	High	Not applicable	Unclear	Comment: High WD rates, imbalance between groups, inappropriate imputation (LOCF); the NRI analysis reported for some outcomes, but adjusted for prednisone use	Unclear	Comment: Protocol not available	High	Comment: Large difference in CS use between groups	Not applicable	Low	Unclear	Comment: Well designed, but high drop-out rate with questionnable methods of imputation
CareRA 2015	Low	Not applicable	Low	Comment: Low WD rate	Low	Comment: All protocol outcomes reported	Unclear	Comment: Leflunomide dose low outcomes only 3 month outcomes	Not applicable	High	High	Comment: Open-label and concerns re timing of outcomes in setting high dose steroid
Mehrotra 2006	Unclear	Unclear	Unclear	Comment: Not well reported	High	Comment: Only abstract published	Low	Comment: No other ROB identified	High	High	High	Comment: Published only as abstract, unblinded with no details on study design
Kremer 2002	Unclear	Not applicable	Low	Comment: 20-30% drop-out, balanced. NRI imputation for dichotomous; imputation for continuous outcomes not clear	Unclear	Comment: No protocol available	Low	Comment: No other ROB identified	Not applicable	Unclear	Unclear	Comment: Moderate withdrawals, but otherwise well designed and reported
MASCOT 2007	High	High	Low	Comment: 30-35% drop-out, approriate imputation	Unclear	Comment: No protocol available	Low	Comment: No other ROB identified	Unclear	Low	Unclear	Comment: Main ROB is drop-out rate
Tascioglu 2003	Unclear	Not applicable	Low	Comment:WD rate ~20% imputation methods not described	Unclear	Comment: No protocol available	Low	Comment: No other ROB identified	Not applicable	High	High	Comment: Open-label, moderate WD rate with imputation not decribed. Other study details also not well described
Islam 2000	Unclear	Not applicable	Low	Comment: Methods of handling missing data not	Unclear	Comment: No protocol available	Low	Comment: No other ROB	Not applicable	High	High	Comment: Open-label, lack of study details

				described				identified				
Dougados 1999	High	High	Low	Comment: WD rate 22-31%, LOCF for imputation	Unclear	Comment: No protocol available	Low	Comment: No other ROB identified	Unclear	Low	Unclear	Comment: Main ROB is WD rate; also some unclear reporting of study details
Haagsma 1997	High	Not applicable	Low	Comment: WD rate 6-35%, imbalanced.	Unclear	Comment: No protocol available	Low	Comment: No other ROB identified	Not applicable	Low	Unclear	Comment: Main ROB is WD rate
Haagsma 1994	Low	Not applicable	Unclear	Comment: WD low, but details not well reported	Unclear	Comment: No protocol available	Low	Comment: No other ROB identified	Not applicable	Unclear	Unclear	Comment: Open-label, but low WD rate
tREACH 2013	Low	Not applicable	Low	Comment: Low WD rate (only 3 months)	High	Comment: Interim results, study ongoing	Low	Comment: No other ROB identified	Not applicable	Unclear	Unclear	Comment: Single blinded, interim report
Gubar 2008	High	Not applicable	High	Comment: Interim report; only 40/60 patients reported. Otherwise low wd rate	Unclear	Comment: Protocol not available	Low	Comment: No other ROB identified	Not applicable	High	High	Comment: Open-label and interim report
Odell 2002	High	Not applicable	Low	Comment: High WD rate by 2 years	Unclear	Comment: No protocol available	Low	Comment: No other ROB identified	Not applicable	Low	Unclear	Comment: Main ROB is drop-out
Odell 1996	High	Not applicable	Low	Comment: High WD rate by 2 years	Unclear	Comment: No protocol available	Low	Comment: No other ROB identified	Not applicable	Low	Unclear	Comment: Main ROB is drop-out rate.
Sigidin Ya 1994	High	High	Low	Comment: 30% WD rate, imbalanced. No discussion over completeness of x-ray data	Unclear	Comment: Protocol not available	Low	Comment: No other ROB identified	High	High	High	Comment: Open-label with a lack of study details and relatively high WD rate
Westedt 1994	Unclear	Not applicable	Low	Comment: 15-20% WD rate, balanced	Unclear	Comment: Protocol not available	Low	Comment: No other ROB identified	Not applicable	High	High	Comment: Open-label, potential concern overrandomization procedures
Jeurissen 1991	High	High	Low	Comment: 30% WD in AZA arm; 1/30 in MTX arm. No imputation	Unclear	Comment: Protocol not available	Low	Comment: No other ROB identified	Unclear	Low	Unclear	Comment: Main ROB is drop-out
Arnold 1990	High	Not applicable	Low	Comment: >50% WD, balanced	High	Comment: Protocol not available; 2 year trial, but only 6 month efficacy outcomes (suspect because of high WD rates)	Low	Comment: No other ROB identified	Not applicable	High	High	Comment: Open-label and high WD rate; 6 month outcomes of a 2-year trial
Hamdy 1987	Unclear	Unclear	Low	Comment: 19% WD rate in AZA arm; 1/21 in MTX arm. No imputation.	Unclear	Comment: Protocol not available	Low	Comment: No other ROB identified	Unclear	Low	Unclear	Comment: Imbalance in WD, but double-blind with adequate reporting
Singh 2000	Unclear	Not applicable	Not applicable	Comment: Missing data not reported	Unclear	Comment: Protocol not available; poor reporting of outcomes	Low	Comment: No other ROB identified	Not applicable	Not applicable	High	Comment: Open-label and poorly reported
Drosos 1998	Low	Unclear	Low	Comment: Low WD rate; missing x-ray data not reported	Unclear	Comment: Protocol not available	Low	Comment: No other ROB identified	High	High	High	Comment: Open-label; concerns over randomization
Alam 2012	Unclear	Not applicable	Not applicable	Comment: Not reported	Unclear	Comment: Protocol not available	Low	Comment: No other identified biases	Not applicable	Not applicable	High	Comment: Quasi-randomized, open-label and poorly reported
Van Jaarsveld 2000	High	Not applicable	High	Comment: No fixed follow-up (patients followed until failed initial treatment); variable between arms; AE data given by drug exposure - therefore can	Unclear	Comment: No protocol available	Low	Comment: No other ROB identified	Not applicable	High	High	Comment: Open-label and variable follow-up between groups

				use								
Hamilton 2001	High	Not applicable	Low	Comment: Drop-out 57% (IMG), 38% (MTX)	Unclear	Comment: Protocol not available	Low	Comment: No other ROB identified	Not applicable	Unclear	High	Comment: Open-label and very high/differential WD rate
Rau 1997	High	Not applicable	Low	Comment: High and differential WD, no imputation	Unclear	Comment: Protocol not available	Low	Comment: No other ROB identified	Not applicable	Low	Unclear	Comment: High and imbalance in WD
Rau 1991	High	High	Low	Comment: Differential loss to follow-up: 84% (MTX) vs 68% (IMGold) completion; efficacy data looked only at completors (did not impute data) and many of IMGold withdrawals were from toxicity	Unclear	Comment: Labelled as "interim report", but subsequent report not published. Trial design different from Rau 1997, therefore unlikely to be interim of this trial (unable to confirm with authors).	Low	Comment: No other ROB identified	High	High	High	Comment: "Interim report" Some study details unclear, differential drop-out main ROB
Morassut 1989	High	Not applicable	Low	Comment: High WD rate: 34%, relatively balanced	Unclear	Comment: Protocol not available	Low	Comment: No other ROB identified	Not applicable	Unclear	Unclear	Comment: Main ROB is high WD rate
Suarez-Almazor 1988	High	Not applicable	Low	Comment: Relatively high and differential WD (MTX 10%, 35% Im Gold)	Unclear	Comment: Protocol not available	Low	Comment: No other ROB identified	Not applicable	Unclear	Unclear	Comment: Lack of study detail and differential drop out but double-blind
Elmuntaser 2014	Low	Not applicable	Low	Comment: No withdrawals	Unclear	Comment: No protocol, measured x-rays did not report	Low	Comment: No other ROB identified	Not applicable	High	High	Comment: Open-label and only published as abstract; unusual leflunomide dose
Fedorenko 2012	Unclear	Not applicable	Not applicable	Comment: WD not reported	Unclear	Comment: Published only as abstract; Protocol not available	Low	Comment: No other ROB identified	Not applicable	Not applicable	High	Comment: No mention of blinding, published only as abstract
Jaimes-Hernandez 2012	High	Not applicable	Unclear	Comment: EE design; WD rate ~30% and balanced	Unclear	Comment: Protocol not available	Low	Comment: No other ROB identified	Not applicable	Unclear	Unclear	Comment: High WD rate and EE design, otherwise designed and reported
Lisbona 2012	High	Not applicable	Unclear	Comment: Initial number of randomized patients not reported by group; WD rate 21% overall	Unclear	Comment: Published only as abstract. Protocol not available	Low	Comment: No other ROB identified	Not applicable	High	High	Comment: Open-label, published only as abstract with incomplete reporting and moderate-high WD rate
Ishaq 2011	High	Not applicable	Low	Comment: WD rate high and unbalanced. No data imputation, only presented as observed continusous outcomes	Unclear	Comment: Protocol not available	Low	Comment: No other identified biases	Not applicable	Unclear	Unclear	Comment: Lack of details and high WD rate main ROB
Fiehn 2007	Unclear	Not applicable	Low	Comment: 15-20% WD rate, no mention of imputation	Unclear	Comment: Protocol not available	Low	Comment: No other ROB identified	Not applicable	Unclear	High	Comment: Open-label and some details not well reported
Bao 2003	High	Not applicable	Unclear	Comment: WD not well characterized; Data (including baseline) only reported on those that completed 12 weeks	High	Comment: Protocol not available; Unusual time points of study - seems like a 12 week trial, with an optional 24 week period, but not well described.	Low	Comment: No other ROB identified	Not applicable	High	High	Comment: Concern over randomization, given imbalance in patient numbers between group; unclear trial design (optional extension to 24 weeks); poor reporting of mising data with unclear imputation
Lau 2002	Unclear	Not applicable	Not applicable	Comment: WD not reported	High	Comment: Published only as abstract. Protocol not available	Low	Comment: No other ROB identified	Not applicable	Not applicable	High	Comment: Published only as abstract, many study details unclear
Reece 2002	Unclear	Not applicable	Unclear	Comment: Missing clinical data not reported; WD not	Unclear	Comment: Protocol not available	Low	Comment: No other ROB	Not applicable	Unclear	Unclear	Comment: Double-blind, but lack of study details

				well characterized				identified				
Shuai 2002	Unclear	Not applicable	Unclear	Comment: WD poorly reported, but appears that 34/40 and 31/40 completed	Unclear	Comment: Protocol not available	Low	Comment: No other ROB identified	Not applicable	Unclear	Unclear	Comment: Some study details unclear, but double-blind, pbo-controlled
Hu 2001	Unclear	Not applicable	Not applicable	Comment: WD and/or loss to follow-up not reported	High	Comment: Not all listed outcomes reported	Low	Comment: No other ROB identified	Not applicable	Not applicable	High	Comment: Overall lack of study detail with seriour concerns about randomization procedure and inadequate reporting of outcomes
Lao 2001	Unclear	Not applicable	Unclear	Comment: No mention of WD	Unclear	Comment: Protocol not available	Low	Comment: No other ROB identified	Not applicable	Unclear	Unclear	Comment: Some study details unclear, but double-blind; no mention of WD
Bao 2000	Unclear	Not applicable	Unclear	Comment: No mention of WD	Unclear	Comment: Protocol not available	Low	Comment: No other ROB identified	Not applicable	Unclear	Unclear	Comment: Some study details unclear, but double-blind, pbo-controlled
Emery 2000	High	High	Low	Comment: High rates of withdrawal, unblanaced between groups, LOCF used for imputation	Unclear	Comment: Protocol not available	Low	Comment: No other identified biases	Unclear	Unclear	Unclear	Comment: Double-blind, but relatively high drop-out rate
Kraan 2000	Low	Not applicable	Unclear	Comment: Low WD rate, but WD not well characterized	Unclear	Comment: Protocol not available	Low	Comment: No other ROB identified	Not applicable	Unclear	Unclear	Comment: Double-blind, but lack of study details
ULTRA 1999	High	High	Unclear	Comment: High rates of WD (early escape design), differential between groups, LOCF used for imputation. 31% of PBO patients completed on assigned Rx.	Unclear	Comment: Protocol not available	Low	Comment: No other ROB identified	High	Unclear	High	Comment: Main ROB is high WD/EE rate
Ferraccioli 2002	Low	Not applicable	Low	Comment: Low drop out rates, relatively balanced	Unclear	Comment: No protocol available	Low	Comment: No other identified biases	Not applicable	Unclear	Unclear	Comment: Open-label is main ROB, also lack of some study details
Salaffi 1995	High	Not applicable	Unclear	Comment: 36% WD rate in SSZ arm, 0% in MTX arm; no imputation. WD not well characterized	Unclear	Comment: No protocol available	Low	Comment: No other identified biases	Not applicable	High	High	Comment: Open-label and poorly reported with imbalance in WD
Ahmed 2010	Unclear	Not applicable	Not applicable	Comment: Not reported	Unclear	Comment: Published only as abstract. Protocol not available	Low	Comment: No other ROB identified	Not applicable	Not applicable	High	Comment: Open-label, single-author, and published only as abstract
Braun 2008	Unclear	Not applicable	Unclear	Comment: 15%/12% drop-out, but EE design (14% EE overall)	Unclear	Comment: Protocol not available	Low	Comment: No other ROB identified	Not applicable	Unclear	Unclear	Comment: Main ROB is EE design and drop-out
Pinheiro 1993	Unclear	Not applicable	Unclear	Comment: Moderate WD rate, not well reported	Unclear	Comment: Protocol not available	Low	Comment: No other ROB identified	Not applicable	Unclear	Unclear	Comment: Double-blind, some lack of study details and moderate WD rates
Furst 1989	Unclear	Not applicable	Unclear	Comment: Low overall WD rate, but early escape design, WD not well reported	Unclear	Comment: Protocol not available	Low	Comment: No other ROB identified	Not applicable	Unclear	Unclear	Comment: EE trial, WD not well reported. Also had a 2 week run0in where all patients received MTX
Anderson 1985	Unclear	Not applicable	Unclear	Comment: Low WD rate, but patients randomized to each arm not reported	Unclear	Comment: Protocol not available	Low	Comment: No other ROB identified	Not applicable	Unclear	Unclear	Comment: Cross-over trial; DB and low WD rate but WD not well reported

Hazlewood GS, Barnabe C, Tomlinson G, Marshall D, Devoe DJA, Bombardier C. Methotrexate monotherapy and methotrexate combination therapy with traditional and biologic disease modifying anti-rheumatic drugs for rheumatoid arthritis: A network meta-analysis. Cochrane Database of Systematic Reviews 2016, Issue 5. Art. No.: CD010227. DOI: 10.1002/14651858.CD010227.

Weinblatt 1985	Low	Not applicable	Low	Comment: WD relatively low and balanced	Unclear	Comment: Protocol not available	Low	Comment: No other ROB identified	Not applicable	Unclear	Unclear	Comment: Lack of study details but DB and low WD rates
Williams 1985	High	Not applicable	Low	Comment: High WD rates in 18 week trial, well reported	Unclear	Comment: Protocol not available	Low	Comment: No other ROB identified	Not applicable	Unclear	Unclear	Comment: Double-blind, high drop-out is main ROB

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