National Institute for Health and Care Excellence

Consultation

Rheumatoid arthritis in adults: diagnosis and management

Evidence review F DMARDs

NICE guideline CG79

Intervention evidence review

January 2018

Consultation

This evidence review was developed by the National Guideline Centre

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1 First line DMARDs

1.1 Review questions:

In adults with Rheumatoid Arthritis (RA) who are DMARD naïve, which conventional DMARDs (alone or combined) are most clinically and cost effective?

In adults with RA who are DMARD naïve, which DMARD treatment strategy (monotherapy, sequential monotherapy, parallel combination therapy, step up therapy or step down therapy) is most clinically and cost effective?

1.2 Introduction

DMARDs suppress disease activity and slow down radiological progression in rheumatoid arthritis, resulting in symptom improvement and reduced long-term disability. There are several conventional DMARDs that can either be prescribed as stand-alone monotherapy or combined. Treatment strategies include monotherapy, sequential monotherapy, parallel combination therapy, step-up therapy, and step-down therapy. At present it is unclear which DMARD or which DMARD treatment strategy is the most effective, both for newly diagnosed rheumatoid arthritis and further treatment.

1.3 PICO table

For full details see the review protocol in appendix A.

Table 1: PICO characteristics of review question

Population	Adults with RA who are DMARD naïve. Studies in adults with poor prognostic factors will be presented separately.
Interventions	• methotrexate (oral) (MTX oral) • methotrexate (subcutaneous) (MTX sc) • hydroxychloroquine (HCQ) • sulfasalazine (SSZ) • leflunomide (LFN) • combinations of the above • sequential combinations of the above. Study treatment arms will be classified into one of the following classes: • monotherapy (a single DMARD used for the duration of the trial) • sequential monotherapy (a single DMARD replaced with a different single DMARD in the case of inadequate response) • parallel combination (two or more DMARDs commenced at the same time without a step-down strategy) • step up (commencing with a single DMARD, followed by the addition of further DMARD(s) in the case of inadequate response) • step down (two or more DMARDs commenced at the same time, with at

	least one drug tapered and stopped once disease is adequately controlled).
Comparison	The intervention medications can be compared against each other or against placebo.
Outcomes	CRITICAL • Disease Activity Score (DAS) (continuous) at 6 and 12 months • Quality of life (continuous) at 6 and 12 months • Function (continuous) at 6 and 12 months IMPORTANT • Low disease activity (dichotomous) at 6 and 12 months • Remission (dichotomous) at 6 and 12 months • ACR50 response (dichotomous) at 6 and 12 months • Pain (continuous) at 6 and 12 months • Radiological progression (continuous) at 12 months • Adverse events – mortality (dichotomous) at longest reported time point • Withdrawal due to adverse events (dichotomous) at longest reported time point • Withdrawal due to inefficacy (dichotomous) at longest reported time point
Study design	Randomised controlled trials (RCTs) Systematic Review / Network Meta-Analysis of RCTs

Studies that enrol people who are not explicitly reported to be DMARD naïve will be excluded, except where: the study states that the only DMARD used previously is an antimalarial or hydroxychloroquine (as hydroxychloroquine is known to be a weak DMARD); or previous DMARDs have been used for no longer than 1 month. These populations will be included on the basis that they would not differ substantially from a DMARD naïve population in terms of disease severity or likely response to DMARD treatment.

1.4 Clinical evidence

1.4.1 Included studies

An existing Cochrane review[59,60] by Hazelwood et al. comparing methotrexate monotherapy with methotrexate in combination with other DMARDs formed the basis of the evidence review. The included studies in that review were checked for inclusion in this evidence review based on the agreed evidence review protocol. Searches were also conducted for randomised controlled trials and systematic reviews as follows:

- the Cochrane review search strategy was re-run to identify relevant trials published since the date of the Cochrane review searches; and
- a search was conducted to identify additional trials of non-methotrexate monotherapies and combinations that would not have been included in the Cochrane review. This was not date limited.

Twenty-one studies were included in the review; [6,7,13,22,27,28,31,33,40,46,48,55,57,68,96,108,118,137,152,171,177] these are summarised in Table 2. Evidence from these studies is summarised in the clinical evidence summaries below in Table 3 - Table 19.

The included studies covered 17 comparisons across a range of monotherapy, sequential monotherapy, parallel combination therapy, step-down therapy and step up therapy treatment regimens compared against each other and in some cases against placebo. No evidence was found for subcutaneous methotrexate.

See also the study selection flow chart in appendix C, study evidence tables in appendix D, forest plots in appendix E and GRADE tables in appendix H.

1 See the excluded studies list in appendix I.

1.4.2 2 Summary of clinical studies included in the evidence review

3 **Table 2: Summary of randomised controlled trials included in the evidence review**

Study	Intervention and comparison	Population	Outcomes	Comments
Monotherapy versus placebo				
Anonymous 1992[7]	Monotherapy: sulfasalazine versus placebo	People with RA for less than 12 months and no evidence of erosions in hands or feet N=122	• Pain • Withdrawal: adverse events • Withdrawal: inefficacy	High dose medication in intervention arm. Short term glucocorticoid treatment not used.
Anonymous 1995[6]	Monotherapy: hydroxychloroquine versus placebo	Adults with RA for less than 2 years. Persistent synovitis despite treatment with aspirin or NSAIDs. N=120	• Function • Pain • Quality of life • Withdrawal: adverse events • Withdrawal: inefficacy	High dose medication in intervention arm. Short term glucocorticoid treatment used.
Clark 1993[22]	Monotherapy: hydroxychloroquine versus placebo	Adults with active RA and ≤5 years since diagnosis and unsuccessful treatment with 2+ NSAIDs or salicylates. N=126	• Pain	High dose medication in intervention arm. Short term glucocorticoid treatment usage unclear.
Davis 1991[27]	Monotherapy: hydroxychloroquine versus placebo	People with RA and palpable synovitis in the hands, wrists or feet N=104	• Withdrawal: inefficacy	High dose medication in intervention arm. Short term glucocorticoids not used.
Hannonen 1993[57]	Monotherapy: sulfasalazine versus placebo	People with active RA with disease symptoms for <12 months. N=80	• Radiological progression • Adverse events - mortality	High dose medication in intervention arm. Short term glucocorticoids used.
Monotherapy versus monotherapy				
Ferraccioli 2002[40]	Monotherapy: sulfasalazine versus monotherapy: methotrexate	People aged 17-70 with active RA and at least 1 erosion and 4 month course of antimalarials. N=84	• ACR50 response	High dose medication in both arms. Short term glucocorticoids used. Considered indirect evidence due to previous course of

Study	Intervention and comparison	Population	Outcomes	Comments
				antimalarials. Combination therapy of both interventions given to non-responders after 6 months.
Jaimes-hernandez 2012[68]	Monotherapy: leflunomide versus monotherapy: methotrexate	Adults with active RA. N=85	• Disease Activity Score (DAS28) • Function • ACR50 response • Remission • Withdrawal: adverse events • Withdrawal: inefficacy	Low dose medication in both arms. Short term glucocorticoids used. 3% had prior DMARD treatment and had washout period. Committee agreed this percentage would not affect overall results.
Lisbona mp 2012[96]	Monotherapy: leflunomide versus monotherapy: methotrexate	People with early RA: symptom duration for less than 1 year. N=78	• Disease Activity Score (DAS28) • Function • Pain	High dose medication. Short term glucocorticoids used.
Nuver-zwart 1989[118]	Monotherapy: hydroxychloroquine versus monotherapy: sulfasalazine	People aged 16-75 years old with definite or classical and active RA. N=60	• Pain • Pain • Radiological progression • Withdrawal: adverse events • Withdrawal: inefficacy	High dose medication in both arms. Short term glucocorticoids not used.
Van jaarsveld 2000[171]	Monotherapy: hydroxychloroquine versus monotherapy: methotrexate	People with RA. Disease duration for less than 1 year. N=231	• Function • ACR remission • Pain • Withdrawal: adverse events • Withdrawal: inefficacy	High dose medication in both arms. Short term glucocorticoids not used. Medications changed if adverse events made discontinuation inevitable.
Monotherapy versus other treatment class				
COBRA trial: Boers 1997[13]	Step-down therapy: sulfasalazine and methotrexate versus monotherapy: sulfasalazine	Adults with active RA and disease duration ≤2 years N=156	• Disease Activity Score (DAS) • Function • Function • Remission • ACR50 response • Pain • Pain • Withdrawal:	Mixed dose level in arm 1 and high dose study in high dose in arm 2. Short term glucocorticoid treatment used. Excluded patients previously or currently treated with DMARDs except antimalarials.

Study	Intervention and comparison	Population	Outcomes	Comments
			adverse events • Withdrawal: inefficacy	
den Uyl 2014[31]	Parallel combination therapy: methotrexate and sulfasalazine versus monotherapy – Methotrexate.	Adults with active RA. Disease duration for 2 years or less. N=164	• Disease Activity Score (DAS) • Function • ACR Remission • ACR50 response • Pain • Withdrawal: adverse events • Withdrawal: inefficacy	High dose medication in both arms. Short term glucocorticoids used. Both arms given a regular dose of prednisone. Sequential change to parenteral methotrexate considered in group 2 though only utilised in 4% of participants.
Dougados 1999[33]	3 treatment arms: Parallel combination therapy: methotrexate and sulfasalazine versus monotherapy: sulfasalazine versus monotherapy methotrexate	People with active RA. Disease duration less than 1 year. N=209	• Withdrawal: adverse events • Withdrawal: inefficacy	High dose medication in all arms. Short term glucocorticoids not used.
FIN-RACo trial: Mottonen 1999[108]	Parallel combination therapy: sulfasalazine and methotrexate and hydroxychloroquine versus monotherapy: sulfasalazine	Adults with active RA and symptom duration <2 years. N=199	• Remission • Withdrawal: adverse events • Withdrawal: inefficacy	Low dose medication in arm 1 and high dose medication in arm 2. Short term glucocorticoids used.
Haagsma 1997[55]	3 treatment arms: Parallel combination therapy: methotrexate and sulfasalazine versus monotherapy: sulfasalazine versus monotherapy: methotrexate	Adults with active RA with disease duration less than 1 year. N=105	• Disease Activity Score (DAS) • Disease Activity Score (DAS) • Function • Pain • Pain • Withdrawal: adverse events • Withdrawal: adverse events • Withdrawal: inefficacy	High dose medication in all arms. Short term glucocorticoids used. If dose was not effective after 24 weeks in study then participant withdrawn from study. Placebos utilised for blinding.
Tascioglu 2003[152]	Parallel combination therapy: methotrexate and sulfasalazine versus monotherapy: methotrexate	Adults with active RA and disease duration for less than 1 year. N=70	• Function • Pain • Withdrawal: adverse events • Withdrawal: adverse events	Low dose medication. Short term glucocorticoids not used. Participants excluded from the study if

Study	Intervention and comparison	Population	Outcomes	Comments
				treatment not effective after 12 weeks or if serious adverse events occurred.
tREACH trial: de Jong 2013[28]	Parallel combination therapy: methotrexate and sulfasalazine and hydroxychloroquine versus monotherapy: methotrexate	Adults with arthritis of 1 or more joints for less than 1 year. Results extracted for those with RA via 1987 ACR criteria. N=189	• Disease Activity Score (DAS) • Function a • Pain • Remission	High dose medication. Short term glucocorticoids used. Outcomes only extracted at time points prior to people beginning biologic treatment.
Comparison of non-monotherapy treatment classes				
BeSt study: Goekoop-Ruiterman 2005[48]	3 treatment arms: Step up therapy: methotrexate then add sulfasalazine then add hydroxychloroquine, then biologic DMARD combinations versus parallel combination therapy: methotrexate and sulfasalazine. Then step-up to biologic DMARD combinations versus sequential monotherapy: methotrexate to sulfasalazine to leflunomide, followed by biologic DMARD combinations.	Adults with active RA and disease duration ≤2 years N=380	• Function • Radiological progression	Outcomes only extracted at time points prior to people beginning biologic treatment. Participants DMARD naïve (other than antimalarials - 9%). High dose medication in all intervention arms. Short term glucocorticoid treatment used in arms 2 and 3. First two treatment arms are effectively methotrexate monotherapy for 6 months and outcomes extracted on that basis.
Ghosh 2008[46]	Parallel combination therapy: sulfasalazine and hydroxychloroquine versus parallel combination therapy: methotrexate and hydroxychloroquine	People with RA with disease duration for less than 6 months. N=110	• Disease Activity Score (DAS28) • Remission	Low dose medication in both arms. Short term glucocorticoids not used.
Saunders 2008[137]	Step up therapy: sulfasalazine then methotrexate then hydroxychloroquine versus parallel combination therapy: methotrexate and sulfasalazine and hydroxychloroquine	People aged 18 to 80 with active RA N=96	• Disease Activity Score (DAS28) • Quality of life • Function at 12 months • Low disease activity • Remission	High dose medication in both arms. Short term glucocorticoids used. No previous DMARD treatment except for hydroxychloroquine.

Study	Intervention and comparison	Population	Outcomes	Comments
			• ACR50 response • Pain • Radiological progression • Withdrawal: adverse events	
Poor-prognosis disease strata				
Verschueren 2016[177]	3 treatment arms: Step up therapy: methotrexate then leflunomide versus parallel combination therapy: methotrexate and leflunomide versus parallel combination therapy: methotrexate and sulfasalazine	People with RA with disease duration ≤1 year. Defined as "high risk" due to erosions, rheumatoid factor, ACPA, disease activity. N=289	• Disease Activity Score (DAS28) • Disease Activity Score (DAS28) • Function • Function • Low disease activity • Low disease activity • Remission • Remission • Radiological progression • Withdrawal: adverse events • Withdrawal: inefficacy	High dose in arms 1 and 3, mixed dose in arm 2. Short term glucocorticoids used. Some participants took biologic medications outside of treatment protocol. Numbers range from 2% to 10% depending on treatment group.

1 See appendix D for full evidence tables.

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1.4.3 Quality assessment of clinical studies included in the evidence review

1.4.3.1 Monotherapy versus placebo

Table 3: Clinical evidence summary: monotherapy: sulfasalazine (SSZ) compared to placebo

Outcomes	No of Participants (studies) Follow up	Quality of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects	
				Risk with Placebo	Risk difference with Monotherapy: SSZ (95% CI)
Disease Activity Score at 6 or 12 months - not reported	-	-	-	-	-
Quality of life at 6 or 12 months - not reported	-	-	-	-	-
Function at 6 or 12 months - not reported	-	-	-	-	-
Pain at 6 months VAS. Scale from: 0 to 100.	65 (1 study) 6 months	⨁⊖⊖⊖ VERY LOW[1,2] due to risk of bias, imprecision		The mean pain (VAS) at 6 months in the control groups was 28.8	The mean pain (VAS) at 6 months in the intervention groups was 8.9 lower (19.07 lower to 1.27 higher)
Radiological progression at 12+ months Modified Sharp score. Scale from: 0 to 32 or 64.	73 (1 study) 44-60 weeks	⨁⨁⊖⊖ LOW[1,2] due to risk of bias, imprecision		The mean radiological progression (modified Sharp score) at 12+ months in the control groups was 7.1	The mean radiological progression (modified Sharp score) at 12+ months in the intervention groups was 3.6 lower (8.21 lower to 1.01 higher)
Adverse events - mortality	78 (1 study) 48 weeks	⨁⊖⊖⊖ VERY LOW[1,2] due to risk of bias, imprecision	RR 1.05 (0.07 to 16.24)	25 per 1000	1 more per 1000 (from 23 fewer to 381 more)

Outcomes	No of Participants (studies) Follow up	Quality of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects	
				Risk with Placebo	Risk difference with Monotherapy: SSZ (95% CI)
Withdrawal: adverse events	105 (1 study) 6 months	⊕⊕⊖⊖ LOW[1] due to risk of bias	RR 3.43 (1.21 to 9.75)	77 per 1000	187 more per 1000 (from 16 more to 673 more)
Withdrawal: inefficacy	105 (1 study) 6 months	⊕⊖⊖⊖ VERY LOW[1,2] due to risk of bias, imprecision	RR 0.39 (0.08 to 1.93)	96 per 1000	59 fewer per 1000 (from 88 fewer to 89 more)

1 Downgraded by 1 increment if the majority of the evidence was at high risk of bias, and downgraded by 2 increments if the majority of the evidence was at very high risk of bias
2 Downgraded by 1 increment if the confidence interval crossed one MID or by 2 increments if the confidence interval crossed both MIDs

1 **Table 4: Clinical evidence summary: monotherapy: hydroxychloroquine (HCQ) compared to placebo**

Outcomes	No of Participants (studies) Follow up	Quality of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects	
				Risk with Placebo	Risk difference with Monotherapy: HCQ (95% CI)
Disease Activity Score at 6 or 12 months - not reported	-	-	-	-	-
Quality of life at 12 months Global well being. Change score in SD units.	115 (1 study) 9 months	⊕⊕⊕⊖ MODERATE[1] due to imprecision		The mean change in quality of life (global well being) at 12 months in the control groups was 0.02	The mean change in quality of life (global well being) at 12 months in the intervention groups was 0.52 lower (0.89 to 0.15 lower)

Outcomes	No of Participants (studies) Follow up	Quality of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects	
				Risk with Placebo	Risk difference with Monotherapy: HCQ (95% CI)
Quality of life at 6 months - not reported	-	-	-	-	-
Function at 12 months Psychological disability via AIMS. Change score in SD units	115 (1 study) 9 months	⊕⊕⊕⊕ HIGH[1]		The mean change in function (psychological disability via AIMS) at 12 months in the control groups was -0.41	The mean change in function (psychological disability via AIMS) at 12 months in the intervention groups was 0.03 lower (0.39 lower to 0.33 higher)
Function at 6 months - not reported	-	-	-	-	-
Pain at 6 months Change in VAS. Scale from: 0 to 100.	121 (1 study) 6 months	⊕⊖⊖⊖ VERY LOW[1,2] due to risk of bias, imprecision		The mean change in pain (VAS) at 6 months in the control groups was -6.5	The mean change in pain (VAS) at 6 months in the intervention groups was 19.3 lower (30.22 to 8.38 lower)
Withdrawal: adverse events	100 (1 study) 9 months	⊕⊖⊖⊖ VERY LOW[1,2] due to risk of bias, imprecision	RR 0.43 (0.04 to 4.55)	43 per 1000	25 fewer per 1000 (from 42 fewer to 154 more)
Withdrawal: inefficacy	215 (2 studies) 10 months	⊕⊕⊖⊖ LOW[1,2] due to risk of bias, imprecision	RR 0.43 (0.23 to 0.8)	262 per 1000	149 fewer per 1000 (from 52 fewer to 201 fewer)

1 Downgraded by 1 increment if the confidence interval crossed one MID or by 2 increments if the confidence interval crossed both MIDs
2 Downgraded by 1 increment if the majority of the evidence was at high risk of bias, and downgraded by 2 increments if the majority of the evidence was at very high risk of bias

1.4.3.2 Monotherapy versus monotherapy

Table 5: Clinical evidence summary: monotherapy sulfasalazine (SSZ) compared to monotherapy: methotrexate (MTX)

Outcomes	No of Participants (studies) Follow up	Quality of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects	
				Risk with Monotherapy MTX	Risk difference with Monotherapy: SSZ (95% CI)
Disease Activity Score at 12 months Change in DAS. Scale from: 0 to 10	55 (1 study) 12 months	⊕⊖⊖⊖ VERY LOW[1,2] due to risk of bias, imprecision		The mean change in Disease Activity Score (DAS) at 12 months in the control groups was -2	The mean change in Disease Activity Score (DAS) at 12 months in the intervention groups was 0.2 higher (0.41 lower to 0.81 higher)
Disease Activity Score at 6 months Change in DAS. Scale from: 0 to 10	55 (1 study) 3 months	⊕⊖⊖⊖ VERY LOW[1,2] due to risk of bias, imprecision		The mean change in Disease Activity Score (DAS) at 6 months in the control groups was -1	The mean change in Disease Activity Score (DAS) at 6 months in the intervention groups was 0.1 lower (0.38 lower to 0.18 higher)
Quality of life at 6 or 12 months - not reported	-	-		-	-
Function at 12 months Change in HAQ. Scale from: 0 to 3.	55 (1 study) 12 months	⊕⊖⊖⊖ VERY LOW[1,2] due to risk of bias, imprecision		The mean change in function (HAQ) at 12 months in the control groups was -0.46	The mean change in function (HAQ) at 12 months in the intervention groups was 0.14 higher (0.16 lower to 0.44 higher)
Function at 6 months - not reported	-	-		-	-
ACR50 response at 6 months	79 (1 study) 6 months	⊕⊖⊖⊖ VERY LOW[1,2,3] due to risk of bias, indirectness, imprecision	RR 0.66 (0.41 to 1.08)	571 per 1000	194 fewer per 1000 (from 337 fewer to 46 more)
Pain at 12 months	55	⊕⊖⊖⊖		The mean change in pain (VAS) at	The mean change in pain (VAS) at

Outcomes	No of Participants (studies) Follow up	Quality of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects	
				Risk with Monotherapy MTX	Risk difference with Monotherapy: SSZ (95% CI)
Change in VAS. Scale from: 0 to 100.	(1 study) 12 months	VERY LOW[1,2] due to risk of bias, imprecision		12 months in the control groups was -25	12 months in the intervention groups was 0.1 lower (13.72 lower to 13.52 higher)
Pain at 6 months Change in VAS. Scale from: 0 to 100.	55 (1 study) 3 months	⊕⊖⊖⊖ VERY LOW[1,2] due to risk of bias, imprecision		The mean change in pain (VAS) at 6 months in the control groups was -12	The mean change in pain (VAS) at 6 months in the intervention groups was 5.8 lower (15.53 lower to 3.93 higher)
Withdrawal: adverse events	184 (2 studies) 12 months	⊕⊖⊖⊖ VERY LOW[1,2] due to risk of bias, imprecision	RR 2.3 (1.1 to 4.82)	94 per 1000	122 more per 1000 (from 9 more to 358 more)
Withdrawal: inefficacy	171 (2 studies) 12 months	⊕⊖⊖⊖ VERY LOW[1,2] due to risk of bias, imprecision	RR 2.16 (0.82 to 5.74)	54 per 1000	63 more per 1000 (from 10 fewer to 258 more)

1 Downgraded by 1 increment if the majority of the evidence was at high risk of bias, and downgraded by 2 increments if the majority of the evidence was at very high risk of bias
2 Downgraded by 1 increment if the confidence interval crossed one MID or by 2 increments if the confidence interval crossed both MIDs
3 Downgraded for indirectness: all patients had previously received at least a 4 month course of antimalarials

1 **Table 6: Clinical evidence summary: monotherapy: leflunomide (LFN) compared to monotherapy: methotrexate (MTX)**

Outcomes	No of Participants (studies) Follow up	Quality of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects	
				Risk with Monotherapy: MTX	Risk difference with Monotherapy: LFN (95% CI)
Disease Activity Score at 12 months	63 (1 study)	⊕⊕⊖⊖ LOW[1,2]		The mean change in Disease Activity Score (DAS28) at 12 months in the	The mean change in Disease Activity Score (DAS28) at 12 months in the

Outcomes	No of Participants (studies) Follow up	Quality of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects	
				Risk with Monotherapy: MTX	Risk difference with Monotherapy: LFN (95% CI)
Change in DAS28. Scale from: 0 to 9.4	12 months	due to risk of bias, imprecision		control groups was -1.93	intervention groups was 0.45 higher (0.78 lower to 1.68 higher)
Disease Activity Score at 6 months Change in DAS28. Scale from: 0 to 9.4	62 (1 study) 4 months	⨁⊖⊖⊖ VERY LOW[1,2] due to risk of bias, imprecision		The mean change in Disease Activity Score (das28) at 6 months in the control groups was -1.46	The mean change in Disease Activity Score (das28) at 6 months in the intervention groups was 0.59 higher (0.11 lower to 1.29 higher)
Quality of life at 6 or 12 months - not reported	-	-		-	-
Function at 12 months Change in HAQ-Di. Scale from: 0 to 3.	63 (1 study) 12 months	⨁⨁⊖⊖ LOW[1,2] due to risk of bias, imprecision		The mean change in function (HAQ-Di) at 12 months in the control groups was -0.44	The mean change in function (HAQ-Di) at 12 months in the intervention groups was 0.29 lower (0.01 to 0.57 lower)
Function at 6 months Change in HAQ. Scale from: 0 to 3.	62 (1 study) 4 months	⨁⊖⊖⊖ VERY LOW[1,2] due to risk of bias, imprecision		The mean change in function (HAQ) at 6 months in the control groups was -0.242	The mean change in function (HAQ) at 6 months in the intervention groups was 0.01 higher (0.22 lower to 0.24 higher)
DAS remission at 12 months	63 (1 study) 12 months	⨁⊖⊖⊖ VERY LOW[1,2] due to risk of bias, imprecision	RR 1.03 (0.53 to 2.03)	344 per 1000	10 more per 1000 (from 162 fewer to 354 more)
Pain at 6 months Change in VAS. Scale from: 0 to 100.	62 (1 study) 4 months	⨁⊖⊖⊖ VERY LOW[1,2] due to risk of bias, imprecision		The mean change in pain (VAS) at 6 months in the control groups was -13	The mean change in pain (VAS) at 6 months in the intervention groups was 3.6 higher (6.09 lower to 13.29 higher)
Withdrawal: adverse events	71	⨁⊖⊖⊖	RR	59 per 1000	104 more per 1000

Outcomes	No of Participants (studies) Follow up	Quality of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects	
				Risk with Monotherapy: MTX	Risk difference with Monotherapy: LFN (95% CI)
	(1 study) 12 months	VERY LOW[1,2] due to risk of bias, imprecision	2.76 (0.6 to 12.74)		(from 24 fewer to 691 more)
Withdrawal: inefficacy	69 (1 study) 12 months	⊕⊖⊖⊖ VERY LOW[1,2] due to risk of bias, imprecision	RR 0.55 (0.11 to 2.78)	111 per 1000	50 fewer per 1000 (from 99 fewer to 198 more)

1 Downgraded by 1 increment if the majority of the evidence was at high risk of bias, and downgraded by 2 increments if the majority of the evidence was at very high risk of bias
2 Downgraded by 1 increment if the confidence interval crossed 1 MID or by 2 increments if the confidence interval crossed both MIDs.

1 **Table 7: Clinical evidence summary: monotherapy: hydroxychloroquine (HCQ) compared to monotherapy: sulfasalazine (SSZ)**

Outcomes	No of Participants (studies) Follow up	Quality of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects	
				Risk with Monotherapy: SSZ	Risk difference with Monotherapy: HCQ (95% CI)
Disease Activity Score at 6 or 12 months - not reported	-	-	-	-	-
Quality of life at 6 or 12 months - not reported	-	-	-	-	-
Function at 6 or 12 months - not reported	-	-	-	-	-
Pain at 12 months VAS. Scale from: 0 to 100.	57 (1 study) 48 weeks	⊕⊖⊖⊖ VERY LOW[1,2] due to risk of		The mean pain (VAS) at 12 months in the control groups was 32.8	The mean pain (VAS) at 12 months in the intervention groups was 0.2 higher (13.22 lower to 13.62 higher)

Outcomes	No of Participants (studies) Follow up	Quality of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects	
				Risk with Monotherapy: SSZ	Risk difference with Monotherapy: HCQ (95% CI)
		bias, imprecision			
Pain at 6 months VAS. Scale from: 0 to 100.	57 (1 study) 24 weeks	⨁⨁⨀⨀ LOW[1,2] due to risk of bias, imprecision		The mean pain (VAS) at 6 months in the control groups was 31.6	The mean pain (VAS) at 6 months in the intervention groups was 6.4 lower (18.4 lower to 5.6 higher)
Radiological progression at 12+ months Change in SvdH score. Scale from: 0 to 448.	57 (1 study) 48 weeks	⨁⨁⨀⨀ LOW[1,2] due to risk of bias, imprecision		The mean change in radiological progression (SvdH score) at 12+ months in the control groups was 7.3	The mean change in radiological progression (SvdH score) at 12+ months in the intervention groups was 10 higher (1.11 to 18.89 higher)
Withdrawal: adverse events	44 (1 study) 48 weeks	⨁⨀⨀⨀ VERY LOW[1,2] due to risk of bias, imprecision	RR 0.33 (0.04 to 2.71)	160 per 1000	107 fewer per 1000 (from 154 fewer to 274 more)
Withdrawal: inefficacy	51 (1 study) 48 weeks	⨁⨁⨀⨀ LOW[1,2] due to risk of bias, imprecision	RR 2.67 (0.82 to 8.72)	125 per 1000	209 more per 1000 (from 23 fewer to 965 more)

1 Downgraded by 1 increment if the majority of the evidence was at high risk of bias, and downgraded by 2 increments if the majority of the evidence was at very high risk of bias
2 Downgraded by 1 increment if the confidence interval crossed 1 MID or by 2 increments if the confidence interval crossed both MIDs.

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1 **Table 8: Clinical evidence summary: monotherapy: hydroxychloroquine (HCQ) compared to monotherapy: methotrexate (MTX)**

Outcomes	No of Participants (studies) Follow up	Quality of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects	
				Risk with Monotherapy: MTX	Risk difference with Monotherapy: HCQ (95% CI)
Disease Activity Score at 6 or 12 months - not reported	-	-	-	-	-
Quality of life at 6 or 12 months - not reported	-	-	-	-	-
Function at 12 months Change in HAQ. Scale from: 0 to 3.	212 (1 study) 12 months	⊕⊕⊖⊖ LOW[1,2] due to risk of bias, indirectness		The mean change in function (HAQ) at 12 months in the control groups was -0.4	The mean change in function (HAQ) at 12 months in the intervention groups was 0.1 higher (0.08 lower to 0.28 higher)
Function at 6 months - not reported	-	-	-	-	-
ACR remission at 12 months	212 (1 study) 12 months	⊕⊖⊖⊖ VERY LOW[1,3,4] due to risk of bias, indirectness, imprecision	RR 0.67 (0.38 to 1.16)	238 per 1000	79 fewer per 1000 (from 148 fewer to 38 more)
Pain at 12 months Change in VAS. Scale from: 0 to 100.	212 (1 study) 12 months	⊕⊖⊖⊖ VERY LOW[1,2] due to risk of bias, indirectness		The mean change in pain (VAS) at 12 months in the control groups was -24	The mean change in pain (VAS) at 12 months in the intervention groups was 3 higher (4.84 lower to 10.84 higher)
Discontinuation of strategy: adverse events	212 (1 study) 12 months	⊕⊖⊖⊖ VERY LOW[1,2,4] due to risk of bias, indirectness, imprecision	Peto OR 0.13 (0.02 to 0.75)	48 per 1000	50 fewer per 1000 (from 90 fewer to 0 more)[5]
Discontinuation of strategy: inefficacy	212 (1 study)	⊕⊖⊖⊖ VERY LOW[1,2,4]	RR 2.36	48 per 1000	65 more per 1000 (from 7 fewer to 260 more)

Outcomes	No of Participants (studies) Follow up	Quality of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects	
				Risk with Monotherapy: MTX	Risk difference with Monotherapy: HCQ (95% CI)
	12 months	due to risk of bias, indirectness, imprecision	(0.86 to 6.45)		

1 Downgraded by 1 increment if the majority of the evidence was at high risk of bias, and downgraded by 2 increments if the majority of the evidence was at very high risk of bias
2 Indirect evidence: out of scope drug utilised in the case of adverse reaction
3 Indirect evidence: out of scope drug utilised in the case of adverse reaction and outcome does not use DAS or similar score
4 Downgraded by 1 increment if the confidence interval crossed one MID or by 2 increments if the confidence interval crossed both MIDs
5 Risk difference utilised to calculate absolute effect

1.4.3.3 Monotherapy versus other treatment class

Table 9: Clinical evidence summary: step-down therapy: sulfasalazine (SSZ), methotrexate (MTX) compared to monotherapy: sulfasalazine (SSZ)

Outcomes	No of Participants (studies) Follow up	Quality of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects	
				Risk with Monotherapy: SSZ	Risk difference with Step-down therapy: SSZ, MTX (95% CI)
Disease Activity Score at 12 months Change in DAS. Scale from: 0 to 10.	155 (1 study) 56 weeks	⨁⨁⨁⨀ MODERATE[1] due to risk of bias		The mean change in Disease Activity Score (DAS) at 12 months in the control groups was -1.3	The mean change in Disease Activity Score (DAS) at 12 months in the intervention groups was 0.1 lower (0.51 lower to 0.31 higher)
Disease Activity Score at 6 months Change in DAS. Scale from: 0 to 10.	155 (1 study) 28 weeks	⨁⨁⨀⨀ LOW[1,2] due to risk of bias, imprecision		The mean change in Disease Activity Score (DAS) at 6 months in the control groups was -1.3	The mean change in Disease Activity Score (DAS) at 6 months in the intervention groups was 0.8 lower (1.18 to 0.42 lower)

Outcomes	No of Participants (studies) Follow up	Quality of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects	
				Risk with Monotherapy: SSZ	Risk difference with Step-down therapy: SSZ, MTX (95% CI)
Quality of life at 6 or 12 months - not reported	-	-	-	-	-
Function at 12 months Change in HAQ. Scale from: 0 to 3.	155 (1 study) 56 weeks	⨁⨁⨀⨀ LOW[1,2] due to risk of bias, imprecision		The mean change in function (HAQ) at 12 months in the control groups was -0.6	The mean change in function (HAQ) at 12 months in the intervention groups was 0.2 lower (0.44 lower to 0.04 higher)
Function at 6 months Change in HAQ. Scale from: 0 to 3.	155 (1 study) 28 weeks	⨁⨁⨀⨀ LOW[1,2] due to risk of bias, imprecision		The mean change in function (HAQ) at 6 months in the control groups was -0.6	The mean change in function (HAQ) at 6 months in the intervention groups was 0.5 lower (0.72 to 0.28 lower)
Function at 12 months Change in MACTAR. Scale from: 0 to 100	155 (1 study) 56 weeks	⨁⨁⨁⨀ MODERATE[1] due to risk of bias		The mean change in function (MACTAR) at 12 months in the control groups was 8	The mean change in function (MACTAR) at 12 months in the intervention groups was 1 lower (3.06 lower to 1.06 higher)
Function at 6 months Change in MACTAR. Scale from: 0 to 100	155 (1 study) 28 weeks	⨁⨁⨀⨀ LOW[1,2] due to risk of bias, imprecision		The mean change in function (MACTAR) at 6 months in the control groups was 7	The mean change in function (MACTAR) at 6 months in the intervention groups was 3 higher (1.26 to 4.74 higher)
ACR remission at 12 months	126 (1 study) 56 weeks	⨁⨀⨀⨀ VERY LOW[1,2,3] due to risk of bias, imprecision, indirectness	RR 0.27 (0.03 to 2.49)	54 per 1000	39 fewer per 1000 (from 52 fewer to 80 more)
ACR50 response at 6 months	137 (1 study) 28 weeks	⨁⨀⨀⨀ VERY LOW[1,2] due to risk of bias, imprecision	RR 1.46 (0.96 to 2.21)	339 per 1000	156 more per 1000 (from 14 fewer to 410 more)

Outcomes	No of Participants (studies) Follow up	Quality of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects	
				Risk with Monotherapy: SSZ	Risk difference with Step-down therapy: SSZ, MTX (95% CI)
Pain at 12 months Change in VAS. Scale from: 0 to 100.	155 (1 study) 56 weeks	⨁⨁⨁⊖ MODERATE[1] due to risk of bias		The mean change in pain (VAS) at 12 months in the control groups was -25	The mean change in pain (VAS) at 12 months in the intervention groups was 2 higher (6.98 lower to 10.98 higher)
Pain at 6 months Change in VAS. Scale from: 0 to 100.	155 (1 study) 28 weeks	⨁⨁⊖⊖ LOW[1,2] due to risk of bias, imprecision		The mean change in pain (VAS) at 6 months in the control groups was 20	The mean change in pain (VAS) at 6 months in the intervention groups was 14 lower (22.68 to 5.32 lower)
Withdrawal: adverse events	139 (1 study) 56 weeks	⨁⊖⊖⊖ VERY LOW[1,2] due to risk of bias, imprecision	RR 0.53 (0.18 to 1.55)	125 per 1000	59 fewer per 1000 (from 102 fewer to 69 more)
Withdrawal: inefficacy	141 (1 study) 56 weeks	⨁⨁⨁⊖ MODERATE[1] due to risk of bias	RR 0.07 (0.01 to 0.52)	200 per 1000	186 fewer per 1000 (from 96 fewer to 198 fewer)

1 Downgraded by 1 increment if the majority of the evidence was at high risk of bias, and downgraded by 2 increments if the majority of the evidence was at very high risk of bias
2 Downgraded by 1 increment if the confidence interval crossed 1 MID or by 2 increments if the confidence interval crossed both MIDs.
3 Indirect evidence: outcome does not use DAS

Table 10: Clinical evidence summary: Parallel combination therapy: methotrexate (MTX), sulfasalazine (SSZ) compared to monotherapy: sulfasalazine (SSZ)

Outcomes	No of Participants (studies) Follow up	Quality of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects	
				Risk with Monotherapy: SSZ	Risk difference with Parallel combination therapy: MTX, SSZ (95% CI)
Disease Activity Score at 12	52	⨁⊖⊖⊖		The mean change in Disease	The mean change in Disease Activity

Outcomes	No of Participants (studies) Follow up	Quality of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects	
				Risk with Monotherapy: SSZ	Risk difference with Parallel combination therapy: MTX, SSZ (95% CI)
months Change in DAS. Scale from: 0 to 10	(1 study) 12 months	VERY LOW[1,2] due to risk of bias, imprecision		Activity Score (DAS) at 12 months in the control groups was -1.8	Score (DAS) at 12 months in the intervention groups was 0.51 lower (1.15 lower to 0.13 higher)
Disease Activity Score at 6 months Change in DAS. Scale from: 0 to 10	52 (1 study) 3 months	⊕⊖⊖⊖ VERY LOW[1,2] due to risk of bias, imprecision		The mean change in Disease Activity Score (DAS) at 6 months in the control groups was -1.1	The mean change in Disease Activity Score (DAS) at 6 months in the intervention groups was 0 higher (0.28 lower to 0.28 higher)
Quality of life at 6 or 12 months - not reported	-	-	-	-	-
Function at 12 months Change in HAQ. Scale from: 0 to 3.	52 (1 study) 12 months	⊕⊖⊖⊖ VERY LOW[1,2] due to risk of bias, imprecision		The mean change in function (HAQ) at 12 months in the control groups was -0.32	The mean change in function (HAQ) at 12 months in the intervention groups was 0.19 lower (0.52 lower to 0.14 higher)
Function at 6 months - not reported	-	-	-	-	-
Pain at 12 months Change in VAS. Scale from: 0 to 100.	52 (1 study) 12 months	⊕⊖⊖⊖ VERY LOW[1,2] due to risk of bias, imprecision		The mean change in pain (VAS) at 12 months in the control groups was -25	The mean change in pain (VAS) at 12 months in the intervention groups was 0.1 higher (14.05 lower to 14.25 higher)
Pain at 6 months Change in VAS. Scale from: 0 to 100.	52 (1 study) 3 months	⊕⊕⊖⊖ LOW[1,2] due to risk of bias, imprecision		The mean change in pain (VAS) at 6 months in the control groups was -18	The mean change in pain (VAS) at 6 months in the intervention groups was 5 higher (5.08 lower to 15.08 higher)
Withdrawal: adverse events	183 (2 studies) 10 months	⊕⊖⊖⊖ VERY LOW[1,2] due to risk of	RR 1.47 (0.79 to	147 per 1000	69 more per 1000 (from 31 fewer to 258 more)

Outcomes	No of Participants (studies) Follow up	Quality of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects	
				Risk with Monotherapy: SSZ	Risk difference with Parallel combination therapy: MTX, SSZ (95% CI)
		bias, imprecision	2.75)		
Withdrawal: inefficacy	164 (2 studies) 10 months	⊕⊖⊖⊖ VERY LOW[1,2] due to risk of bias, imprecision	RR 0.38 (0.12 to 1.15)	127 per 1000	78 fewer per 1000 (from 111 fewer to 19 more)

1 Downgraded by 1 increment if the majority of the evidence was at high risk of bias, and downgraded by 2 increments if the majority of the evidence was at very high risk of bias
2 Downgraded by 1 increment if the confidence interval crossed one MID or by 2 increments if the confidence interval crossed both MIDs

1

2 **Table 11: Clinical evidence summary: parallel combination therapy: methotrexate (MTX), sulfasalazine (SSZ) compared to**
3 **monotherapy: methotrexate (MTX)**

Outcomes	No of Participants (studies) Follow up	Quality of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects	
				Risk with Monotherapy: MTX	Risk difference with Parallel combination therapy: MTX, SSZ (95% CI)
Disease Activity Score at 12 months Change in DAS. Scale from: 0 to 10	63 (1 study) 12 months	⊕⊖⊖⊖ VERY LOW[1,2] due to risk of bias, imprecision		The mean change in Disease Activity Score (DAS) at 12 months in the control groups was -2	The mean change in Disease Activity Score (DAS) at 12 months in the intervention groups was 0.3 lower (0.83 lower to 0.23 higher)
Disease Activity Score at 6 months Change in DAS. Scale from: 0 to 10	225 (2 studies) 4.5 months	⊕⊕⊖⊖ LOW[1] due to risk of bias		The mean change in Disease Activity Score (DAS/DAS44) at 6 months in the control groups was -1.59	The mean change in Disease Activity Score (DAS/DAS44) at 6 months in the intervention groups was 0.19 lower (0.41 lower to 0.04 higher)

Outcomes	No of Participants (studies) Follow up	Quality of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects	
				Risk with Monotherapy: MTX	Risk difference with Parallel combination therapy: MTX, SSZ (95% CI)
Quality of life at 6 or 12 months - not reported	-	-	-	-	-
Function at 12 months Change/final HAQ. Scale from: 0 to 3.	118 (2 studies) 12 months	⨁⨁⊖⊖ LOW[1] due to risk of bias		The mean change/final function (HAQ) at 12 months in the control groups was 0.89 final HAQ or -0.46 change score	The mean change/final function (HAQ) at 12 months in the intervention groups was 0.1 higher (0.04 to 0.15 higher)
Function at 6 months Change/final HAQ. Scale from: 0 to 3.	217 (2 studies) 6 months	⨁⨁⨁⊖ MODERATE[1] due to risk of bias		The mean change/final function (HAQ) at 6 months in the control groups was 0.91 final HAQ or -0.8 change score	The mean change/final function (HAQ) at 6 months in the intervention groups was 0.12 higher (0.06 to 0.19 higher)
ACR remission at 6 months	162 (1 study) 6 months	⨁⊖⊖⊖ VERY LOW[1,2,3] due to risk of bias, imprecision, indirectness	RR 0.81 (0.42 to 1.58)	198 per 1000	38 fewer per 1000 (from 115 fewer to 115 more)
ACR50 response at 6 months	162 (1 study) 6 months	⨁⨁⊖⊖ LOW[1,2] due to risk of bias, imprecision	RR 0.92 (0.71 to 1.19)	617 per 1000	49 fewer per 1000 (from 179 fewer to 117 more)
Pain at 12 months Change/final VAS. Scale from: 0 to 100.	118 (2 studies) 12 months	⨁⊖⊖⊖ VERY LOW[1,2] due to risk of bias, imprecision		The mean change/final pain (VAS) at 12 months in the control groups was 25 final pain or -25 change score	The mean change/final pain (VAS) at 12 months in the intervention groups was 0.89 higher (9.01 lower to 10.79 higher)
Pain at 6 months	280	⨁⊖⊖⊖		The mean change/final pain (VAS)	The mean change/final pain (VAS) at

Outcomes	No of Participants (studies) Follow up	Quality of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects	
				Risk with Monotherapy: MTX	Risk difference with Parallel combination therapy: MTX, SSZ (95% CI)
Change/final VAS. Scale from: 0 to 100.	(3 studies) 5 months	VERY LOW[1,2] due to risk of bias, imprecision		at 6 months in the control groups was 29 final pain or -23 change score	6 months in the intervention groups was 0.52 higher (5.96 lower to 7 higher)
Withdrawal: adverse events	410 (4 studies) 9 months	⨁⊖⊖⊖ VERY LOW[1,2] due to risk of bias, imprecision	RR 1.59 (0.8 to 3.16)	59 per 1000	35 more per 1000 (from 12 fewer to 127 more)
Withdrawal: inefficacy	394 (4 studies) 9 months	⨁⊖⊖⊖ VERY LOW[1,2] due to risk of bias, imprecision	RR 0.82 (0.3 to 2.19)	40 per 1000	7 fewer per 1000 (from 28 fewer to 48 more)
1 Downgraded by 1 increment if the majority of the evidence was at high risk of bias, and downgraded by 2 increments if the majority of the evidence was at very high risk of bias 2 Downgraded by 1 increment if the confidence interval crossed one MID or by 2 increments if the confidence interval crossed both MIDs 3 Indirect evidence: outcome does not use DAS					

Table 12: Clinical evidence summary: parallel combination therapy: methotrexate (MTX), sulfasalazine (SSZ), hydroxychloroquine (HCQ) compared to monotherapy: methotrexate (MTX)

Outcomes	No of Participants (studies) Follow up	Quality of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects	
				Risk with Monotherapy: MTX	Risk difference with Parallel combination therapy: MTX, SSZ, HCQ (95% CI)
The outcomes reported here are from 1 study with 2 intervention groups which are identical for the purposes of this review. Where possible the data for the identical groups have been combined though the pain outcomes are reported separately due to the use of median (IQR)					
Disease Activity Score at 12	-	-	-	-	-

Outcomes	No of Participants (studies) Follow up	Quality of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects	
				Risk with Monotherapy: MTX	Risk difference with Parallel combination therapy: MTX, SSZ, HCQ (95% CI)
months - not reported					
Disease Activity Score at 6 months Change in DAS. Scale from: 0 to 10.	180 (1 study) 3 months	⊕⊕⊖⊖ LOW[1,2] due to risk of bias, imprecision		The mean change in Disease Activity Score (DAS) at 6 months in the control groups was -1.41	The mean change in Disease Activity Score (DAS) at 6 months in the intervention groups was 0.24 lower (0.55 lower to 0.07 higher)
Quality of life at 6 or 12 months - not reported	-	-	-	-	-
Function at 12 months - not reported	-	-	-	-	-
Function at 6 months Change in HAQ. Scale from: 0 to 3.	153 (1 study) 3 months	⊕⊖⊖⊖ VERY LOW[1,2] due to risk of bias, imprecision		The mean change in function (HAQ) at 6 months in the control groups was -0.42	The mean change in function (HAQ) at 6 months in the intervention groups was 0.05 lower (0.23 lower to 0.13 higher)
DAS remission at 6 months	180 (1 study) 3 months	⊕⊖⊖⊖ VERY LOW[1,2] due to risk of bias, imprecision	RR 1.30 (0.86 to 1.96)	333 per 1000	100 more per 1000 (from 47 fewer to 320 more)
Pain at 6 months Median VAS. Scale from: 0 to 100.	132 (1 study)	MODERATE[1,3] due to risk of bias		Pain (VAS) (median (IQR)) in the control group was 35 (18-55)	Pain (VAS) (median (IQR)) in the intervention group was 21 (14-52) (median difference: 14 lower in the intervention group.)
Pain at 6 months Median VAS. Scale from: 0 to 100.	120 (1 study)	MODERATE[1,3] due to risk of bias		Pain (VAS) (median (IQR)) in the control group was 35 (18-55)	Pain (VAS) (median (IQR)) was 22 (13-34) in the intervention group (median difference: 13 lower in the intervention group)

1 Downgraded by 1 increment if the majority of the evidence was at high risk of bias, and downgraded by 2 increments if the majority of the evidence was

Outcomes	No of Participants (studies) Follow up	Quality of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects	
				Risk with Monotherapy: MTX	Risk difference with Parallel combination therapy: MTX, SSZ, HCQ (95% CI)
at very high risk of bias 2 Downgraded by 1 increment if the confidence interval crossed 1 MID or by 2 increments if the confidence interval crossed both MIDs					

1 **Table 13: Clinical evidence summary: parallel combination therapy: methotrexate (MTX), sulfasalazine (SSZ), Hydroxychloroquine**
2 **(HCQ) compared to Monotherapy SSZ**

Outcomes	No of Participants (studies) Follow up	Quality of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects	
				Risk with Monotherapy SSZ	Risk difference with Parallel combination therapy: MTX, SSZ, HCQ (95% CI)
Disease Activity Score at 6 or 12 months - not reported	-	-	-	-	-
Quality of life at 6 or 12 months - not reported	-	-	-	-	-
Function at 6 or 12 months - not reported	-	-	-	-	-
DAS remission at 6 months	169 (1 study) 6 months	⨁⊖⊖⊖ VERY LOW[1,2] due to risk of bias, imprecision	RR 1.8 (1.31 to 2.46)	367 per 1000	293 more per 1000 (from 114 more to 535 more)
Withdrawal: adverse events	190 (1 study) 6 months	⨁⊖⊖⊖ VERY LOW[1,2] due to risk of bias, imprecision	Not estimable	See comment	0 fewer per 1000 (from 20 fewer to 20 more)[3]
Withdrawal: inefficacy	190 (1 study) 6 months	⨁⊖⊖⊖ VERY LOW[1,2] due to risk of bias, imprecision	Not estimable	See comment	0 fewer per 1000 (from 20 fewer to 20 more)[3]
1 Downgraded by 1 increment if the majority of the evidence was at high risk of bias, and downgraded by 2 increments if the majority of the evidence was at very high risk of bias 2 Downgraded by 1 increment if the confidence interval crossed one MID or by 2 increments if the confidence interval crossed both MIDs 3 Risk difference utilised to calculate absolute effect					

1.4.3.4 Comparison of non-monotherapy treatment classes

Table 14: Clinical evidence summary: step up therapy: methotrexate (MTX), sulfasalazine (SSZ), hydroxychloroquine (HCQ) compared to sequential monotherapy: methotrexate (MTX), sulfasalazine (SSZ), leflunomide (LFN)

Outcomes	No of Participants (studies) Follow up	Quality of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects	
				Risk with Sequential monotherapy: MTX, SSZ, LFN	Risk difference with Step up therapy: MTX, SSZ, HCQ (95% CI)
Disease Activity Score at 6 or 12 months - not reported	-	-	-	-	-
Quality of life at 6 or 12 months - not reported	-	-	-	-	-
Function at 12 months Change in HAQ. Scale from: 0 to 3.	237 (1 study) 12 months	⨁⨁⨁⨀ MODERATE [1] due to risk of bias		The mean change in function (HAQ) score at 12 months in the control groups was -0.7	The mean change in function (HAQ) score at 12 months in the intervention groups was 0 higher (0.18 lower to 0.18 higher)
Function at 6 months - not reported	-	-	-	-	-
Radiographic progression at 12+ months Change in SvdH. Scale from: 0 to 448.	237 (1 study) 12 months	⨁⨁⨁⨀ MODERATE [1] due to risk of bias		The mean change in radiographic score (SvdH) at 12 months in the control groups was 9	The mean change in radiographic score (SvdH) at 12 months in the intervention groups was 3.8 lower (7.3 to 0.3 lower)

1 Downgraded by 1 increment if the majority of the evidence was at high risk of bias, and downgraded by 2 increments if the majority of the evidence was at very high risk of bias

Table 15: Clinical evidence summary: parallel combination therapy: sulfasalazine (SSZ), hydroxychloroquine (HCQ) compared to parallel combination therapy: methotrexate (MTX), hydroxychloroquine (HCQ)

Outcomes	No of	Quality of the	Relative	Anticipated absolute effects

	Participants (studies) Follow up	evidence (GRADE)	effect (95% CI)	Risk with Parallel combination therapy: MTX, HCQ	Risk difference with Parallel combination therapy: SSZ, HCQ (95% CI)
Disease Activity Score at 12 months - not reported	-	-	-	-	-
Disease Activity Score at 6 months DAS28. Scale from: 0 to 9.4	110 (1 study) 6 months	⨁⊖⊖⊖ VERY LOW[1,2] due to risk of bias, imprecision		The mean Disease Activity Score (DAS28) at 6 months in the control groups was 4.4	The mean Disease Activity Score (DAS28) at 6 months in the intervention groups was 0.8 lower (1.4 to 0.2 lower)
Quality of life at 6 or 12 months - not reported	-	-	-	-	-
Function at 6 or 12 months - not reported	-	-	-	-	-
DAS remission at 6 months	110 (1 study) 6 months	⨁⊖⊖⊖ VERY LOW[1,2] due to risk of bias, imprecision	RR 1.48 (0.84 to 2.62)	250 per 1000	120 more per 1000 (from 40 fewer to 405 more)

1 Downgraded by 1 increment if the majority of the evidence was at high risk of bias, and downgraded by 2 increments if the majority of the evidence was at very high risk of bias
2 Downgraded by 1 increment if the confidence interval crossed 1 MID or by 2 increments if the confidence interval crossed both MIDs.

Table 16: Clinical evidence summary: step up therapy: sulfasalazine (SSZ), methotrexate (MTX), hydroxychloroquine (HCQ) compared to parallel combination therapy: methotrexate (MTX), sulfasalazine (SSZ), hydroxychloroquine (HCQ)

Outcomes	No of Participants (studies) Follow up	Quality of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects	
				Risk with Parallel combination therapy: MTX, SSZ, HCQ	Risk difference with Step up therapy: SSZ, MTX, HCQ (95% CI)
Disease Activity Score at 12 months Change in DAS28. Scale from: 0 to 9.4	91 (1 study) 12 months	⨁⨁⊖⊖ LOW[1,2] due to risk of bias, imprecision		The mean change in Disease Activity Score (DAS28) at 12 months in the control groups was -3.3	The mean change in Disease Activity Score (DAS28) at 12 months in the intervention groups was 0.7 lower (1.4 lower to 0 higher)

Outcomes	No of Participants (studies) Follow up	Quality of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects	
				Risk with Parallel combination therapy: MTX, SSZ, HCQ	Risk difference with Step up therapy: SSZ, MTX, HCQ (95% CI)
Disease Activity Score at 6 months - not reported	-	-	-	-	-
Health related quality of life at 12 months Change in SF-36. Scale from: 0 to 100.	91 (1 study) 12 months	⊕⊕⊕⊖ MODERATE[1] due to risk of bias		The mean change in health related quality of life (SF-36) at 12 months in the control groups was 9	The mean change in health related quality of life (SF-36) at 12 months in the intervention groups was 1 higher (3.94 lower to 5.94 higher)
Quality of life at 6 months - not reported	-	-	-	-	-
Function at 12 months Change in HAQ. Scale from: 0 to 3.	91 (1 study) 12 months	⊕⊕⊖⊖ LOW[1,2] due to risk of bias, imprecision		The mean change in function (HAQ) at 12 months in the control groups was -0.8	The mean change in function (HAQ) at 12 months in the intervention groups was 0.1 lower (0.39 lower to 0.19 higher)
Function at 6 months - not reported	-	-	-	-	-
Low disease activity at 12 months	96 (1 study) 12 months	⊕⊕⊖⊖ LOW[1,2] due to risk of bias, imprecision	RR 1.46 (0.97 to 2.2)	408 per 1000	188 more per 1000 (from 12 fewer to 490 more)
DAS remission at 12 months	96 (1 study) 12 months	⊕⊕⊖⊖ LOW[1,2] due to risk of bias, imprecision	RR 1.37 (0.82 to 2.28)	327 per 1000	121 more per 1000 (from 59 fewer to 418 more)
ACR50 response at 12 months	96 (1 study) 12	⊕⊕⊖⊖ LOW[1,2] due to risk of	RR 1.17 (0.81	510 per 1000	87 more per 1000 (from 97 fewer to 347 more)

Outcomes	No of Participants (studies) Follow up	Quality of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects	
				Risk with Parallel combination therapy: MTX, SSZ, HCQ	Risk difference with Step up therapy: SSZ, MTX, HCQ (95% CI)
	months	bias, imprecision	to 1.68)		
Pain at 12 months Change in VAS. Scale from: 0 to 100.	91 (1 study) 12 months	⊕⊕⊕⊖ MODERATE[1] due to risk of bias		The mean change in pain score (VAS) at 12 months in the control groups was -43	The mean change in pain score (VAS) at 12 months in the intervention groups was 1 higher (12.56 lower to 14.56 higher)
Radiographic progression at 12+ months Change in Sharp score. Scale from: 0 to 97 or 109.	91 (1 study) 12 months	⊕⊕⊕⊖ MODERATE[2] due to imprecision		The mean change in radiographic progression (Sharp score) at 12+ months in the control groups was 6.6	The mean change in radiographic progression (Sharp score) at 12+ months in the intervention groups was 0.6 lower (3.14 lower to 1.94 higher)

1 Downgraded by 1 increment if the majority of the evidence was at high risk of bias, and downgraded by 2 increments if the majority of the evidence was at very high risk of bias
2 Downgraded by 1 increment if the confidence interval crossed 1 MID or by 2 increments if the confidence interval crossed both MIDs.

1.4.3.5 1 Poor prognosis disease strata

2 **Table 17: Clinical evidence summary: parallel combination therapy: methotrexate (MTX), leflunomide (LFN) compared to parallel**
3 **combination therapy: methotrexate (MTX), sulfasalazine (SSZ)**

Outcomes	No of Participants (studies) Follow up	Quality of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects	
				Risk with Parallel combination therapy: MTX, SSZ	Risk difference with Parallel combination therapy: MTX, LFN (95% CI)
Disease Activity Score at 12 months Change in DAS28. Scale	175 (1 study) 12 months	⊕⊕⊖⊖ LOW[1] due to risk of		The mean change in Disease Activity Score (DAS28) at 12 months in the control groups was	The mean change in disease Activity Score (DAS28) at 12 months in the intervention groups was

Outcomes	No of Participants (studies) Follow up	Quality of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects	
				Risk with Parallel combination therapy: MTX, SSZ	Risk difference with Parallel combination therapy: MTX, LFN (95% CI)
from: 0 to 9.4		bias		-2.5	0.2 higher (0.24 lower to 0.64 higher)
Disease Activity Score at 6 months Change in DAS28. Scale from: 0 to 9.4	192 (1 study) 3 months	⊕⊖⊖⊖ VERY LOW[1,2] due to risk of bias, imprecision		The mean change in Disease Activity Score (DAS28) at 6 months in the control groups was -2.8	The mean change in Disease Activity Score (DAS28) at 6 months in the intervention groups was 0.4 higher (0.05 to 0.75 higher)
Quality of life at 6 or 12 months - not reported	-	-	-	-	-
Function at 12 months Change in HAQ. Scale from: 0 to 3.	175 (1 study) 12 months	⊕⊕⊖⊖ LOW[1] due to risk of bias		The mean change in function (HAQ) at 12 months in the control groups was -0.7	The mean change in function (HAQ) at 12 months in the intervention groups was 0.1 higher (0.09 lower to 0.29 higher)
Function at 6 months Change in HAQ. Scale from: 0 to 3.	192 (1 study) 3 months	⊕⊕⊖⊖ LOW[1] due to risk of bias		The mean change in function (HAQ) at 6 months in the control groups was -0.8	The mean change in function (HAQ) at 6 months in the intervention groups was 0.1 higher (0.07 lower to 0.27 higher)
Low disease activity at 12 months	191 (1 study) 12 months	⊕⊕⊖⊖ LOW[1] due to risk of bias	RR 1.07 (0.91 to 1.25)	745 per 1000	52 more per 1000 (from 67 fewer to 186 more)
Low disease activity at 6 months	192 (1 study) 3 months	⊕⊕⊖⊖ LOW[1] due to risk of bias	RR 1.03 (0.92 to 1.15)	847 per 1000	25 more per 1000 (from 68 fewer to 127 more)
DAS remission at 12 months	191 (1 study) 12 months	⊕⊖⊖⊖ VERY LOW[1,2] due to risk of bias,	RR 0.97 (0.78 to 1.2)	643 per 1000	19 fewer per 1000 (from 141 fewer to 129 more)

Outcomes	No of Participants (studies) Follow up	Quality of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects	
				Risk with Parallel combination therapy: MTX, SSZ	Risk difference with Parallel combination therapy: MTX, LFN (95% CI)
		imprecision			
DAS remission at 6 months	192 (1 study) 3 months	⊕⊕⊖⊖ LOW[1] due to risk of bias	RR 0.97 (0.8 to 1.17)	704 per 1000	21 fewer per 1000 (from 141 fewer to 120 more)
Radiological progression at 12+ months Change in SvdH. Scale from: 0 to 448.	175 (1 study) 12 months	⊕⊕⊖⊖ LOW[1] due to risk of bias		The mean change in radiological progression (SvdH) at 12 months in the control groups was -0.3	The mean change in radiological progression (SvdH) at 12 months in the intervention groups was 0 higher (0.16 lower to 0.16 higher)
Withdrawal: adverse events	184 (1 study) 3 months	⊕⊖⊖⊖ VERY LOW[1,2] due to risk of bias, imprecision	Peto OR 0.14 (0.01 to 2.2)	22 per 1000	20 fewer per 1000 (from 60 fewer to 10 more)[3]
Withdrawal: inefficacy	185 (1 study) 3 months	⊕⊖⊖⊖ VERY LOW[1,2] due to risk of bias, imprecision	RR 0.51 (0.05 to 5.48)	22 per 1000	11 fewer per 1000 (from 20 fewer to 96 more)

1 Downgraded by 1 increment if the majority of the evidence was at high risk of bias, and downgraded by 2 increments if the majority of the evidence was at very high risk of bias
2 Downgraded by 1 increment if the confidence interval crossed one MID or by 2 increments if the confidence interval crossed both MIDs
3 Risk difference utilised to calculate absolute effect

Table 18: Clinical evidence summary: step up therapy: methotrexate (MTX), leflunomide (LFN) compared to parallel combination therapy: methotrexate (MTX), sulfasalazine (SSZ)

Outcomes	No of	Quality of	Relativ	Anticipated absolute effects

	Participants (studies) Follow up	the evidence (GRADE)	e effect (95% CI)	Risk with Parallel combination therapy: MTX, SSZ	Risk difference with Step up therapy: MTX, LFN (95% CI)
Disease Activity Score at 12 months Change in DAS28. Scale from: 0 to 9.4	179 (1 study) 12 months	⊕⊕⊖⊖ LOW[1] due to risk of bias		The mean change in Disease Activity Score (DAS28) at 12 months in the control groups was -2.5	The mean change in Disease Activity Score (DAS28) at 12 months in the intervention groups was 0.2 higher (0.23 lower to 0.63 higher)
Disease Activity Score at 6 months Change in DAS28. Scale from: 0 to 9.4	196 (1 study) 3 months	⊕⊕⊖⊖ LOW[1] due to risk of bias		The mean change in Disease Activity Score (DAS28) at 6 months in the control groups was -2.8	The mean change in Disease Activity Score (DAS28) at 6 months in the intervention groups was 0.2 higher (0.14 lower to 0.54 higher)
Quality of life at 6 or 12 months (no data) - not reported	-	-	-	-	-
Function at 12 months Change in HAQ. Scale from: 0 to 3.	179 (1 study) 12 months	⊕⊖⊖⊖ VERY LOW[1,2] due to risk of bias, imprecision		The mean change in function (HAQ) at 12 months in the control groups was -0.7	The mean change in function (HAQ) at 12 months in the intervention groups was 0.2 higher (0.01 lower to 0.41 higher)
Change in function (HAQ) at 6 months Change in HAQ. Scale from: 0 to 3.	196 (1 study) 3 months	⊕⊖⊖⊖ VERY LOW[1,2] due to risk of bias, imprecision		The mean change in function (HAQ) at 6 months in the control groups was -0.8	The mean change in function (HAQ) at 6 months in the intervention groups was 0.2 higher (0.03 to 0.37 higher)
Low disease activity at 12 months	196 (1 study) 12 months	⊕⊕⊖⊖ LOW[1] due to risk of bias	RR 1 (0.85 to 1.17)	755 per 1000	0 fewer per 1000 (from 113 fewer to 128 more)
Low disease activity at 6 months	196 (1 study) 3 months	⊕⊕⊖⊖ LOW[1] due to risk of bias	RR 1.02 (0.91 to 1.15)	847 per 1000	17 more per 1000 (from 76 fewer to 127 more)
DAS remission at 12 months	196 (1 study)	⊕⊖⊖⊖ VERY LOW[1,2]	RR 0.94	643 per 1000	39 fewer per 1000 (from 161 fewer to 109 more)

Outcomes	No of Participants (studies) Follow up	Quality of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects	
				Risk with Parallel combination therapy: MTX, SSZ	Risk difference with Step up therapy: MTX, LFN (95% CI)
	12 months	due to risk of bias, imprecision	(0.75 to 1.17)		
DAS remission at 6 months	196 (1 study) 3 months	⊕⊕⊖⊖ LOW[1] due to risk of bias	RR 1.04 (0.88 to 1.24)	704 per 1000	28 more per 1000 (from 84 fewer to 169 more)
Radiological progression at 12+ months Change in SvdH. Scale from: 0 to 448.	179 (1 study) 12 months	⊕⊕⊖⊖ LOW[1] due to risk of bias		The mean change in radiological progression (SvdH) at 12 months in the control groups was -0.3	The mean change in radiological progression (SvdH) at 12 months in the intervention groups was 0.1 lower (0.35 lower to 0.15 higher)
Withdrawal: adverse events	190 (1 study) 3 months	⊕⊖⊖⊖ VERY LOW[1,2] due to risk of bias, imprecision	RR 0.48 (0.04 to 5.2)	22 per 1000	11 fewer per 1000 (from 21 fewer to 90 more)
Withdrawal: inefficacy	189 (1 study) 3 months	⊕⊖⊖⊖ VERY LOW[1,2] due to risk of bias, imprecision	Peto OR 0.13 (0.01 to 2.09)	22 per 1000	20 fewer per 1000 (from 60 fewer to 10 more)3

1 Downgraded by 1 increment if the majority of the evidence was at high risk of bias, and downgraded by 2 increments if the majority of the evidence was at very high risk of bias
2 Downgraded by 1 increment if the confidence interval crossed one MID or by 2 increments if the confidence interval crossed both MIDs
3 Risk difference utilised to calculate absolute effect

Table 19: Clinical evidence summary: step up therapy: methotrexate (MTX), leflunomide (LFN) compared to parallel combination therapy: methotrexate (MTX), leflunomide (LFN)

Outcomes	No of	Quality of	Relativ	Anticipated absolute effects

	Participants (studies) Follow up	the evidence (GRADE)	e effect (95% CI)	Risk with	Risk difference with Step up therapy: MTX, LFN (95% CI)
Disease Activity Score at 12 months Change in DAS28. Scale from: 0 to 9.4	174 (1 study) 12 months	⊕⊕⊖⊖ LOW[1] due to risk of bias		The mean change in Disease Activity Score (das28) at 12 months in the control groups was -2.3	The mean change in Disease Activity Score (das28) at 12 months in the intervention groups was 0 higher (0.43 lower to 0.43 higher)
Disease Activity Score at 6 months Change in DAS28. Scale from: 0 to 9.4	192 (1 study) 3 months	⊕⊕⊖⊖ LOW[1] due to risk of bias		The mean change in Disease Activity Score (DAS28) at 6 months in the control groups was -2.4	The mean change in Disease Activity Score (DAS28) at 6 months in the intervention groups was 0.2 lower (0.55 lower to 0.15 higher)
Quality of life at 6 or 12 months - not reported	-	-	-	-	-
Function at 12 months Change in HAQ. Scale from: 0 to 3.	174 (1 study) 12 months	⊕⊕⊖⊖ LOW[1] due to risk of bias		The mean change in function (HAQ) at 12 months in the control groups was -0.6	The mean change in function (HAQ) at 12 months in the intervention groups was 0.1 higher (0.11 lower to 0.31 higher)
Function at 6 months Change in HAQ. Scale from: 0 to 3.	192 (1 study) 3 months	⊕⊕⊖⊖ LOW[1] due to risk of bias		The mean change in function (HAQ) at 6 months in the control groups was -0.7	The mean change in function (HAQ) at 6 months in the intervention groups was 0.1 higher (0.07 lower to 0.27 higher)
Low disease activity at 12 months	191 (1 study) 12 months	⊕⊕⊖⊖ LOW[1] due to risk of bias	RR 0.95 (0.81 to 1.11)	796 per 1000	40 fewer per 1000 (from 151 fewer to 88 more)
Low disease activity at 6 months	192 (1 study) 3 months	⊕⊕⊖⊖ LOW[1] due to risk of bias	RR 0.99 (0.89 to 1.11)	872 per 1000	9 fewer per 1000 (from 96 fewer to 96 more)
DAS remission at 12 months	191 (1 study)	⊕⊕⊖⊖ LOW[1]	RR 0.97	624 per 1000	19 fewer per 1000 (from 143 fewer to 131 more)

Outcomes	No of Participants (studies) Follow up	Quality of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects	
				Risk with	Risk difference with Step up therapy: MTX, LFN (95% CI)
	12 months	due to risk of bias	(0.77 to 1.21)		
DAS remission at 6 months	192 (1 study) 3 months	⊕⊖⊖⊖ VERY LOW[1,2] due to risk of bias, imprecision	RR 1.08 (0.9 to 1.3)	681 per 1000	54 more per 1000 (from 68 fewer to 204 more)
Radiological progression at 12+ months Change in SvdH. Scale from: 0 to 448.	174 (1 study) 12 months	⊕⊕⊖⊖ LOW[1] due to risk of bias		The mean change in radiological progression (SvdH) at 12+ months in the control groups was -0.3	The mean change in radiological progression (SvdH) at 12+ months in the intervention groups was 0.1 lower (0.36 lower to 0.16 higher)
Withdrawal: adverse events	188 (1 study) 3 months	⊕⊖⊖⊖ VERY LOW[1,2] due to risk of bias, imprecision	Peto OR 6.95 (0.14 to 351)	0 per 1000	10 more per 1,000 (from 20 fewer to 40 more)[3]
Withdrawal: inefficacy	188 (1 study) 3 months	⊕⊖⊖⊖ VERY LOW[1,2] due to risk of bias, imprecision	Peto OR 0.13 (0.00 to 6.54)	11 per 1000	10 fewer per 1000 (from 40 fewer to 20 more)[3]

1 Downgraded by 1 increment if the majority of the evidence was at high risk of bias, and downgraded by 2 increments if the majority of the evidence was at very high risk of bias
2 Downgraded by 1 increment if the confidence interval crossed one MID or by 2 increments if the confidence interval crossed both MIDs
3 Risk difference utilised to calculate absolute effect

1 See appendix F for full GRADE tables.

2

1.5 Economic evidence

1.5.1 Included studies

Two health economic studies were identified with the relevant comparison and have been included in this review.[157,162] These are summarised in the health economic evidence profile below (Table 20) and the health economic evidence tables in appendix H.

1.5.2 Excluded studies

One economic study relating to this review question was identified but was excluded due to combination of limited applicability and methodological limitations.[139] This is listed in appendix I, with reasons for exclusion given.

See also the health economic study selection flow chart in appendix G.

See also the health economic study selection flow chart in appendix G.

1.5.3 1 Summary of studies included in the economic evidence review

2 **Table 20: Health economic evidence profile: multiple DMARD comparators**

Study	Applicability	Limitations	Other comments	Costs (a)	Effects (QALYs) (a)	Incremental cost (b)	Incremental effects (b)	Cost effectiveness (b)	Uncertainty
Tosh 2011[157] (UK)	Partially applicable (c)	Potentially serious limitations (d)	• Discreet event simulation: Cost-utility analysis (QALYs) • Population: Adults with recent onset rheumatoid arthritis. Mean disease duration 0.68 years. Mean baseline HAQ 1.11. • Six comparators in full analysis but only five meet the protocol: ○ 1. Monotherapy DMARD ○ 2. Parallel combination (≥2 DMARDs) ○ 3. Step-up combination ○ 4. Step-down combination ○ 5. Intensive step-up combination	3. £50,791	3. 11.91	Dominated (4 has lower costs and greater effects)			Probabilistic sensitivity analysis undertaken but only for all 6 comparators, not for the 5 comparators reported here. Range of one-way sensitivity analyses. Overall results were robust to all sensitivity analyses.
				2. £55,573	2.13.42	Dominated (4 has lower costs and greater effects)			
				1. £55,996	1. 13.73	Dominated (4 has lower costs and greater effects)			
				4. £48,849	4.15.32	Baseline			
				5. £61,046 (e)	5.15.77	5 vs. 4: £12,197	5 vs. 4: 0.45	£27,392 per QALY	

Study	Applicability	Limitations	Other comments	Costs (a)	Effects (QALYs) (a)	Incremental cost (b)	Incremental effects (b)	Cost effectiveness (b)	Uncertainty
			• Time horizon: Lifetime						
Van den Hout 2009 [162] (Netherlands)	Partially applicable (f)	Potentially serious limitations (g)	• Within-trial analysis (RCT: BeST trial): Cost-utility analysis (QALYs) • Population: Adults with early RA (<2years) with active disease and who have not previously received DMARDs. • Four comparators in full analysis but only 2 meet the protocol: ○ 1. Sequential monotherapy ○ 2. Step-up combination • Follow-up: 2 years	N/A		2-1: Saves £2,158 (h)	2-1: 0.02	Intervention 2 dominates intervention 1	Bootstrapping undertaken but only for all 4 comparators, not 2 comparators reported here.

Abbreviations: ICER: incremental cost-effectiveness ratio; QALY: quality-adjusted life years
(a) Cost/effect in order of least to most effective intervention
(b) Full incremental analysis of available strategies: first strategies are ruled out that are dominated (another strategy is more effective and has lower costs) or subject to extended dominance (the strategy is more effective and more costly but the incremental cost effectiveness ratio is higher than the next most effective option and so it

would never be the most cost effective option); incremental costs, incremental effects and incremental cost effectiveness ratios are calculated for the remaining strategies by comparing each to the next most effective option.

(c) Does not specify DMARDs but rather refers to treatment strategies, although authors note that a systematic review of monotherapy found no statistically significant difference between DMARDs. EQ-5D mapped from HAQ rather than directly elicited from patients in trials.

(d) Patient covariates are not included to determine differences in clinical response or treatment withdrawal as both of these inputs are based on trials not a registry. Criteria set by NICE for biologic eligibility is failing 2 DMARDs (incl. methotrexate) and having a DAS >5.1. As model is HAQ based and conversion from HAQ to DAS is not possible, this requirement not included in model. This analysis is based on 5 of the 22 studies included for this question and includes 8 studies that were not included in the clinical review and so does not reflect full body of evidence and may provide treatment effect estimates that do not reflect that identified in the clinical review.

(e) Costs components incorporated: Drug costs (including drugs, monitoring, review and administration where applicable); annual costs of managing RA stratified by HAQ score (hospital days, outpatient visits and joint replacements).Cost of adverse events not directly quantified, indirectly quantified through treatment withdrawal.

(f) Evidence from a Dutch healthcare perspective. Discounting at 3% rather than 3.5% as required by the NICE reference case. Does not include a comparison of all possible treatment combinations identified in the clinical evidence.

(g) 2 year follow-up unlikely to be sufficient to capture all downstream costs and treatment effects. Dutch unit costs may not reflect current NHS costs. Within trial analysis based on RCT BeST. This analysis is based on 1 of the 22 studies included for this question and so does not reflect full body of evidence.

(h) 2008 Euro converted to UK pounds[123]. Cost components incorporated: medication costs, consultations, admissions and homecare.

1.5.4 Unit costs

Table 21: UK costs of conventional DMARDs

Drug	Dosage	Cost – annual
Methotrexate, oral tablets	Max. 20mg weekly	£39.49
Methotrexate, subcutaneous, prefilled syringe	Max. 25 mg weekly	£960.96
Hydroxychloroquine, oral tables	200-400mg daily	£45.38
Sulfasalazine, gastro-resistant tablets	Max. 2-3g daily	£164.39
Leflunomide, oral tablet	10-20mg	£92.94

Sources: Dosage: BNF March 2017[11]; Unit cost: NHS Drug Tariff, March 2017.[116]

In addition to the cost of the drugs, there are also costs associated with monitoring of conventional DMARDs.

NICE technology appraisal TA375 has estimated that the monthly cost of monitoring methotrexate to be £134. This cost includes a full blood count, biochemical profile and a hospital outpatient appointment.

The British Society for Rheumatology and British Health Professionals in Rheumatology published a guideline for prescription and monitoring of non-biologic DMARDs in 2017. The standard laboratory monitoring schedule recommended is 9 monitoring blood tests in first 12 months. The blood tests include full blood count, creatinine/calculated GFR, ALT and/or AST and albumin. Table 22 below outlines a summary of monitoring requirements for each drug.

Table 22: Monitoring of conventional DMARDs

Drug	Laboratory monitoring	Other monitoring
Methotrexate	Standard monitoring schedule	None
Hydroxychloroquine	No routine laboratory monitoring	Annual eye assessment if continued >5 years
Sulfasalazine	Standard monitoring schedule for 12 months, then no routine monitoring needed	None
Leflunomide	Standard monitoring schedule	Blood pressure and weight at each monitoring visit

Source: BSR and BHPR monitoring guideline 2017[93]

1.6 Resource costs

The recommendations made in this review are not expected to have a substantial impact on resources.

1.7 Evidence statements

1.7.1 Clinical evidence statements

- Monotherapy: sulfasalazine compared to placebo

A benefit for sulfasalazine was found in radiological progression and withdrawal due to inefficacy though adversely there was a benefit for placebo in withdrawals due to adverse events. No difference was seen for pain at 6 months or mortality (low to very low quality evidence; 1 study for each outcome; n=65 to 105). No evidence was available for disease activity, quality of life or function.

- Monotherapy: hydroxychloroquine compared to placebo

Hydroxychloroquine showed a benefit in quality of life at 12 months, pain at 6 months and withdrawal due to adverse events or withdrawal due to inefficacy. No difference was seen between the treatments in terms of psychological function at 12 months (high to very low quality evidence; 1 to 2 studies for each outcome; n=100 to 215). No evidence was available for disease activity.

- Monotherapy: sulfasalazine compared to monotherapy: methotrexate

Methotrexate was beneficial for function at 12 months, ACR50 response, withdrawal due to adverse events and withdrawal due to inefficacy. No difference between treatments was seen for disease activity at 6 or 12 months or pain at 6 or 12 months (very low quality evidence, 1 to 2 studies for each outcome, n=55 to 184). No evidence was available for quality of life data.

- Monotherapy: leflunomide compared to monotherapy: methotrexate

A benefit was found for leflunomide in function at 12 months and withdrawal due to inefficacy. Methotrexate was seen to be beneficial in withdrawal due to adverse events. No difference was seen between the treatments for disease activity at 6 or 12 months, function at 6 months, remission at 12 months or pain at 6 months (low to very low quality evidence; 1 study for each outcome; n=62 to 71). No evidence was available for quality of life data.

- Monotherapy: hydroxychloroquine compared to monotherapy: sulfasalazine

Sulfasalazine was beneficial in radiological progression and withdrawal due to inefficacy while hydroxychloroquine was more effective in terms of withdrawal due to adverse events. No difference was found in terms of pain at 6 or 12 months (low to very low quality evidence; 1 study; n=60). No evidence was available for disease activity, quality of life or function.

- Monotherapy: hydroxychloroquine compared to monotherapy: methotrexate

Methotrexate showed a clinical benefit in function at 12 months, ACR remission at 12 months and withdrawal due to inefficacy, while hydroxychloroquine was beneficial in withdrawal due to adverse events. No difference was seen for pain (low to very low quality evidence; 1 study; n=212). No evidence was available for disease activity or quality of life.

- Step-down therapy: sulfasalazine, methotrexate compared to monotherapy: sulfasalazine

A benefit was found for the step-down therapy in Disease Activity Score at 6 months, function at 6 or 12 months in three of the four outcomes reported, ACR50 response at 6 months, pain at 6 months, withdrawal due to adverse events and withdrawal due to inefficacy. A benefit was found for sulfasalazine in terms of remission at 12 months and no clinical difference for Disease Activity Score at 12 months, one function outcome at 6 months and pain at 12 months (moderate to very low quality evidence; 1 study; n=156). No evidence was available for quality of life.

- Parallel combination therapy: methotrexate, sulfasalazine compared to monotherapy: sulfasalazine

A benefit for the parallel combination therapy for function at 12 months and withdrawal due to inefficacy and there was a benefit for sulfasalazine in withdrawal due to adverse events. There was no clinical difference for disease activity at 6 or 12 months or pain at 6 or 12 months (low to very low quality evidence; 1 to 2 studies for each outcome; n=55 to 183). No evidence was available for quality of life.

- Parallel combination therapy: methotrexate, sulfasalazine compared to monotherapy: methotrexate

A clinical benefit was found for methotrexate in function at 6 or 12 months, withdrawal due to adverse events. Other outcomes indicated no difference between treatments: disease activity at 6 or 12 months, remission at 6 months, ACR50 response at 6 months, pain at 6 or 12 months and withdrawal due to inefficacy (moderate to very low quality evidence; 1 to 4 studies for each outcome; n=63 to 410). No evidence was available for quality of life.

- Parallel combination therapy: methotrexate, sulfasalazine, hydroxychloroquine compared to monotherapy: methotrexate

The parallel combination therapy was of clinical benefit in terms of remission at 6 months and pain at 6 months. Disease activity at 6 months and function at 6 months outcomes showed no difference between the treatments (moderate to very low quality evidence; 1 study; n=189). No evidence was available for quality of life.

- Parallel combination therapy: methotrexate, sulfasalazine, Hydroxychloroquine compared to monotherapy: sulfasalazine

A benefit was found for the parallel combination therapy in remission at 6 months but the other two withdrawal outcomes indicated no clinical difference (very low quality evidence; 1 study; n=199). No evidence was available for disease activity, quality of life or function.

- Step up therapy: methotrexate, sulfasalazine, hydroxychloroquine compared to sequential monotherapy: methotrexate, sulfasalazine, leflunomide

A benefit was found for the step-up therapy for radiographic progression but no clinical difference was found for function at 12 months (moderate quality evidence; 1 study; n=237). No evidence was available for disease activity or quality of life.

- Parallel combination therapy: sulfasalazine, hydroxychloroquine compared to parallel combination therapy: methotrexate, hydroxychloroquine

Parallel combination therapy utilising sulfasalazine and hydroxychloroquine showed a clinical benefit in disease activity at 6 months and remission at 6 months (very low quality evidence; 1 study; n=110). No evidence was available for quality of life or function.

- Step up therapy: sulfasalazine, methotrexate, hydroxychloroquine compared to parallel combination therapy: methotrexate, sulfasalazine, hydroxychloroquine

The step-up regime showed a clinical benefit in terms of disease activity at 12 months, function at 12 months, low disease activity at 12 months, remission at 12 months and radiographic progression. No clinical difference was found for quality of life at 12 months, ACR50 response at 12 months and pain at 12 months (moderate to low quality evidence; 1 study; n=96).

- Parallel combination therapy: methotrexate, leflunomide compared to parallel combination therapy: methotrexate, sulfasalazine in people with poor prognosis.

Parallel combination therapy utilising methotrexate and sulfasalazine showed a clinical benefit in terms of function at 6 or 12 months and parallel combination therapy utilising methotrexate and leflunomide showed a benefit through two withdrawal outcomes. No clinical difference was seen for disease activity at 6 or 12 months, remission at 6 or 12 months and radiological progression. (Low to very low quality evidence; 1 study; n=192). No evidence was available for quality of life.

- Step up therapy: methotrexate, leflunomide compared to parallel combination therapy: methotrexate, sulfasalazine in people with poor prognosis.

The parallel combination regime showed a clinical benefit in terms of function at 6 or 12 months though the step-up therapy regime was beneficial in radiological progression and two withdrawal outcomes. No difference was found for disease activity at 6 or 12 months and

remission at 6 or 12 months. (Low to very low quality evidence; 1 study; n=196). No evidence was available for quality of life.

- Step up therapy: methotrexate, leflunomide compared to parallel combination therapy: methotrexate, leflunomide in people with poor prognosis.

The parallel combination regime showed a clinical benefit in terms of function at 6 or 12 months and withdrawal due to adverse events. The step-up regimen showed a benefit through radiological progression and withdrawal due to inefficacy. No difference was seen between the treatments for disease activity at 6 or 12 months and remission at 6 or 12 months. (Low to very low quality evidence; 1 study; n=192). No evidence was available for quality of life.

1.7.2 Health economic evidence statements

- One cost-utility analysis found that step-down combination DMARD therapy was dominant (less costly and more effective) for treating adults with recent onset rheumatoid arthritis compared to monotherapy DMARD, parallel combination DMARD and step-down combination DMARD. It was also found that step-down combination DMARD therapy was cost effective compared to intensive step-up combination DMARD (ICER: £27,392 per QALY). This analysis was assessed as partially applicable with potentially serious limitations.
- One cost-utility analysis found that step-down combination DMARD therapy was dominant (less costly and more effective) compared to sequential monotherapy for treating adults with early rheumatoid arthritis. This analysis was assessed as partially applicable with potentially serious limitations.

1.8 Recommendations

F1. For adults with newly diagnosed active RA:

- Offer first-line treatment with conventional disease-modifying anti-rheumatic drug (cDMARD) monotherapy using oral methotrexate, leflunomide or sulfasalazine as soon as possible and ideally within 3 months of onset of persistent symptoms.
- Consider hydroxychloroquine for first-line treatment as an alternative to oral methotrexate, leflunomide or sulfasalazine for mild or palindromic disease.
- Escalate dose as tolerated.

F2. Offer additional cDMARDs (oral methotrexate, leflunomide, sulfasalazine or hydroxycholorquine) in combination in a step-up strategy when the treatment target (remission or low disease activity) has not been achieved despite dose escalation.

F3. For adults who have maintained the treatment target (remission or low disease activity) for at least 1 year without glucocorticoids, consider cautiously reducing drug doses or stopping drugs in a step-down strategy. Return promptly to the previous DMARD regimen if the treatment target is no longer met.

1.8.1 Research recommendations

F.RR1. What is the clinical and cost effectiveness of subcutaneous methotrexate compared with oral methotrexate for adults with early onset RA starting a new DMARD?

See also the rationale in appendix J.

1.9 Rationale and impact

1.9.1 Why the committee made the recommendations

First-line treatment

Evidence showed that starting treatment with more than 1 conventional DMARD (cDMARD) was no more effective than starting with a single cDMARD. The committee agreed that cDMARD monotherapy might have fewer side effects and recommended cDMARD monotherapy as first-line treatment. This differed from the 2009 guideline which recommended combination therapy. The difference is largely a result of inclusion of different evidence and a different approach to analysing that evidence.

Many of the studies included in the 2009 guideline used cDMARDs that are no longer commonly used in UK practice (for example, ciclosporin), and these studies were excluded from the evidence for the 2018 update. In addition, the 2018 update included new evidence published after the 2009 guideline. Further, a different approach to analysing the evidence was taken, with the 2018 update aiming to identify the most effective cDMARD strategy (monotherapy, sequential monotherapy, step-up therapy, step-down therapy or parallel combination therapy) as well as which cDMARD should be used. The 2009 guideline compared treatment strategies only, regardless of the particular cDMARDs, and combined evidence according to treatment strategy.

The evidence included in the 2018 update was therefore different to that included in 2009 and supported cDMARD monotherapy as first-line treatment.

Evidence from randomised controlled trials in people who had never had a DMARD showed no consistent differences in the effectiveness of methotrexate, leflunomide and sulfasalazine as monotherapies. The drugs also had similar costs. The committee agreed that any of these drugs can be used as first-line treatment.

Hydroxychloroquine was less effective, but fewer people stopped treatment because of side effects. The committee agreed that hydroxychloroquine could be considered for people with mild or palindromic disease.

People at risk of poor outcomes

Evidence for different first-line treatment in people with a poor prognosis was limited so the committee decided not to make a separate recommendation for this group. They agreed that the recommendation for dose increases and treating to target (with the aim of keeping disease activity low) should ensure adequate treatment for these people. Given the limited evidence in this area, the committee also decided that the possible benefit of managing RA with a poor prognosis with a different strategy was a priority for future research (see evidence review B: Risk factors).

Further treatment

Evidence supported adding another cDMARD when needed (step-up strategy) rather than replacing the cDMARD with another (sequential monotherapy). The committee acknowledged that more side effects were possible with a step-up strategy, but in their experience these could be managed by drug monitoring and were outweighed by the clinical benefit of combination treatment when monotherapy was inadequate. A published cost analysis supported a step-up approach rather than sequential monotherapy.

Subcutaneous methotrexate

No evidence was found for subcutaneous methotrexate, but the committee agreed that the effects may be superior and side effects fewer than with oral cDMARDs. However, because subcutaneous methotrexate is significantly more expensive than other cDMARD options, the

committee was not able to recommend this without evidence of clinical benefit and cost effectiveness relative to oral cDMARDs. The committee decided to make a research recommendation to inform future guidance.

Why we need recommendations on this topic

DMARDs suppress disease activity and slow down radiological progression in rheumatoid arthritis, resulting in symptom improvement and reduced long-term disability. There are several conventional DMARDs that can either be prescribed as stand-alone monotherapy or combined. Treatment strategies include monotherapy, sequential monotherapy, parallel combination therapy, step-up therapy, and step-down therapy. At present it is unclear which DMARD or which DMARD treatment strategy is the most effective, both for newly diagnosed rheumatoid arthritis and further treatment.

1.9.2 Impact of the recommendations on practice

The 2009 guideline recommended a combination of cDMARDs (including methotrexate and at least 1 other cDMARD) for newly diagnosed RA and emphasised the importance of starting effective cDMARD therapy as soon as possible.

The 2009 recommendation to start with combination therapy was not widely adopted. The 2016 National Clinical Audit for Rheumatoid Arthritis and Early Inflammatory Arthritis reported that only 46% of people with RA received combination cDMARDs at any time. Currently there is variation in practice regarding the choice of cDMARD(s) and treatment strategy, with many healthcare professionals preferring to start with monotherapy and only use combination therapy when response is inadequate.

The 2018 recommendations to start with monotherapy and add drugs when the response is inadequate are unlikely to have a substantial impact on practice or resources, as they align with the current approach taken by many healthcare professionals. However, the recommendations should result in a more consistent treatment strategy and reduce the number of people prescribed combination therapy on diagnosis.

The 2009 guideline recommended methotrexate as one of the first drugs used in combination therapy. The 2018 recommendations do not specify which cDMARD should be used at any stage of treatment. Again, this will be unlikely to have a significant impact on practice, and methotrexate is likely to remain one of the most commonly prescribed drugs.

The recommendations on dose escalation and reduction have not changed substantially from the 2009 guideline and reflect current clinical practice. The committee clarified that dose reduction and the use of a step-down strategy should only be considered after a person has maintained the treatment target for at least 1 year without the use of glucocorticoids.

1.10 The committee's discussion of the evidence

1.10.1 Interpreting the evidence

1.10.1.1 The outcomes that matter most

The outcomes were the same across both reviews. The critical outcomes were agreed to be the Disease Activity Score (DAS), quality of life and function.

The important outcomes were agreed as the number of people achieving remission and low disease activity, using DAS thresholds. The committee agreed that data reported in this format are not as informative as continuous DAS data but still give an indication of symptom relief and disease activity improvement. Other important outcomes were mortality, the

number of people who withdrew from trial due to adverse events or inefficacy, ACR50 response, as well as the level of pain and radiographic progression.

For most outcomes, 6- and 12-month data was sought to determine the short-term and longer-term benefits of different DMARDs and treatment strategies. The benefits in terms of radiographic progression were not expected earlier than 12 months and that outcome was restricted to data after 12 months or more of treatment. For mortality and withdrawal from trial, data covering the duration of the trial were sought.

In the first-line treatment review, no data were available for quality of life at 6 months. Some data were available for all other outcomes, though this was obtained across 16 different comparisons and so within each comparison there were significant gaps in the outcome data available for each DMARD.

In the further treatment review, no data were available for the outcomes of mortality, radiological progression, remission and quality of life.

1.10.11 The quality of the evidence

First-line treatment

This review included 21 studies of first-line DMARD treatment, which spanned 17 comparisons of a range of different monotherapy, sequential monotherapy, parallel combination therapy, step-down therapy and step-up therapy regimens. Most studies compared different treatment regimens or reported different outcomes. Because of these differences, it was not possible to perform an NMA to compare all drugs and strategies to each other. It was not possible to create a strong, connected network using any of the outcomes the committee prioritised (such as DAS, ACR50 response, DAS remission or DAS low disease activity). Any network that could be connected was considered too limited in both the comparisons included (key comparators were not connected) and the amount of evidence for each comparison (data from only 1 study was available for each comparison) to inform a recommendation which DMARD or strategy to recommend.

A standard pair-wise meta-analysis was performed, though it was still not possible to pool much of the evidence due to the differences in treatment regimens and outcomes reported. In addition, where evidence was pooled, the committee noted there was variation in the DMARD doses and titration regimes used and variable use of glucocorticoids which could have influenced the relative effectiveness of the different regimens.

The quality of the evidence was varied, ranging from high to very low quality, with the majority of the outcomes graded either low or very low quality. The failure to blind participants and outcome assessors was a common source of risk of bias in the included studies, as many of the outcomes (including all of the critical outcomes) had a subjective element and therefore their scoring could be affected by knowledge of the treatment allocation. The other area where risk of bias was common was in terms of selection bias. Studies often failed to report allocation concealment or the method used to randomise people to treatment groups. Missing data also contributed as a source of risk of bias for many comparisons, in that significant numbers of participants left the trial, which could affect the reliability of the results. In addition, much of the evidence for each comparison was from single trials, leading to wide confidence intervals and uncertainty about whether a particular drug or strategy was more effective than another.

<u>People with a poor prognosis</u>

The committee had identified people with a poor prognosis as a population stratum to establish whether a different treatment strategy or different DMARDs should be used. People with a poor prognosis were considered to be those with one or more of the key prognostic factors identified in a separate review, which were anti-CCP positive status and the presence

of erosions at baseline. Only 1 study was identified in people with a poor prognosis, which studied people identified as "high risk" due to erosions, rheumatoid factor, anti-CCP and disease activity. Similarly to the rest of the review, evidence was of low to very low quality due to risk of bias and imprecision. The main risk of bias issues stemmed from a lack of blinding and no reporting of adequate allocation concealment.

Further treatment

This review included 4 studies, all of which reported people who had an insufficient response to a specific DMARD monotherapy and were then treated by either adding another DMARD in a step-up strategy or switching to another DMARD monotherapy. While all participants in each study had previously been treated with the same DMARD, in some of the studies, people had tried (and presumably not responded to) a number of DMARDs *prior to* that specific DMARD. The committee acknowledged this was a limitation of the evidence base, as the populations were mixed. However, 1 of the 4 studies avoided this issue by recruiting and following people who were DMARD-naïve as they progressed through various treatment strategies. As the results of this study were consistent with the results of the other studies, the committee considered all of the evidence to be direct and relevant to the review question.

The evidence quality was variable, ranging from moderate to very low quality across the outcomes and comparisons. Most of the evidence could not be pooled as the studies enrolled different populations, compared different drugs or treatment regimens or reported different outcomes. The evidence was generally at very high or high risk of bias due to incomplete outcome data (for example, unexplained or high numbers of missing data) and lack of blinding in the studies; only withdrawal due to adverse events, reported in 1 study, was at low risk of bias. One of the studies was also a post-hoc analysis of a subset of participants from an RCT, which was considered a further source of potential bias.

Further, for some of the important outcomes, there were small numbers of participants and low numbers of events, resulting in wide confidence intervals, meaning there was some uncertainty as to which treatment approach was superior.

1.10.12 Benefits and harms

First-line treatment

The evidence demonstrated benefits for DMARD monotherapy compared to placebo and furthermore, when compared to parallel combination of 2 DMARDS monotherapy was equally effective or in some cases, demonstrated better results in terms of function and withdrawal due to adverse events. The remainder of the critical outcomes often showed no clinical difference between treatment arms; however where benefit was seen, it was not generalisable to a specific strategy. Similarly, the important outcomes did not uniformly support a treatment regimen; benefits were seen at times for varying strategies. Overall, the committee did not consider that the evidence indicated consistent benefits of any specific treatment strategy over another.

The committee reviewed the recommendations from the 2009 guideline, which recommended combination therapy on the basis of a network meta-analysis (NMA) and accompanying economic model. The committee concluded that the updated evidence review did not support the use of multiple DMARDs in combination as first-line treatment as there was no convincing evidence that it was more effective than monotherapy, and benefits were seen for monotherapy compared to placebo in terms of radiological progression, quality of life and reduction in pain. The committee also agreed that monotherapy would have fewer side effects than combination therapy, and starting with monotherapy would eliminate the challenge of identifying which drugs were causing side effects. It was therefore agreed that people newly diagnosed with rheumatoid arthritis should be offered DMARD monotherapy as first-line treatment.

The committee discussed the reasons for the change in the recommended approach to first line since the 2009 guideline.

Although this review was an update of an existing area of the guideline, the evidence that was included and the approach to analysing that evidence was different. Of note is that the internationally accepted methods for best practice systematic reviewing and appraisal of clinical evidence have changed in that time. In particular NICE now uses GRADE[10] to appraise evidence quality and formally considers whether the magnitude of any difference between treatments is clinically important, rather than whether it is statistically significant. More specifically, many of the studies included in the 2009 guideline used DMARDs that are no longer commonly used in UK practice (for example, ciclosporin). These studies were excluded from the update. In addition, the update included new evidence published after the 2009 guideline. Further, a different approach to the analysis was taken; the update aimed to identify not only which cDMARD strategy was most effective (monotherapy, sequential monotherapy, step-up therapy, step down therapy or parallel combination therapy), but also whether any of the cDMARDs were more or less effective than the others. In contrast, the 2009 guideline compared treatment strategies only, regardless of the particular DMARDs used in those strategies, and combined evidence within each treatment strategy. Other changes included a narrower population (studies were only included if they enrolled people who were DMARD naïve, rather than the only requirement being RA of recent onset, as the committee agreed that was the most important factor for the population of interest), and the exclusion of studies, study arms, or outcome data at particular time points where biological DMARDs formed part of the treatment strategy, due to biologics being outside the scope of the guideline.

Taken together, changes in the review approach, including those outlined above, meant that the evidence base included in the 2018 guideline was quite different to that included in 2009. Unlike in 2009, it was not possible to conduct an NMA or construct an economic model in the 2018 guideline. The results of the 2009 economic model were not considered to be influential by the committee, as they were based on a substantially different evidence base as described above.

The committee emphasised that for all people, the treatment strategy should be adjusted in the event of inadequate response to a particular DMARD monotherapy regimen, informed by the separate ‘further treatment’ and ‘treat-to-target’ reviews.

The recommendation to commence treatment as soon as possible was maintained as timing of treatment initiation was not within the scope of this review.

The committee discussed the relative effectiveness of the different DMARDs considered in the evidence review. It was agreed that the evidence review did not show consistent evidence in favour of any particular DMARD over another. In addition, there was no evidence to suggest that the adverse event profiles differed substantially between the different DMARDs.

The only possible exception to this was hydroxychloroquine, which the committee agreed might be a less effective drug based on the evidence reviewed. No clinically important benefit for hydroxychloroquine was seen over placebo in change in function. It was outperformed by methotrexate in terms of function and achieving remission and outperformed by sulfasalazine in radiological progression. In both cases, more people discontinued hydroxychloroquine due to ineffectiveness. That said, it showed no clinically important difference from methotrexate and sulfasalazine and was more effective than placebo, in terms of pain relief. It was also associated with fewer withdrawals due to adverse events than methotrexate, sulfasalazine and placebo.The committee agreed that generally, the choice of DMARD should be left to the discretion of the treating clinician and the person with rheumatoid arthritis. However, given the possibility that hydroxychloroquine may be less effective than other DMARDs, the committee acknowledged that, in many instances, it may not be the most suitable drug. The committee agreed that hydroxychloroquine is a drug that is low in toxicity which people find

easier to take as there is no requirement for regular blood monitoring. Reduced side effects were supported by the evidence as withdrawal due to adverse events was the only outcome in which hydroxychloroquine demonstrated benefit over the other DMARDs. The committee suggested that it might be helpful in people with mild disease or in palindromic rheumatoid arthritis and should be considered for this group.

No evidence was found for subcutaneous methotrexate, but the committee agreed that the effects may be superior and side effects fewer than with oral cDMARDs. However, because subcutaneous methotrexate is significantly more expensive than other cDMARD options, the committee was not able to recommend this without evidence of clinical benefit over oral cDMARDs. The committee decided to make a research recommendation to inform future guidance.

On balance, the committee decided that the recommendation should be to offer oral methotrexate, leflunomide or sulfasalazine as DMARD monotherapy, and to consider hydroxycholorquine as an alternative in people with mild or palindromic disease. The recommendation was worded as a strong recommendation to offer the DMARD therapy rather than consider because DMARDs are the only effective first line treatment for rheumatoid arthritis and there are no alternative treatments that can be considered. This recommendation will not limit the choice of DMARDs, allowing rheumatologists to utilise their expertise and experience when deciding upon the most appropriate treatment with their patient.

<u>People at risk of poor outcomes</u>

The committee considered whether the evidence of people with a poor prognosis suggested that they should be treated any differently to the rheumatoid arthritis population as a whole. The committee noted that the evidence for this subpopulation was limited to a single study where 2 forms of parallel combination therapy were compared with each other and with step-up therapy. Most of the outcomes were of low or very low quality, and showed no clinical difference between the 2 strategies. Where a clinically important difference was seen between the strategies, it did not consistently favour one strategy over the other (for example, a small clinically important benefit for step-up therapy was seen in terms of radiological progression, and a small clinical benefit for parallel combination therapy over step-up therapy was seen for function assessed using HAQ). The data tended to have wide confidence intervals, which in some instances, ranged from a benefit of combination therapy to a benefit of step-up therapy. Similarly, there was no consistent evidence suggesting that a methotrexate and sulfasalazine combination therapy performed better or worse than a methotrexate and leflunomide combination in this subgroup.

The committee decided that this evidence did not support a recommendation to treat people with a poor prognosis any differently to the general rheumatoid arthritis population. As in all people with rheumatoid arthritis, the treatment strategy and/or DMARDs used should be adjusted in the event of inadequate response to a particular DMARD monotherapy regimen. The committee agreed that dose escalation and treatment to target should ensure that people with a poor prognosis receive effective DMARD treatment.

Further treatment

The data from the 4 RCTs provided moderate to very low quality evidence that after failing a DMARD, adding another DMARD (‘step-up therapy’) yielded better clinical results than replacing the DMARD (‘sequential monotherapy’) based on the differences in DAS, ACR50 response and low disease activity. However, some of the other important outcomes did not consistently show a difference between the interventions (for example, HAQ and pain), and the number of dropouts due to adverse events was lower in sequential monotherapy compared to step-up therapy in some trials. The committee agreed improvement in various disease activity measures was most important, as seen with step-up therapy. While the difference between the treatment strategies was not as consistent for other outcomes, there

were no clinical outcomes for which sequential monotherapy performed better than step-up therapy.

A similar pattern was observed across the trials using different DMARDs, suggesting that it is not necessarily the choice of drug that leads to improvement in outcomes but rather the therapy strategy. The committee therefore agreed not to make a recommendation on which DMARD should be used after inadequate response to monotherapy; instead, the committee emphasised the treatment strategy.

In the event of inadequate response to monotherapy, the committee decided to recommend a step-up approach (adding another DMARD) rather than replacing the DMARD to which there had been insufficient response initially (sequential monotherapy). The committee acknowledged the possibility of increased adverse events when using step-up therapy rather than sequential monotherapy, but the committee considered that these could be managed, and often avoided, by appropriate drug monitoring; the committee thought that the clinical benefit outweighed this risk. For people who have experienced adverse events on monotherapy or are at an increased risk of adverse events, switching to an alternative monotherapy may be preferable to adding a second drug.

The committee agreed that the selection of DMARD should be determined on a case-by-case basis, similar to the selection of first-line therapy.

1.10.12 Cost effectiveness and resource use

Two health economic analyses were identified for first-line DMARD therapy. One was the cost-utility analysis that was conducted as part of the 2009 NICE rheumatoid arthritis guideline. This analysis compared 6 different strategies or regimens of conventional DMARD; only 5 of these comparators met the review protocol and were therefore reported. These were monotherapy, parallel combination, step-down combination and intensive step-up combination. The analysis found that step-down combination was the most cost-effective strategy for people who are newly diagnosed and DMARD naïve. This analysis was assessed as partially applicable with potentially serious limitations. This model did not specify DMARDs but rather refers to treatment strategies, although authors note that a systematic review of monotherapy conducted for the 2009 guideline found no statistically significant difference between DMARDs. EQ-5D was mapped from HAQ rather than directly elicited from people in trials. In terms of methodology, the key limitation was that this analysis is based on 5 of the 22 studies included in the clinical review. Furthermore, it includes 8 studies that were not included in the clinical review; therefore, it does not reflect the full body of evidence and may provide treatment effect estimates that do not reflect those identified in the clinical review. The committee agreed that the results of this analysis were not helpful in terms of evaluating which strategy would be most cost-effective.

The second study included was a cost-utility analysis of the BeST RCT. This analysis included 4 comparators but only 2 were reported, as the others did not meet the review protocol. The comparators reported were sequential monotherapy and step-up combination. Step-up combination dominated sequential monotherapy; that is, it was less costly and more effective. This analysis was assessed as partially applicable with potential serious limitations. The applicability of the analysis was downgraded primarily due to the Dutch healthcare perspective and lack of inclusion of comparison of all possible treatment combinations identified in the clinical evidence. In terms of methodological limitations, the follow-up was only 2 years, which was deemed unlikely to be sufficient to capture all downstream costs and treatment effects. Dutch unit costs may not reflect current NHS costs. Finally, this analysis is based on 1 of the 22 studies included for this question and so does not reflect the full body of evidence.

No health economic analyses were identified for second-line DMARD therapy.

The unit costs of individual conventional DMARDs were presented to the committee. These did not differ significantly (between £39 and £164 per year), with the exception of subcutaneous methotrexate. No clinical evidence in support of the use of subcutaneous methotrexate was identified, so no clinical recommendation was made. In addition to these drug costs, an estimate of the cost of drug monitoring was presented as well as the schedule for drug monitoring recommended by the British Society for Rheumatology and British Health Professionals in Rheumatology. The cost of monitoring, particularly in the first year, is likely to be greater than the drugs themselves but does not differ significantly between different conventional DMARDs or whether 1 or more conventional DMARDs are being prescribed.

The committee considered that the clinical evidence showed no evidence of superiority of any particular strategy or any individual drug for first-line therapy. As a result, the committee agreed to recommend monotherapy as the first-line approach, as this would achieve similar outcomes to combination treatment at a lower cost. The committee considered, however, the importance of frequently monitoring people receiving DMARDs to ensure outcomes are achieved (either remission or low disease activity score). The committee highlighted the importance of reflecting individual patient needs and agreed that if a person is not achieving their target, then a step-up approach is required, whereby the dose is escalated or additional, conventional DMARDs are added. The committee noted that this approach is not unusual and would not be a significant shift in current practice. This is also supported in part by the BeST trial economic analysis.

All other recommendations were ones that were carried over from the previous guideline in 2009. This includes considering reducing doses of conventional DMARDs in those who have a sustained and satisfactory level of disease activity.

Overall, it is not considered that these recommendations will have a significant impact on NHS resources. The committee do not think the previous guideline recommendation to initiate combination conventional DMARDs was being implemented nationally. This is partially due to reluctance to start on combination DMARDs. When combination DMARDs are initiated, there may be more adverse events that are difficult to attribute to a particular DMARD and are costly for the NHS to manage. Although in some areas prescribing conventional DMARDs for people newly diagnosed with rheumatoid arthritis may reduce, overall the committee considered it is likely to remain unchanged.

1.10.32 Other factors the committee took into account

The 2009 guideline recommended that where a person's disease was adequately controlled, it may be appropriate to reduce drug doses or stop treatment with 1 or more DMARDs. While this area was not the focus of these update reviews, the committee noted that many of the included studies did allow or require tapering of drugs once the treatment target was achieved.

The committee agreed that reducing DMARD doses or tapering drugs in a step-down strategy may be appropriate in people who have maintained the treatment target (remission or low disease activity) for at least one year, without requiring glucocorticoid treatment in that time. The committee decided that this should be a 'consider' recommendation, as there are possible risks and benefits to be assessed on a case-by-case basis. Factors to consider would include the previous degree of response to the drug to be reduced or withdrawn and the severity of the person's disease prior to treatment. The committee noted that no evidence was found for subcutaneous methotrexate. The committee's view was that the effects are more immediate when administering via this route and there are reduced side effects. However, given it is significantly more expensive than the other DMARD options, without evidence demonstrating greater effectiveness, the committee was unable to provide advice about its use. It was agreed that this is an important topic for a research recommendation, as it may be a better option for some people who have failed to adequately respond to

conventional DMARDs administered orally, especially if the alternative is progression to biologic DMARDs.

The management of rheumatoid arthritis in pregnancy was identified as an equalities issue in the equalities impact assessment. The committee agreed that it should be an individualised and consultant-led service, with involvement of obstetric services and broader rheumatology MDT as indicated. Patients and their rheumatology team need to consider many aspects of each individual patient's care. These include pre-conception advice and management of pharmacological therapies, assessment of potential impact of disease on the pregnancy, advice on disease course during pregnancy, and discussions regarding the disease and its treatment in the post-partum period. Particular attention should be paid to therapeutic management of rheumatoid arthritis, especially conventional DMARDs and biologic DMARDs, to ensure potentially teratogenic therapies are not continued in the pre-conception stage or into early pregnancy. Alternative management strategies should be considered, depending on each patient's level of disease control and symptoms, for the duration of the pregnancy.

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2 Further treatment after first line DMARD treatment failure

2.1 Review questions:

In adults with RA who have had an inadequate response to, or failed treatment with, one or more conventional DMARDs, which conventional DMARDs (alone or combined) are most clinically and cost effective as subsequent treatments?

In adults with RA who have had an inadequate response to, or failed treatment with, one or more conventional DMARDs, which DMARD treatment strategy (monotherapy, sequential monotherapy, parallel combination therapy, step up therapy or step down therapy) is most clinically and cost effective as subsequent treatment?

2.2 Introduction

DMARDs suppress disease activity and slow down radiological progression in rheumatoid arthritis, resulting in symptom improvement and reduced long-term disability. There are several conventional DMARDs that can either be prescribed as stand-alone monotherapy or combined. Treatment strategies include monotherapy, sequential monotherapy, parallel combination therapy, step-up therapy, and step-down therapy. At present it is unclear which DMARD or which DMARD treatment strategy is the most effective, both for newly diagnosed rheumatoid arthritis and further treatment.

2.3 PICO table

For full details, see the review protocol in appendix A.

Table 23: PICO characteristics of review question

Population	Adults with RA who have failed one or more conventional DMARDs
Interventions	• Methotrexate (oral; MTX oral) • Methotrexate (subcutaneous; MTX sc) • Hydroxychloroquine (HCQ) • Sulfasalazine (SSZ) • Leflunomide (LFN) • Combinations of the above • Sequential combinations of the above Study treatment arms will be classified into one of the following classes: • Monotherapy (a single DMARD used for the duration of the trial)

	• Sequential monotherapy (a single DMARD replaced with a different single DMARD in the case of inadequate response) • Parallel combination (two or more DMARDS commenced at the same time without a step-down strategy) • Step up (commencing with a single DMARD, followed by the addition of further DMARD(s) in the case of inadequate response) Step down (two or more DMARDs commenced at the same time, with drug doses and/or number of drugs reduced once disease is adequately controlled)
Comparisons	The above drugs will be compared against each other or against placebo.
Outcomes	CRITICAL • Disease Activity Score (continuous) at 6 and 12 months • Quality of life (continuous) at 6 and 12 months • Function (continuous) at 6 and 12 months IMPORTANT • Low disease activity (dichotomous) at 6 and 12 months • Remission (dichotomous) at 6 and 12 months • ACR50 response (dichotomous) at 6 and 12 months • Pain (continuous) at 6 and 12 months • Radiological progression (continuous) at 12 months • Adverse events – mortality (dichotomous) at longest reported time point • Withdrawal due to adverse events (dichotomous) at longest reported time point • Withdrawal due to inefficacy (dichotomous) at longest reported time point
Study design	RCTs Systematic Review / Network Meta-Analysis of RCTs

2.4 Methods and process

This evidence review was developed using the methods and process described in Developing NICE guidelines: the manual.[10] Methods specific to this review question are described in the review protocol in appendix A.

Declarations of interest were recorded according to NICE's 2014 conflicts of interest policy.

2.5 Clinical evidence

2.5.1 Included studies

A search was conducted for randomised controlled trials and systematic reviews of randomised controlled trials comparing conventional DMARDs with each other following inadequate response to treatment with one or more conventional DMARDs in adults with rheumatoid arthritis. Four studies (5 papers) were included in the review;[19,34,56,168,48] these are summarised in Table 2 below. The studies reported populations who had failed to response to a variety of monotherapies and were subsequently prescribed a range of different DMARD treatments as either sequential monotherapy or step-up therapy:

- Two studies reported on people who had failed sulfasalazine monotherapy that were subsequently treated with either step-up therapy (a combination of methotrexate and sulfasalazine) or sequential monotherapy (replacement with methotrexate)

- One study treated people who had failed leflunomide monotherapy with either step-up therapy (combination of leflunomide and sulfasalazine) or sequential monotherapy (sulfasalazine)
- One study treated people who had failed methotrexate monotherapy with either step-up therapy (combination of methotrexate and sulfasalazine, with the further addition of hydroxychloroquine if continued inadequate response) or sequential monotherapy (sulfasalazine, replaced by leflunomide if continued inadequate response)

Evidence from these studies is summarised in the clinical evidence summary below (Table 25).

See also the study selection flow chart in appendix C, study evidence tables in appendix D, forest plots in appendix E and GRADE tables in appendix H.

2.5.2 Excluded studies

See the excluded studies list in appendix I.

2.5.3 Summary of clinical studies included in the evidence review

Table 24: Summary of randomised controlled trials included in the evidence review

Study	Intervention and comparison	Population	Outcomes	Comments
Capell 2007[19]	Methotrexate plus sulfasalazine (n=56) versus methotrexate plus placebo (n=54)	Adults with active rheumatoid arthritis (RA; DAS >2.4) for whom sulfasalazine monotherapy failed age (mean): 55	• DAS at 12 months • Health Assessment Questionnaire (HAQ) at 12 months • Pain at 12 months • ACR50 response at 12 months • Withdrawal due to side effects at 12 months • Withdrawal due to inefficacy at 12 months	People who failed Sulfasalazine after 6 months of treatment (DAS≥2.4) were randomised to three treatment arms for 12 months: either sulfasalazine alone, methotrexate alone, or a combination of the two. Only the data of the latter two arms are relevant to this review and presented here. Unclear whether people were DMARD naïve before sulfasalazine treatment.
Dougados 2005[34]	Leflunomide plus sulfasalazine (n=56) versus sulfasalazine plus placebo (n=50)	Adults with active RA and inadequate DAS28 response to leflunomide monotherapy Age (mean): 56	• HAQ change at 24 weeks • Pain intensity change at 24 weeks • ACR50 response at 24 weeks • Withdrawal due to adverse events at 24 weeks	People who had failed leflunomide monotherapy after 24 weeks open label phase were randomised to leflunomide plus sulfasalazine or sulfasalazine for 24 weeks. At the time of leflunomide treatment 67% of

Study	Intervention and comparison	Population	Outcomes	Comments
			• Withdrawal due to inefficacy at 24 weeks	people had already used other DMARDs before.
Haagsma 1994[56]	Methotrexate plus sulfasalazine (n=22) versus methotrexate monotherapy (n=18)	Adults with RA and insufficient response to sulfasalazine monotherapy Age (mean): 56	• DAS change at 24 weeks • VAS pain change at 24 weeks • Withdrawal due to adverse events at 24 weeks • Withdrawal due to inefficacy at 24 weeks	People who had failed sulfasalazine monotherapy were randomised to methotrexate plus sulfasalazine or methotrexate for 24 weeks. Before starting on sulfasalazine in the first phase of the study people in both groups had used median 1 (range 0-4) DMARD previously.
van der Kooij 2007[168]; Goekoop-Ruiterman 2005[48]	Sequential monotherapy (sulfasalazine then leflunomide if inadequate response) (n=69) versus step-up therapy (methotrexate plus sulfasalazine then methotrexate plus sulfasalazine plus hydroxychloroquine if inadequate response) (n=69)	Adults with RA for whom methotrexate monotherapy failed (persistent DAS>2.4) Age (mean): 54	• Low disease activity (LDA; DAS ≤2.4) after step 1 (sulfasalazine mono- or combination therapy) • LDA after step 2 (sulfasalazine failure, followed by leflunomide monotherapy or methotrexate plus sulfasalazine plus hydroxychloroquine step-up therapy) • LDA total ('successes' from step 1 and step 2 combined) • Withdrawal due to adverse event during step 1 • Withdrawal due to adverse event during step 2 • Withdrawal	Post hoc analysis of subset of people from 2 out of 4 treatment arm RCT (BeSt trial) who failed methotrexate (persistent DAS>2.4) and who had been randomised to either sequential monotherapy or step-up therapy for up to 2 years. Only the data of the first two steps was extracted from the study; the protocol involved escalation to biologics thereafter. All people with RA were DMARD naïve at the start of the BeSt trial.

Study	Intervention and comparison	Population	Outcomes	Comments
			due to adverse event total • Discontinuation due to inefficacy (DAS>2.4) after step 1 • Discontinuation due to inefficacy after step 2	

1 See appendix D for full evidence tables.

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2.5.4 Quality assessment of clinical studies included in the evidence review

Table 25: Clinical evidence summary: Step-up therapy (sulfasalazine plus leflunomide) versus sequential monotherapy (sulfasalazine plus placebo) in people who failed leflunomide monotherapy

Outcomes	No of Participants (studies) Follow up	Quality of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects	
				Risk with sequential monotherapy	Risk difference with step-up therapy (95% CI)
Disease Activity Score at 6 or 12 months - not reported	-	-	-	-	-
Quality of life at 6 or 12 months - not reported	-	-	-	-	-
Function at 12 months - not reported	-	-	-	-	-
Function at 6 months Change in HAQ. Scale from: 0 to 3.	106 (1 study) 24 weeks	⊕⊖⊖⊖ VERY LOW[1,2] due to risk of bias, imprecision		The mean change in function (HAQ) at 6 months in the control groups was -0.02	The mean change in function (HAQ) at 6 months in the intervention groups was 0.07 lower (0.2 lower to 0.06 higher)
ACR50 response at 6 months	106 (1 study) 24 weeks	⊕⊖⊖⊖ VERY LOW[1,2] due to risk of bias, imprecision	Peto OR 7.16 (1.19 to 42.87)[4]	0 per 1000	90 more per 1000 (from 10 more to 170 more)[3]
Pain at 6 months Change in VAS. Scale from: 0 to 100.	106 (1 study) 24 weeks	⊕⊕⊖⊖ LOW[1] due to risk of bias		The mean change in pain (VAS) at 6 months in the control groups was -8.32	The mean change in pain (VAS) at 6 months in the intervention groups was 0.89 lower (9.77 lower to 7.99 higher)
Withdrawal: side effects	106 (1 study) 24 weeks	⊕⊕⊖⊖ LOW[1,2] due to risk of bias, imprecision	RR 1.29 (0.81 to 2.05)	360 per 1000	104 more per 1000 (from 68 fewer to 378 more)

Outcomes	No of Participants (studies) Follow up	Quality of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects	
				Risk with sequential monotherapy	Risk difference with step-up therapy (95% CI)
Withdrawal: inefficacy	106 (1 study) 24 weeks	⨁⊖⊖⊖ VERY LOW[1,2] due to risk of bias, imprecision	RR 0.67 (0.16 to 2.85)	80 per 1000	26 fewer per 1000 (from 67 fewer to 148 more)

1 Downgraded by 1 increment if the majority of the evidence was at high risk of bias, and downgraded by 2 increments if the majority of the evidence was at very high risk of bias
2 Downgraded by 1 increment if the confidence interval crossed one MID or by 2 increments if the confidence interval crossed both MIDs
3 Risk difference for the absolute effect.
4 Peto Odds ratio was used due to low numbers of events.

Table 26: Clinical evidence summary: Step-up therapy (methotrexate plus sulfasalazine) versus sequential monotherapy (methotrexate) in people who failed sulfasalazine monotherapy

Outcomes	No of Participants (studies) Follow up	Quality of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects	
				Risk with sequential monotherapy	Risk difference with step-up therapy (95% CI)
Disease Activity Score at 6 months - not reported	-	-	-	-	-
Quality of life at 6 or 12 months - not reported	-	-	-	-	-
Function at 6 months - not reported	-	-	-	-	-
Disease Activity Score at 12 months Change in DAS. Scale from: 0 to 10.	110 (1 study) 1 year	MODERATE[1,3] due to risk of bias		The change in DAS from baseline (median (IQR)) in the control groups was -0.26 (-0.99 to 0)	The change in DAS from baseline (median (IQR)) in the intervention groups was -0.67 (-1.38 to -0.21) (median difference 0.41)
Disease Activity Score at 6 months Change in DAS. Scale from: 0 to 10.	40 (1 study) 24 weeks	⨁⨁⨁⊖ MODERATE1 due to risk of		The mean change in DAS at 12 months in the control groups was	The mean change in DAS at 12 months in the intervention groups was 1.6 lower

Outcomes	No of Participants (studies) Follow up	Quality of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects	
				Risk with sequential monotherapy	Risk difference with step-up therapy (95% CI)
		bias		-1.0	(2.16 to 1.04 lower)
Function at 12 months Change in HAQ. Scale from: 0 to 3.	110 (1 study) 1 year	MODERATE[1,3] due to risk of bias		The change in HAQ from baseline (median (IQR)) in the control groups was -0.19 (-10.25 to 0.13)	The change in HAQ from baseline (median (IQR)) in the intervention groups was -0.5 (-10.25 to 0.06) (median difference 0.31)
ACR50 response at 12 months	110 (1 study) 1 year	⊕⊖⊖⊖ VERY LOW[1,2] due to risk of bias, imprecision	RR 1.45 (0.43 to 4.84)	74 per 1000	33 more per 1000 (from 42 fewer to 284 more)
Pain at 6 months Change in VAS. Scale from: 0 to 100	40 (1 study) 24 weeks	⊕⊖⊖⊖ VERY LOW[1,2] due to risk of bias, imprecision		The mean change in pain score at 12 months in the control groups was -14	The mean change in pain score at 12 months in the intervention groups was 16 lower (30.26 to 1.74 lower)
Pain score at 12 months Change score. Scale: unclear range	110 (1 study) 1 year	MODERATE[1,3] due to risk of bias		The change in pain score change from baseline (median (IQR)) in the control groups was 0 (-23 to 11)	The change in pain score from baseline (median (IQR)) in the intervention groups was -8 (-27.5 to 2) (median difference 8)
Withdrawal: side effects	150 (2 studies) 38 weeks	⊕⊕⊖⊖ LOW[2] due to imprecision	RR 0.83 (0.42 to 1.62)3	194 per 1000	33 fewer per 1000 (from 113 fewer to 121 more)
Withdrawal: inefficacy	150 (2 studies) 38 weeks	⊕⊕⊖⊖ LOW[2] due to imprecision	RR 0.96 (0.14 to 6.6)	28 per 1000	1 fewer per 1000 (from 24 fewer to 156 more)

Outcomes	No of Participants (studies) Follow up	Quality of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects	
				Risk with sequential monotherapy	Risk difference with step-up therapy (95% CI)

1 Downgraded by 1 increment if the majority of the evidence was at high risk of bias, and downgraded by 2 increments if the majority of the evidence was at very high risk of bias
2 Downgraded by 1 increment if the confidence interval crossed one MID or by 2 increments if the confidence interval crossed both MIDs
3 Cannot assess imprecision using median (IQR)

Table 27: Clinical evidence summary: Step-up therapy (methotrexate plus sulfasalazine then methotrexate plus sulfasalazine plus hydroxychloroquine) versus sequential monotherapy (sulfasalazine then leflunomide) in people who failed methotrexate monotherapy

Outcomes	No of Participants (studies) Follow up	Quality of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects	
				Risk with sequential monotherapy	Risk difference with step-up therapy (95% CI)
Disease Activity Score at 6 or 12 months - not reported	-	-	-	-	-
Quality of life at 6 or 12 months - not reported	-	-	-	-	-
Change in function at 6 or 12 months - not reported	-	-	-	-	-
Low disease activity total at 12 months after step and step 2 DAS<2.4	138 (1 study) 9 months	⊕⊖⊖⊖ VERY LOW[1,2] due to risk of bias, imprecision	RR 1.41 (0.91 to 2.17)	319 per 1000	131 more per 1000 (from 29 fewer to 373 more)
Low disease activity at 6 months after step 1 DAS<2.4	138 (1 study) 6 months	⊕⊖⊖⊖ VERY LOW[1,2] due to risk of bias, imprecision	RR 1 (0.53 to 1.88)	217 per 1000	0 fewer per 1000 (from 102 fewer to 191 more)
Low disease activity) at 6 months after step 2 DAS<2.4	98 (1 study) 3 months	⊕⊕⊖⊖ LOW[1,2] due to risk of bias, imprecision	RR 2.81 (1.27 to 6.21)	130 per 1000	235 more per 1000 (from 35 more to 675 more)
Withdrawal: adverse events total	138	⊕⊖⊖⊖	RR 1.38	188 per 1000	72 more per 1000

Outcomes	No of Participants (studies) Follow up	Quality of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects	
				Risk with sequential monotherapy	Risk difference with step-up therapy (95% CI)
	(1 study) 9 months	VERY LOW[1,2] due to risk of bias, imprecision	(0.74 to 2.6)		(from 49 fewer to 301 more)
Withdrawal: adverse events during step 1	138 (1 study) 6 months	⊕⊖⊖⊖ VERY LOW[1,2] due to risk of bias, imprecision	RR 1.86 (0.79 to 4.37)	101 per 1000	87 more per 1000 (from 21 fewer to 342 more)
Withdrawal: adverse events during step 2	98 (1 study) 3 months	⊕⊖⊖⊖ VERY LOW[1,2] due to risk of bias, imprecision	RR 1.02 (0.33 to 3.13)	111 per 1000	2 more per 1000 (from 74 fewer to 237 more)
Withdrawal: inefficacy during step 1 DAS >2.4	138 (1 study) 6 months	⊕⊕⊖⊖ LOW[1,2] due to risk of bias, imprecision	RR 0.87 (0.68 to 1.12)	681 per 1000	89 fewer per 1000 (from 218 fewer to 82 more)
Withdrawal: inefficacy during step 2 DAS >2.4	98 (1 study) 3 months	⊕⊖⊖⊖ VERY LOW[2] due to risk of bias, imprecision	RR 0.63 (0.45 to 0.89)	759 per 1000	281 fewer per 1000 (from 84 fewer to 418 fewer)

1 Downgraded by 1 increment if the majority of the evidence was at high risk of bias, and downgraded by 2 increments if the majority of the evidence was at very high risk of bias
2 Downgraded by 1 increment if the confidence interval crossed one MID or by 2 increments if the confidence interval crossed both MIDs

1 See appendix F for full GRADE tables.

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2.6 Economic evidence

2.6.1 Included studies

No relevant health economic studies were identified.

2.6.2 Excluded studies

No health economic studies that were relevant to this question were excluded due to assessment of limited applicability or methodological limitations.

See also the health economic study selection flow chart in appendix G.

2.6.3 Unit costs

Table 28: UK costs of conventional DMARDs

Drug	Dosage	Cost – annual
Methotrexate, oral tablets	Max. 20mg weekly	£39.49
Methotrexate, subcutaneous, prefilled syringe	Max. 25 mg weekly	£960.96
Hydroxychloroquine, oral tables	200-400mg daily	£45.38
Sulfasalazine, gastro-resistant tablets	Max. 2-3g daily	£164.39
Leflunomide, oral tablet	10-20mg	£92.94

Sources: Dosage: BNF March 2017[11]; Unit cost: NHS Drug Tariff, March 2017.[116]

In addition to the cost of the drugs, there are also costs associated with monitoring of conventional DMARDs.

NICE technology appraisal TA375 has estimated that the monthly cost of monitoring methotrexate to be £134. This cost includes a full blood count, biochemical profile and a hospital outpatient appointment.

The British Society for Rheumatology and British Health Professionals in Rheumatology published a guideline for prescription and monitoring of non-biologic DMARDs in 2017. The standard laboratory-monitoring schedule recommended is nine monitoring blood tests in first 12 months. The blood tests include full blood count, creatinine/calculated GFR, ALT and/or AST and albumin. Table 22 below outlines a summary of monitoring requirements for each drug.

Table 29: Monitoring of conventional DMARDs

Drug	Laboratory monitoring	Other monitoring
Methotrexate	Standard monitoring schedule	None
Hydroxychloroquine	No routine laboratory monitoring	Annual eye assessment if continued >5 years
Sulfasalazine	Standard monitoring schedule for 12 months, then no routine monitoring needed	None
Leflunomide	Standard monitoring schedule	Blood pressure and weight at each monitoring visit

Source: BSR and BHPR monitoring guideline 2017[93]

2.7 Resource costs

The recommendations made in this review are not expected to have a substantial impact on resources.

2.8 Evidence statements

2.8.1 Clinical evidence statements

- Step-up therapy (sulfasalazine plus leflunomide) versus sequential monotherapy (sulfasalazine plus placebo) in people who failed leflunomide monotherapy

Evidence from 1 study showed no clinically important difference between the therapies in terms of function and pain; however step-up therapy was associated with a clinically important benefit in terms of ACR50 response and withdrawal due to inefficacy. Fewer people on sequential monotherapy withdrew due to side effects (low to very low quality; n=106). No evidence was available for disease activity or quality of life.

- Step-up therapy (methotrexate plus sulfasalazine) versus sequential monotherapy (methotrexate) in people who failed sulfasalazine monotherapy

Evidence from 1 study showed a clinically important benefit of step-up therapy over sequential monotherapy alone on function (moderate quality; n=110). Evidence for step-up therapy on disease activity and pain was inconsistent, with some measures showing a clinically important benefit associated with step-up therapy, but other measures of the same outcomes finding no clinically important difference (2 studies; range of n=40-110; moderate to very low quality).No clinically importance difference was seen between the therapies for withdrawal due to side effects or inefficacy. No evidence was available for quality of life.

- Step-up therapy (methotrexate plus sulfasalazine, then adding hydroxychloroquine) versus sequential monotherapy (sulfasalazine, then replacing with leflunomide) in people who failed methotrexate monotherapy

Evidence from 1 study showed a clinically important benefit of step-up therapy in terms of low disease activity after the second ‘step’ of the protocol and over the full trial period. Withdrawal due to inefficacy after the second step in the protocol also showed a clinically important benefit in favour of step-up therapy. No clinically importance difference was seen between the therapies in terms of low disease activity or withdrawal due to inefficacy after the first step of the protocol. Sequential monotherapy was associated with fewer withdrawals due to adverse events after the first step of the protocol and over the full trial period, though no clinically important difference was seen after the second step of the protocol (low to very low quality, n=138). No evidence was available for disease activity, quality of life or function.

2.8.2 Health economic evidence statements

- No relevant economic evaluations were identified.

2.9 Recommendations

F1. For adults with newly diagnosed active RA:

- offer first-line treatment with conventional disease modifying anti-rheumatic drug (cDMARD) monotherapy using oral methotrexate, leflunomide or sulfasalazine as soon as possible and ideally within 3 months of onset of persistent symptoms.
- Consider hydroxychloroquine for first-line treatment as an alternative to oral methotrexate, leflunomide orsulfasalazine for mild or palindromic disease.
- Escalate dose as tolerated.

F2. Offer additional cDMARDs (oral methotrexate, leflunomide, sulfasalazine or hydroxycholorquine) in combination in a step-up strategy when the treatment target (remission or low disease activity) has not been achieved despite dose escalation.

F3. For adults who have maintained the treatment target (remission or low disease activity) for at least 1 year without glucocorticoids, consider cautiously reducing drug doses or stopping drugs in a step-down strategy. Return promptly to the previous DMARD regimen if the treatment target is no longer met.

2.9.11 Research recommendations

F.RR1. What is the clinical and cost effectiveness of subcutaneous methotrexate compared with oral methotrexate for adults with early onset RA starting a new DMARD?

2.10 Rationale and impact

2.10.1 Why the committee made the recommendations

First-line treatment

Evidence showed that starting treatment with more than 1 conventional DMARD (cDMARD) was no more effective than starting with a single cDMARD. The committee agreed that cDMARD monotherapy might have fewer side effects and recommended cDMARD monotherapy as first-line treatment. This differed from the 2009 guideline which recommended combination therapy. The difference is largely a result of inclusion of different evidence and a different approach to analysing that evidence.

Many of the studies included in the 2009 guideline used cDMARDs that are no longer commonly used in UK practice (for example, ciclosporin), and these studies were excluded from the evidence for the 2018 update. In addition, the 2018 update included new evidence published after the 2009 guideline. Further, a different approach to analysing the evidence was taken, with the 2018 update aiming to identify the most effective cDMARD strategy (monotherapy, sequential monotherapy, step-up therapy, step-down therapy or parallel combination therapy) as well as which cDMARD should be used. The 2009 guideline compared treatment strategies only, regardless of the particular cDMARDs, and combined evidence according to treatment strategy.

The evidence included in the 2018 update was therefore different to that included in 2009 and supported cDMARD monotherapy as first-line treatment.

Evidence from randomised controlled trials in people who had never had a DMARD showed no consistent differences in the effectiveness of methotrexate, leflunomide and sulfasalazine as monotherapies. The drugs also had similar costs. The committee agreed that any of these drugs can be used as first-line treatment.

Hydroxychloroquine was less effective, but fewer people stopped treatment because of side effects. The committee agreed that hydroxychloroquine could be considered for people with mild or palindromic disease.

People at risk of poor outcomes

Evidence for different first-line treatment in people with a poor prognosis was limited so the committee decided not to make a separate recommendation for this group. They agreed that

the recommendation for dose increases and treating to target (with the aim of keeping disease activity low) should ensure adequate treatment for these people. Given the limited evidence in this area, the committee also decided that the possible benefit of managing RA with a poor prognosis with a different strategy was a priority for future research (see evidence review B: Risk factors).

Further treatment

Evidence supported adding another cDMARD when needed (step-up strategy) rather than replacing the cDMARD with another (sequential monotherapy). The committee acknowledged that more side effects were possible with a step-up strategy, but in their experience these could be managed by drug monitoring and were outweighed by the clinical benefit of combination treatment when monotherapy was inadequate. A published cost analysis supported a step-up approach rather than sequential monotherapy.

Subcutaneous methotrexate

No evidence was found for subcutaneous methotrexate, but the committee agreed that the effects may be superior and side effects fewer than with oral cDMARDs. However, because subcutaneous methotrexate is significantly more expensive than other cDMARD options, the committee was not able to recommend this without evidence of clinical benefit and cost effectiveness relative to oral cDMARDs. The committee decided to make a research recommendation to inform future guidance.

Why we need recommendations on this topic

DMARDs suppress disease activity and slow down radiological progression in rheumatoid arthritis, resulting in symptom improvement and reduced long-term disability. There are several conventional DMARDs that can either be prescribed as stand-alone monotherapy or combined. Treatment strategies include monotherapy, sequential monotherapy, parallel combination therapy, step-up therapy, and step-down therapy. At present it is unclear which DMARD or which DMARD treatment strategy is the most effective, both for newly diagnosed rheumatoid arthritis and further treatment.

2.102 Impact of the recommendations on practice

The 2009 guideline recommended a combination of cDMARDs (including methotrexate and at least 1 other cDMARD) for newly diagnosed RA and emphasised the importance of starting effective cDMARD therapy as soon as possible.

The 2009 recommendation to start with combination therapy was not widely adopted. The 2016 National Clinical Audit for Rheumatoid Arthritis and Early Inflammatory Arthritis reported that only 46% of people with RA received combination cDMARDs at any time. Currently there is variation in practice regarding the choice of cDMARD(s) and treatment strategy, with many healthcare professionals preferring to start with monotherapy and only use combination therapy when response is inadequate.

The 2018 recommendations to start with monotherapy and add drugs when the response is inadequate are unlikely to have a substantial impact on practice or resources, as they align with the current approach taken by many healthcare professionals. However, the recommendations should result in a more consistent treatment strategy and reduce the number of people prescribed combination therapy on diagnosis.

The 2009 guideline recommended methotrexate as one of the first drugs used in combination therapy. The 2018 recommendations do not specify which cDMARD should be used at any stage of treatment. Again, this will be unlikely to have a significant impact on practice, and methotrexate is likely to remain one of the most commonly prescribed drugs.

The recommendations on dose escalation and reduction have not changed substantially from the 2009 guideline and reflect current clinical practice. The committee clarified that dose reduction and the use of a step-down strategy should only be considered after a person has maintained the treatment target for at least 1 year without the use of glucocorticoids.

2.11 The committee's discussion of the evidence

2.11.1 Interpreting the evidence

2.11.1.1 The outcomes that matter most

The outcomes were the same across both reviews. The critical outcomes were agreed to be the Disease Activity Score (DAS), quality of life and function.

The important outcomes were agreed as the number of people achieving remission and low disease activity, using DAS thresholds. The committee agreed that data reported in this format are not as informative as continuous DAS data but still give an indication of symptom relief and disease activity improvement. Other important outcomes were mortality, the number of people who withdrew from trial due to adverse events or inefficacy, ACR50 response, as well as the level of pain and radiographic progression.

For most outcomes, 6- and 12-month data was sought to determine the short-term and longer-term benefits of different DMARDs and treatment strategies. The benefits in terms of radiographic progression were not expected earlier than 12 months and that outcome was restricted to data after 12 months or more of treatment. For mortality and withdrawal from trial, data covering the duration of the trial were sought.

In the first-line treatment review, no data were available for quality of life at 6 months. Some data were available for all other outcomes, though this was obtained across 16 different comparisons and so within each comparison there were significant gaps in the outcome data available for each DMARD.

In the further treatment review, no data were available for the outcomes of mortality, radiological progression, remission and quality of life.

2.11.1.2 The quality of the evidence

First-line treatment

This review included 21 studies of first-line DMARD treatment, which spanned 17 comparisons of a range of different monotherapy, sequential monotherapy, parallel combination therapy, step-down therapy and step-up therapy regimens. Most of studies compared different treatment regimens or reported different outcomes. Because of these differences, it was not possible to perform an NMA to compare all drugs and strategies to each other. It was not possible to create a strong, connected network using any of the outcomes the committee prioritised (such as DAS, ACR50 response, DAS remission or DAS low disease activity). Any network that could be connected was considered too limited in both the comparisons included (key comparators were not connected) and the amount of evidence for each comparison (data from only 1 study was available for each comparison) to inform a recommendation which DMARD or strategy to recommend.

A standard pair-wise meta-analysis was performed, though it was still not possible to pool much of the evidence due to the differences in treatment regimens and outcomes reported. In addition, where evidence was pooled, the committee noted there was variation in the

DMARD doses and titration regimes used and variable use of glucocorticoids which could have influenced the relative effectiveness of the different regimens.

The quality of the evidence was varied, ranging from high to very low quality, with the majority of the outcomes graded either low or very low quality. The failure to blind participants and outcome assessors was a common source of risk of bias in the included studies, as many of the outcomes (including all of the critical outcomes) had a subjective element and therefore their scoring could be affected by knowledge of the treatment allocation. The other area where risk of bias was common was in terms of selection bias. Studies often failed to report allocation concealment or the method used to randomise people to treatment groups. Missing data also contributed as a source of risk of bias for many comparisons, in that significant numbers of participants left the trial, which could affect the reliability of the results. In addition, much of the evidence for each comparison was from single trials, leading to wide confidence intervals and uncertainty about whether a particular drug or strategy was more effective than another.People with a poor prognosis

The committee had identified people with a poor prognosis as a population stratum to establish whether a different treatment strategy or different DMARDs should be used. People with a poor prognosis were considered to be those with one or more of the key prognostic factors identified in a separate review, which were anti-CCP positive status and the presence of erosions at baseline. Only 1 study was identified in people with a poor prognosis, which studied people identified as "high risk" due to erosions, rheumatoid factor, anti-CCP and disease activity. Similarly to the rest of the review, evidence was of low to very low quality due to risk of bias and imprecision. The main risk of bias issues stemmed from a lack of blinding and no reporting of adequate allocation concealment.

Further treatment

This review included 4 studies, all of which reported people who had an insufficient response to a specific DMARD monotherapy and were then treated by either adding another DMARD in a step-up strategy or switching to another DMARD monotherapy. While all participants in each study had previously been treated with the same DMARD, in some of the studies, people had tried (and presumably not responded to) a number of DMARDs *prior to* that specific DMARD. The committee acknowledged this was a limitation of the evidence base, as the populations were mixed. However, 1 of the 4 studies avoided this issue by recruiting and following people who were DMARD-naïve as they progressed through various treatment strategies. As the results of this study were consistent with the results of the other studies, the committee considered all of the evidence to be direct and relevant to the review question.

The evidence quality was variable, ranging from moderate to very low quality across the outcomes and comparisons. Most of the evidence could not be pooled as the studies enrolled different populations, compared different drugs or treatment regimens or reported different outcomes. The evidence was generally at very high or high risk of bias due to incomplete outcome data (for example, unexplained or high numbers of missing data) and lack of blinding in the studies; only withdrawal due to adverse events, reported in 1 study, was at low risk of bias. One of the studies was also a post-hoc analysis of a subset of participants from an RCT, which was considered a further source of potential bias.

Further, for some of the important outcomes, there were small numbers of participants and low numbers of events, resulting in wide confidence intervals, meaning there was some uncertainty as to which treatment approach was superior.

2.11.146 Benefits and harms

First-line treatment

The evidence demonstrated benefits for DMARD monotherapy compared to placebo and furthermore, when compared to parallel combination of 2 DMARDS monotherapy was

equally effective or in some cases, demonstrated better results in terms of function and withdrawal due to adverse events. The remainder of the critical outcomes often showed no clinical difference between treatment arms; however where benefit was seen, it was not generalisable to a specific strategy. Similarly, the important outcomes did not uniformly support a treatment regimen; benefits were seen at times for varying strategies. Overall, the committee did not consider that the evidence indicated consistent benefits of any specific treatment strategy over another.

The committee reviewed the recommendations from the 2009 guideline, which recommended combination therapy on the basis of a network meta-analysis (NMA) and accompanying economic model. The committee concluded that the updated evidence review did not support the use of multiple DMARDs in combination as first-line treatment as there was no convincing evidence that it was more effective than monotherapy, and benefits were seen for monotherapy compared to placebo in terms of radiological progression, quality of life and reduction in pain. The committee also agreed that monotherapy would have fewer side effects than combination therapy, and starting with monotherapy would eliminate the challenge of identifying which drugs were causing side effects. It was therefore agreed that people newly diagnosed with rheumatoid arthritis should be offered DMARD monotherapy as first-line treatment.

The committee discussed the reasons for the change in the recommended approach to first line since the 2009 guideline.

Although this review was an update of an existing area of the guideline, the evidence that was included and the approach to analysing that evidence was different. Of note is that the internationally accepted methods for best practice systematic reviewing and appraisal of clinical evidence have changed in that time. In particular NICE now uses GRADE[10] to appraise evidence quality and formally considers whether the magnitude of any difference between treatments is clinically important, rather than whether it is statistically significant. More specifically, many of the studies included in the 2009 guideline used DMARDs that are no longer commonly used in UK practice (for example, ciclosporin). These studies were excluded from the update. In addition, the update included new evidence published after the 2009 guideline. Further, a different approach to the analysis was taken; the update aimed to identify not only which cDMARD strategy was most effective (monotherapy, sequential monotherapy, step-up therapy, step down therapy or parallel combination therapy), but also whether any of the cDMARDs were more or less effective than the others. In contrast, the 2009 guideline compared treatment strategies only, regardless of the particular DMARDs used in those strategies, and combined evidence within each treatment strategy. Other changes included a narrower population (studies were only included if they enrolled people who were DMARD naïve, rather than the only requirement being RA of recent onset, as the committee agreed that was the most important factor for the population of interest), and the exclusion of studies, study arms, or outcome data at particular time points where biological DMARDs formed part of the treatment strategy, due to biologics being outside the scope of the guideline.

Taken together, changes in the review approach, including those outlined above, meant that the evidence base included in the 2018 guideline was quite different to that included in 2009. Unlike in 2009, it was not possible to conduct an NMA or construct an economic model in the 2018 guideline. The results of the 2009 economic model were not [given much weight?] by the committee, as they were based on a substantially different evidence base as described above.

The committee emphasised that for all people, the treatment strategy should be adjusted in the event of inadequate response to a particular DMARD monotherapy regimen, informed by the separate ‘further treatment’ and ‘treat-to-target’ reviews.

The recommendation to commence treatment as soon as possible was maintained as timing of treatment initiation was not within the scope of this review.

The committee discussed the relative effectiveness of the different DMARDs considered in the evidence review. It was agreed that the evidence review did not show consistent evidence in favour of any particular DMARD over another. In addition, there was no evidence to suggest that the adverse event profiles differed substantially between the different DMARDs.

The only possible exception to this was hydroxychloroquine, which the committee agreed might be a less effective drug based on the evidence reviewed. No clinically important benefit for hydroxychloroquine was seen over placebo in change in function. It was outperformed by methotrexate in terms of function and achieving remission and outperformed by sulfasalazine in radiological progression. In both cases, more people discontinued hydroxychloroquine due to ineffectiveness. That said, it showed no clinically important difference from methotrexate and sulfasalazine and was more effective than placebo, in terms of pain relief. It was also associated with fewer withdrawals due to adverse events than methotrexate, sulfasalazine and placebo.

The committee agreed that generally, the choice of DMARD should be left to the discretion of the treating clinician and the person with rheumatoid arthritis. However, given the possibility that hydroxychloroquine may be less effective than other DMARDs, the committee acknowledged that, in many instances, it may not be the most suitable drug. The committee agreed that hydroxychloroquine is a drug that is low in toxicity which people find easier to take as there is no requirement for regular blood monitoring. Reduced side effects were supported by the evidence as withdrawal due to adverse events was the only outcome in which hydroxychloroquine demonstrated benefit over the other DMARDs. The committee suggested that it might be helpful in people with mild disease or in palindromic rheumatoid arthritis and should be considered for this group.

No evidence was found for subcutaneous methotrexate, but the committee agreed that the effects may be superior and side effects fewer than with oral cDMARDs. However, because subcutaneous methotrexate is significantly more expensive than other cDMARD options, the committee was not able to recommend this without evidence of clinical benefit over oral cDMARDs. The committee decided to make a research recommendation to inform future guidance.On balance, the committee decided that the recommendation should be to offer oral methotrexate, leflunomide or sulfasalazine as DMARD monotherapy, and to consider hydroxycholorquine as an alternative in people with mild or palindromic disease. The recommendation was worded as a strong recommendation to offer the DMARD therapy rather than consider because DMARDs are the only effective first line treatment for rheumatoid arthritis and there are no alternative treatments that can be considered. This recommendation will not limit the choice of DMARDs, allowing rheumatologists to utilise their expertise and experience when deciding upon the most appropriate treatment with their patient.

People at risk of poor outcomes

The committee considered whether the evidence of people with a poor prognosis suggested that they should be treated any differently to the rheumatoid arthritis population as a whole. The committee noted that the evidence for this subpopulation was limited to a single study where 2 forms of parallel combination therapy were compared with each other and with step-up therapy. Most of the outcomes were of low or very low quality, and showed no clinical difference between the 2 strategies. Where a clinically important difference was seen between the strategies, it did not consistently favour one strategy over the other (for example, a small clinically important benefit for step-up therapy was seen in terms of radiological progression, and a small clinical benefit for parallel combination therapy over step-up therapy was seen for function assessed using HAQ). The data tended to have wide confidence intervals, which in some instances, ranged from a benefit of combination therapy to a benefit of step-up therapy. Similarly, there was no consistent evidence suggesting that a

methotrexate and sulfasalazine combination therapy performed better or worse than a methotrexate and leflunomide combination in this subgroup.

The committee decided that this evidence did not support a recommendation to treat people with a poor prognosis any differently to the general rheumatoid arthritis population. As in all people with rheumatoid arthritis, the treatment strategy and/or DMARDs used should be adjusted in the event of inadequate response to a particular DMARD monotherapy regimen. The committee agreed that dose escalation and treatment to target should ensure that people with a poor prognosis receive effective DMARD treatment.

Further treatment

The data from the 4 RCTs provided moderate to very low quality evidence that after failing a DMARD, adding another DMARD ('step-up therapy') yielded better clinical results than replacing the DMARD ('sequential monotherapy') based on the differences in DAS, ACR50 response and low disease activity. However, some of the other important outcomes did not consistently show a difference between the interventions (for example, HAQ and pain), and the number of dropouts due to adverse events was lower in sequential monotherapy compared to step-up therapy in some trials. The committee agreed improvement in various disease activity measures was most important, as seen with step-up therapy. While the difference between the treatment strategies was not as consistent for other outcomes, there were no clinical outcomes for which sequential monotherapy performed better than step-up therapy.

A similar pattern was observed across the trials using different DMARDs, suggesting that it is not necessarily the choice of drug that leads to improvement in outcomes but rather the therapy strategy. The committee therefore agreed not to make a recommendation on which DMARD should be used after inadequate response to monotherapy; instead, the committee emphasised the treatment strategy.

In the event of inadequate response to monotherapy, the committee decided to recommend a step-up approach (adding another DMARD) rather than replacing the DMARD to which there had been insufficient response initially (sequential monotherapy). The committee acknowledged the possibility of increased adverse events when using step-up therapy rather than sequential monotherapy, but the committee considered that these could be managed, and often avoided, by appropriate drug monitoring; the committee thought that the clinical benefit outweighed this risk. For people who have experienced adverse events on monotherapy or are at an increased risk of adverse events, switching to an alternative monotherapy may be preferable to adding a second drug.

The committee agreed that the selection of DMARD should be determined on a case-by-case basis, similar to the selection of first-line therapy.

2.113 Cost effectiveness and resource use

Two health economic analyses were identified for first-line DMARD therapy. One was the cost-utility analysis that was conducted as part of the 2009 NICE rheumatoid arthritis guideline. This analysis compared 6 different strategies or regimens of conventional DMARD; only 5 of these comparators met the review protocol and were therefore reported. These were monotherapy, parallel combination, step-down combination and intensive step-up combination. The analysis found that step-down combination was the most cost-effective strategy for people who are newly diagnosed and DMARD naïve. This analysis was assessed as partially applicable with potentially serious limitations. This model did not specify DMARDs but rather refers to treatment strategies, although authors note that a systematic review of monotherapy conducted for the 2009 guideline found no statistically significant difference between DMARDs. EQ-5D was mapped from HAQ rather than directly elicited from people in trials. In terms of methodology, the key limitation was that this analysis is based on 5 of the 22 studies included in the clinical review. Furthermore, it includes 8

studies that were not included in the clinical review; therefore, it does not reflect the full body of evidence and may provide treatment effect estimates that do not reflect those identified in the clinical review. The committee agreed that the results of this analysis were not helpful in terms of evaluating which strategy would be most cost-effective.

The second study included was a cost-utility analysis of the BeST RCT. This analysis included 4 comparators but only 2 were reported, as the others did not meet the review protocol. The comparators reported were sequential monotherapy and step-up combination. Step-up combination dominated sequential monotherapy; that is, it was less costly and more effective. This analysis was assessed as partially applicable with potential serious limitations. The applicability of the analysis was downgraded primarily due to the Dutch healthcare perspective and lack of inclusion of comparison of all possible treatment combinations identified in the clinical evidence. In terms of methodological limitations, the follow-up was only 2 years, which was deemed unlikely to be sufficient to capture all downstream costs and treatment effects. Dutch unit costs may not reflect current NHS costs. Finally, this analysis is based on 1 of the 22 studies included for this question and so does not reflect the full body of evidence.

No health economic analyses were identified for second-line DMARD therapy.

The unit costs of individual conventional DMARDs were presented to the committee. These did not differ significantly, with the exception of subcutaneous methotrexate. No clinical evidence in support of the use of subcutaneous methotrexate was identified, so no clinical recommendation was made. In addition to these drug costs, an estimate of the cost of drug monitoring was presented as well as the schedule for drug monitoring recommended by the British Society for Rheumatology and British Health Professionals in Rheumatology. The cost of monitoring, particularly in the first year, is likely to be greater than the drugs themselves but does not differ significantly between different conventional DMARDs or whether 1 or more conventional DMARDs are being prescribed.

The committee considered that the clinical evidence showed no evidence of superiority of any particular strategy or any individual drug for first-line therapy. As a result, the committee agreed to recommend monotherapy as the first-line approach, as this would achieve similar outcomes to combination treatment at a lower cost. The committee considered, however, the importance of frequently monitoring people receiving DMARDs to ensure outcomes are achieved (either remission or low disease activity score). The committee highlighted the importance of reflecting individual patient needs and agreed that if a person is not achieving their target, then a step-up approach is required, whereby the dose is escalated or additional, conventional DMARDs are added. The committee noted that this approach is not unusual and would not be a significant shift in current practice. This is also supported in part by the BeST trial economic analysis.

All other recommendations were ones that were carried over from the previous guideline in 2009. This includes considering reducing doses of conventional DMARDs in those who have a sustained and satisfactory level of disease activity.

Overall, it is not considered that these recommendations will have a significant impact on NHS resources. The committee do not think the previous guideline recommendation to initiate combination conventional DMARDs was being implemented nationally. This is partially due to reluctance to start on combination DMARDs. When combination DMARDs are initiated, there may be more adverse events that are difficult to attribute to a particular DMARD and are costly for the NHS to manage. Although in some areas prescribing conventional DMARDs for people newly diagnosed with rheumatoid arthritis may reduce, overall the committee considered it is likely to remain unchanged.

2.11.3 Other factors the committee took into account

The 2009 guideline recommended that where a person's disease was adequately controlled, it may be appropriate to reduce drug doses or stop treatment with 1 or more DMARDs. While this area was not the focus of these update reviews, the committee noted that many of the included studies did allow or require tapering of drugs once the treatment target was achieved.

The committee agreed that reducing DMARD doses or tapering drugs in a step-down strategy may be appropriate in people who have maintained the treatment target (remission or low disease activity) for at least one year, without requiring glucocorticoid treatment in that time. The committee decided that this should be a 'consider' recommendation, as there are possible risks and benefits to be assessed on a case-by-case basis. Factors to consider would include the previous degree of response to the drug to be reduced or withdrawn and the severity of the person's disease prior to treatment. The committee noted that no evidence was found for subcutaneous methotrexate. The committee's view was that the effects are more immediate when administering via this route and there are reduced side effects. However, given it is significantly more expensive than the other DMARD options, without evidence demonstrating greater effectiveness, the committee was unable to provide advice about its use. It was agreed that this is an important topic for a research recommendation, as it may be a better option for some people who have failed to adequately respond to conventional DMARDs administered orally, especially if the alternative is progression to biologic DMARDs.

The management of rheumatoid arthritis in pregnancy was identified as an equalities issue in the equalities impact assessment. The committee agreed that it should be an individualised and consultant-led service, with involvement of obstetric services and broader rheumatology MDT as indicated. Patients and their rheumatology team need to consider many aspects of each individual patient's care. These include pre-conception advice and management of pharmacological therapies, assessment of potential impact of disease on the pregnancy, advice on disease course during pregnancy, and discussions regarding the disease and its treatment in the post-partum period. Particular attention should be paid to therapeutic management of rheumatoid arthritis, especially conventional DMARDs and biologic DMARDs, to ensure potentially teratogenic therapies are not continued in the pre-conception stage or into early pregnancy. Alternative management strategies should be considered, depending on each patient's level of disease control and symptoms, for the duration of the pregnancy.

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1 Appendices

2 Appendix A: Review protocols

3 **Table 30: Review protocol: First-line DMARDs**

ID	Field	Content
I	Review question	In adults with RA who are DMARD naïve, which conventional DMARDs (alone or combined) are most clinically and cost effective? In adults with RA who are DMARD naïve, which DMARD treatment strategy (monotherapy, sequential monotherapy, parallel combination therapy, step up therapy or step down therapy) is most clinically and cost effective?
II	Type of review question	Intervention review. A review of health economic evidence related to the same review question was conducted in parallel with this review. For details see the health economic review protocol for this NICE guideline.
III	Objective of the review	To establish which conventional DMARDs, and which DMARD treatment strategy, is most clinically and cost effective in adults with newly diagnosed rheumatoid arthritis who are commencing DMARD therapy for the first time.
IV	Eligibility criteria – population / disease / condition / issue / domain	Adults with RA according to validated classification criteria who are DMARD naïve. Studies in patients with prognostic factors indicating that their disease has a poor prognosis will be presented separately. Pregnant women will also be treated as a stratum.
V	Eligibility criteria – intervention(s) / exposure(s) / prognostic factor(s)	• methotrexate (oral) (MTX oral) • methotrexate (subcutaneous) (MTX sc) • hydroxychloroquine (HCQ) • sulfasalazine (SSZ) • leflunomide (LFN) • combinations of the above • sequential combinations of the above Study treatment arms will be classified into one of the following classes: • monotherapy (a single DMARD used for the duration of the trial) • sequential monotherapy (a single DMARD replaced with a different single DMARD in the case of inadequate response) • parallel combination (two or more DMARDs commenced at the same time without a step-down strategy) • step-up therapy (commencing with a single DMARD, followed by the addition of further DMARD(s) in the case of inadequate response) • step-down therapy (two or more DMARDs commenced at the same time, with at least one drug tapered and stopped once disease is adequately controlled) Studies will be combined regardless of whether glucocorticoids are used alongside the DMARD therapy. Studies using different doses of the same drug will be pooled in the meta-

ID	Field	Content
		analysis where drug doses or dosing strategies are the only difference between the study arms. Studies using biologic DMARDs or other DMARDs not listed above will be excluded, except where the out-of-scope DMARD is prescribed as part of a step-up treatment strategy and data is available prior to patients reaching that stage of the treatment escalation strategy.
VI	Eligibility criteria – comparator(s) / control or reference (gold) standard	The above drugs will be compared against each other or against placebo.
VII	Outcomes and prioritisation	CRITICAL • Disease Activity Score (DAS) (continuous) at 6 and 12 months • Quality of life (for example, EQ5D, SF-36, RA Quality of Life instrument) (continuous) at 6 and 12 months • Function (for example, Health Assessment Questionnaire, activities of daily living) (continuous) at 6 and 12 months IMPORTANT • Low disease activity (dichotomous) at 6 and 12 months • Remission (dichotomous) at 6 and 12 months • ACR50 response (dichotomous) at 6 and 12 months • Pain (for example, Visual Analogue Scale) (continuous) at 6 and 12 months • Radiological progression (continuous) at 12 months • adverse events – mortality (dichotomous) at longest reported time point • Withdrawal due to adverse events (dichotomous) at longest reported time point • Withdrawal due to inefficacy (dichotomous) at longest reported time point
VIII	Eligibility criteria – study design	Systematic Review / Network Meta-Analysis (NMA) of RCTs RCTs
IX	Other inclusion exclusion / criteria	Studies in mixed inflammatory arthritis populations will be excluded, unless the results are presented separately for RA patients. Studies in patients with RA as well as another rheumatic disease (e.g. lupus) will be excluded. Studies that enrol patients who are not explicitly stated to be DMARD naïve will be excluded, except where: • the study states that the only DMARD used previously is an antimalarial/HCQ (as HCQ is known to be a weak DMARD); or • previous DMARDs have been used for no longer than 1 month. These populations will be included on the basis that they would not differ substantially from a DMARD naïve population in terms of disease severity or likely response to DMARD treatment. Studies in which prior DMARD use is unclear or not reported will be excluded.

ID	Field	Content
X	Proposed sensitivity / subgroup analysis, or meta-regression	Where a study reports multiple time points, the closest time point to the specified time points (6 months and 12 months) will be extracted. Data reported at time points less than 12 weeks will not be extracted. 12 month data will be analysed in an NMA for outcomes prioritised by the committee where there is enough evidence to form treatment loops and sufficient homogeneity of data. The priority outcome for the NMA is DAS, if sufficient data is available. Otherwise, data on ACR50 response, DAS remission or DAS low disease activity may be analysed. The following DMARDs will be included only if necessary to connect the network: • Ciclosporingold injections • penicillamine • azathioprine • biologics
XI	Selection process – duplicate screening / selection / analysis	A sample of at least 10% of the abstract lists were double-sifted by a senior research fellow and discrepancies rectified, with committee input where consensus could not be reached, for more information please see the separate Methods report for this guideline.
XII	Data management (software)	• Pairwise meta-analyses were performed using Cochrane Review Manager (RevMan5). • GRADEpro was used to assess the quality of evidence for each outcome. • Endnote was used for bibliography, citations, sifting and reference management
XIII	Information sources – databases and dates	An existing Cochrane review[59,60] by Hazelwood at al. comparing methotrexate monotherapy with methotrexate in combination with other DMARDs formed the basis of the evidence review.. The included studies in that review were checked against the agreed evidence review protocol. Searches were also conducted for randomised controlled trials and systematic reviews. Firstly the Cochrane review search strategy was re-run to identify relevant trials published since the date of the Cochrane review searches and secondly a search was conducted to identify additional trials of non-methotrexate monotherapies and combinations, as well as strategy trials, that would not have been included in the Cochrane review. Clinical search databases: Medline, Embase and the Cochrane Library. Date limits for search: None Language: English Health economics search databases: Medline, Embase, NHSEED and HTA Date limits for search: Medline and Embase from 2014 NHSEED and HTA from 2001 Language: English
XIV	Identify if an update	This review is an update of a clinical area covered in NICE guideline: Rheumatoid arthritis in adults: management[111] published in 2009. However the protocol for this updated review differed from the previous review and thus the search was undertaken for all years.

ID	Field	Content
XV	Author contacts	https://www.nice.org.uk/guidance/indevelopment/gid-ng10014
XVI	Highlight if amendment to previous protocol	For details please see section 4.5 of Developing NICE guidelines: the manual.
XVII	Search strategy – for one database	For details please see appendix B
XVIII	Data collection process – forms / duplicate	A standardised evidence table format will be used, and published as appendix D of the evidence report.
XIX	Data items – define all variables to be collected	For details please see evidence tables in Appendix D (clinical evidence tables) or H (health economic evidence tables).
XX	Methods for assessing bias at outcome / study level	Standard study checklists were used to critically appraise individual studies. For details please see section 6.2 of Developing NICE guidelines: the manual The risk of bias across all available evidence was evaluated for each outcome using an adaptation of the 'Grading of Recommendations Assessment, Development and Evaluation (GRADE) toolbox' developed by the international GRADE working group http://www.gradeworkinggroup.org/
XXI	Criteria for quantitative synthesis	For details please see section 6.4 of Developing NICE guidelines: the manual.
XXII	Methods for quantitative analysis – combining studies and exploring (in)consistency	For details please see the separate Methods report for this guideline.
XXIII	Meta-bias assessment – publication bias, selective reporting bias	For details please see section 6.2 of Developing NICE guidelines: the manual.
XXIV	Confidence in cumulative evidence	For details please see sections 6.4 and 9.1 of Developing NICE guidelines: the manual.
XXV	Rationale / context – what is known	For details please see the introduction to the evidence review.
XXVI	Describe contributions of authors and guarantor	A multidisciplinary committee (https://www.nice.org.uk/guidance/indevelopment/gid-ng10014/documents) developed the evidence review. The committee was convened by the National Guideline Centre (NGC) and chaired by Stephen Ward in line with section 3 of Developing NICE guidelines: the manual. Staff from NGC undertook systematic literature searches, appraised the evidence, conducted meta-analysis and cost-effectiveness analysis where appropriate, and drafted the evidence review in collaboration with the

ID	Field	Content
		committee. For details please see Developing NICE guidelines: the manual.
XX VII	Sources of funding / support	NGC is funded by NICE and hosted by the Royal College of Physicians.
XX VIII	Name of sponsor	NGC is funded by NICE and hosted by the Royal College of Physicians.
XXI X	Roles of sponsor	NICE funds NGC to develop guidelines for those working in the NHS, public health and social care in England.
XX X	PROSPERO registration number	Not registered

Table 31: Review protocol: Conventional DMARDs for rheumatoid arthritis – subsequent lines of treatment

ID	Field	Content
I	Review question	In adults with RA who have had an inadequate response to, or failed treatment with, one or more conventional DMARDs, which conventional DMARDs (alone or combined) are most clinically and cost effective as subsequent treatment? In adults with RA who have had an inadequate response to, or failed treatment with, one or more conventional DMARDs, which DMARD treatment strategy (monotherapy, sequential monotherapy, parallel combination therapy, step up therapy or step down therapy) is most clinically and cost effective as subsequent treatment?
II	Type of review question	Intervention review A review of health economic evidence related to the same review question was conducted in parallel with this review. For details see the health economic review protocol for this NICE guideline.
III	Objective of the review	To establish which conventional DMARDs, and which DMARD treatment strategy, is most clinically and cost effective in adults with rheumatoid arthritis who have already failed or inadequately responded to ("failed") one or more DMARDs.
IV	Eligibility criteria – population / disease / condition / issue / domain	Adults with RA according to validated classification criteria who have failed one or more conventional DMARDs. The review population will be stratified based on the particular DMARD(s) failed by the population enrolled in the trial. Pregnant women will also be treated as a stratum.
V	Eligibility criteria – intervention(s) / exposure(s) / prognostic factor(s)	methotrexate (oral) (MTX oral) methotrexate (subcutaneous) (MTX sc) hydroxychloroquine (HCQ) sulfasalazine (SSZ) leflunomide (LFN) combinations of the above sequential combinations of the above Study treatment arms will be classified into one of the following classes: • monotherapy (a single DMARD used for the duration of the trial) • sequential monotherapy (a single DMARD replaced with a

ID	Field	Content
		different single DMARD in the case of inadequate response) • parallel combination (two or more DMARDs commenced at the same time without a step-down strategy) • step-up therapy (commencing with a single DMARD, followed by the addition of further DMARD(s) in the case of inadequate response) • step-down therapy (two or more DMARDs commenced at the same time, with at least one drug tapered and stopped once disease is adequately controlled) Studies will be combined regardless of whether glucocorticoids are used alongside the DMARD therapy. Studies using different doses of the same drug will be pooled in the meta-analysis where drug doses or dosing strategies are the only difference between the study arms. Studies using biologic DMARDs or other DMARDs not listed above will be excluded, except where the out-of-scope DMARD is prescribed as part of a step-up treatment strategy and data is available prior to patients reaching that stage of the treatment escalation strategy.
VI	Eligibility criteria – comparator(s) / control or reference (gold) standard	The above drugs will be compared against each other or against placebo.
VII	Outcomes and prioritisation	CRITICAL • Disease Activity Score (DAS or DAS28) (continuous) at 6 and 12 months • Quality of life (for example, EQ5D, SF-36, RA Quality of Life instrument) (continuous) at 6 and 12 months • Function (for example, Health Assessment Questionnaire, activities of daily living) (continuous) at 6 and 12 months. IMPORTANT • Low disease activity (dichotomous) at 6 and 12 months • Remission (dichotomous) at 6 and 12 months • ACR50 response (dichotomous) at 6 and 12 months • Pain (for example, Visual Analogue Scale) (continuous) at 6 and 12 months • Radiological progression (continuous) at 12 months • Adverse events – mortality (dichotomous) at longest reported time point • Withdrawal due to adverse events (dichotomous) at longest reported time point • Withdrawal due to inefficacy (dichotomous) at longest reported time point
VIII	Eligibility criteria – study design	Systematic Review / Network Meta-Analysis (NMA) of RCTs RCTs
IX	Other inclusion exclusion criteria	Studies in mixed inflammatory arthritis populations will be excluded, unless the results are presented separately for RA patients.

ID	Field	Content
		Studies in patients with RA as well as another rheumatic disease (e.g. lupus) will be excluded. Studies where the enrolled patients have not all failed the same DMARD(s) will be excluded (for example, where some patients have failed MTX and others have failed SSZ).
X	Proposed sensitivity / subgroup analysis, or meta-regression	Where a study reports multiple time points, the closest time point to the specified time points (6 and 12 months) will be extracted. Data reported at time points less than 12 weeks will not be extracted. Data may be considered for analysis in an NMA for outcomes prioritised by the committee if there is enough evidence to form treatment loops and sufficient homogeneity of data within a specific population stratum. The priority outcome for the NMA is DAS, if sufficient data is available. Otherwise, data on ACR50 response, DAS remission or DAS low disease activity may be analysed. The following DMARDs will be included only if necessary to connect the network: Ciclosporingold injections penicillamine azathioprine biologics
XI	Selection process – duplicate screening / selection / analysis	A sample of at least 10% of the abstract lists were double-sifted by a senior research fellow and discrepancies rectified, with committee input where consensus could not be reached. For more information please see the separate Methods report for this guideline.
XII	Data management (software)	• Pairwise meta-analyses were performed using Cochrane Review Manager (RevMan5). • GRADEpro was used to assess the quality of evidence for each outcome. • Endnote was used for bibliography, citations, sifting and reference management
XIII	Information sources – databases and dates	Databases: The databases to be searched are Medline, Embase, The Cochrane Library. Date limits for search: No limits Language: English
XIV	Identify if an update	This review is an update of a clinical area covered in NICE guideline: Rheumatoid arthritis in adults: management[111] published in 2009. However the protocol for this updated review differed from the previous review and thus the search was undertaken for all years.
XV	Author contacts	https://www.nice.org.uk/guidance/indevelopment/gid-ng10014
XVI	Highlight if amendment to previous protocol	For details, please see section 4.5 of Developing NICE guidelines: the manual.
XVI	Search	For details, please see appendix B

ID	Field	Content
I	strategy – for one database	
XVIII	Data collection process – forms / duplicate	A standardised evidence table format will be used, and published as appendix D of the evidence report.
XIX	Data items – define all variables to be collected	For details, please see evidence tables in Appendix D (clinical evidence tables) or H (health economic evidence tables).
XX	Methods for assessing bias at outcome / study level	Standard study checklists were used to appraise individual studies critically. For details please see section 6.2 of Developing NICE guidelines: the manual The risk of bias across all available evidence was evaluated for each outcome using an adaptation of the 'Grading of Recommendations Assessment, Development and Evaluation (GRADE) toolbox' developed by the international GRADE working group http://www.gradeworkinggroup.org/
XXI	Criteria for quantitative synthesis	For details, please see section 6.4 of Developing NICE guidelines: the manual.
XXII	Methods for quantitative analysis – combining studies and exploring (in)consistency	For details, please see the separate Methods report for this guideline.
XXIII	Meta-bias assessment – publication bias, selective reporting bias	For details, please see section 6.2 of Developing NICE guidelines: the manual.
XXIV	Confidence in cumulative evidence	For details, please see sections 6.4 and 9.1 of Developing NICE guidelines: the manual.
XXV	Rationale / context – what is known	For details, please see the introduction to the evidence review.
XXVI	Describe contributions of authors and guarantor	A multidisciplinary committee (https://www.nice.org.uk/guidance/indevelopment/gid-ng10014/documents) developed the evidence review. The committee was convened by the National Guideline Centre (NGC) and chaired by Stephen Ward in line with section 3 of Developing NICE guidelines: the manual. Staff from NGC undertook systematic literature searches, appraised the evidence, conducted meta-analysis and cost-effectiveness analysis where appropriate, and drafted the evidence review in collaboration with the committee. For details, please see Developing NICE guidelines: the manual.
XXVII	Sources of funding / support	NGC is funded by NICE and hosted by the Royal College of Physicians.
XXVIII	Name of sponsor	NGC is funded by NICE and hosted by the Royal College of Physicians.

ID	Field	Content
XXIX	Roles of sponsor	NICE funds NGC to develop guidelines for those working in the NHS, public health and social care in England.
XXX	PROSPERO registration number	Not registered

1

2 **Table 32: Health economic review protocol**

Review question	All questions – health economic evidence
Objectives	To identify health economic studies relevant to any of the review questions.
Search criteria	Populations, interventions and comparators must be as specified in the clinical review protocol above. Studies must be of a relevant health economic study design (cost–utility analysis, cost-effectiveness analysis, cost–benefit analysis, cost–consequences analysis, comparative cost analysis). Studies must not be a letter, editorial or commentary, or a review of health economic evaluations. (Recent reviews will be ordered although not reviewed. The bibliographies will be checked for relevant studies, which will then be ordered.) Unpublished reports will not be considered unless submitted as part of a call for evidence. Studies must be in English.
Search strategy	A health economic study search will be undertaken using population-specific terms and a health economic study filter – see appendix B below.
Review strategy	Studies not meeting any of the search criteria above will be excluded. Studies published before 2001, abstract-only studies and studies from non-OECD countries or the USA will also be excluded. Each remaining study will be assessed for applicability and methodological limitations using the NICE economic evaluation checklist which can be found in appendix H of Developing NICE guidelines: the manual (2014).112 Inclusion and exclusion criteria If a study is rated as both 'Directly applicable' and with 'Minor limitations' then it will be included in the guideline. A health economic evidence table will be completed and it will be included in the health economic evidence profile. If a study is rated as either 'Not applicable' or with 'Very serious limitations' then it will usually be excluded from the guideline. If it is excluded then a health economic evidence table will not be completed and it will not be included in the health economic evidence profile. If a study is rated as 'Partially applicable', with 'Potentially serious limitations' or both then there is discretion over whether it should be included. Where there is discretion The health economist will make a decision based on the relative applicability and quality of the available evidence for that question, in discussion with the guideline committee if required. The ultimate aim is to include health economic studies that are helpful for decision-making in the context of the guideline and the current NHS setting. If several studies are considered of sufficiently high applicability and methodological quality that they could all be included, then the health economist, in discussion with the committee if required, may decide to include only the most applicable studies and to selectively exclude the remaining studies. All studies excluded on the basis of applicability or methodological limitations will be listed with explanation in the excluded health economic studies appendix below.

Review question	All questions – health economic evidence
	The health economist will be guided by the following hierarchies. Setting: UK NHS (most applicable). OECD countries with predominantly public health insurance systems (for example, France, Germany, Sweden). OECD countries with predominantly private health insurance systems (for example, Switzerland). Studies set in non-OECD countries or in the USA will be excluded before being assessed for applicability and methodological limitations. Health economic study type: Cost–utility analysis (most applicable). Other type of full economic evaluation (cost–benefit analysis, cost-effectiveness analysis, cost–consequences analysis). Comparative cost analysis. Non-comparative cost analyses including cost-of-illness studies will be excluded before being assessed for applicability and methodological limitations. Year of analysis: The more recent the study, the more applicable it will be. Studies published in 2001 or later but that depend on unit costs and resource data entirely or predominantly from before 2001 will be rated as 'Not applicable'. Studies published before 2001 will be excluded before being assessed for applicability and methodological limitations. Quality and relevance of effectiveness data used in the health economic analysis: The more closely the clinical effectiveness data used in the health economic analysis match with the outcomes of the studies included in the clinical review the more useful the analysis will be for decision-making in the guideline.

Appendix B: Literature search strategies

Searches were constructed using a PICO framework where population (P) terms were combined with Intervention (I) and in some cases Comparison (C) terms. Outcomes (O) are rarely used in search strategies for interventions as these concepts may not be well described in title, abstract or indexes and therefore difficult to retrieve. Search filters were applied to the search where appropriate.

Table 33: Database date parameters and filters used

Database	Dates searched	Search filter used
Medline (Ovid)	1946 – 06 October 2017	Exclusions Randomised controlled trials Systematic review studies
Embase (Ovid)	1974 – 06 October 2017	Exclusions Randomised controlled trials Systematic review studies
The Cochrane Library (Wiley)	Cochrane Reviews to 2017 Issue 10 of 12 CENTRAL to 2017 Issue 9 of 12 DARE, and NHSEED to 2015 Issue 2 of 4	None

Database	Dates searched	Search filter used
	HTA to 2016 Issue 4 of 4	

1 **Methotrexate –** only searched from 2016 onwards as there is an existing Cochrane review
2 CD10227 (Source : DOI: 10.1002/14651858.CD010227.pub2) published 29 August 2016.

3 **Medline (Ovid) search terms**

1.	exp Arthritis, Rheumatoid/
2.	(rheumatoid adj2 (arthritis or arthrosis)).ti,ab.
3.	(caplan* adj2 syndrome).ti,ab.
4.	(felty* adj2 syndrome).ti,ab.
5.	(rheumatoid adj2 factor).ti,ab.
6.	((inflammatory or idiopathic) adj2 arthritis).ti,ab.
7.	"inflammatory polyarthritis".ti,ab.
8.	or/1-7
9.	limit 8 to English language
10.	letter/
11.	editorial/
12.	news/
13.	exp historical article/
14.	Anecdotes as Topic/
15.	comment/
16.	case report/
17.	(letter or comment*).ti.
18.	or/10-17
19.	randomized controlled trial/ or random*.ti,ab.
20.	18 not 19
21.	animals/ not humans/
22.	Animals, Laboratory/
23.	exp Animal Experimentation/
24.	exp Models, Animal/
25.	exp Rodentia/
26.	(rat or rats or mouse or mice).ti.
27.	or/20-26
28.	9 not 27
29.	Methotrexate/
30.	(Methotrexate or amet?opterin* or mexate or Abitrexate or Met?opterin* or Antifolan or Emt?exate or Enthexate or Farmitrexate or Folex or Ledertrexate or Methoblastin* or Methohexate or Methotrate or Methylaminopterin* or Metotrexate or Mtx or Novatrex or Rheumatrex or maxtrex).ti,ab.
31.	29 or 30
32.	28 and 31
33.	Hydroxychloroquine/
34.	(hydroxychloroquin* or Plaquenil or Quinoric or hydroxychlorochin* or oxychlorochin* or oxychloroquin*).ti,ab.
35.	(Leflunomide or Arava).ti,ab.
36.	Sulfasalazine/

37.	(sulfasalazin* or Salazopyrin* or Sulazin* or asulfidin* or azulfadin* or azulfidin* or colo-pleon or pleon or pyralin* or salazosulfapyridin* or salicylazosulfapyridin* or ucine or ulcol).ti,ab.
38.	or/33-37
39.	28 and 38
40.	randomized controlled trial.pt.
41.	controlled clinical trial.pt.
42.	randomi#ed.ti,ab.
43.	placebo.ab.
44.	drug therapy.fs.
45.	randomly.ti,ab.
46.	trial.ab.
47.	groups.ab.
48.	or/40-47
49.	Clinical Trials as topic.sh.
50.	trial.ti.
51.	or/40-43,45,49-50
52.	Meta-Analysis/
53.	Meta-Analysis as Topic/
54.	(meta analy* or metanaly* or metaanaly* or meta regression).ti,ab.
55.	((systematic* or evidence*) adj3 (review* or overview*)).ti,ab.
56.	(reference list* or bibliograph* or hand search* or manual search* or relevant journals).ab.
57.	(search strategy or search criteria or systematic search or study selection or data extraction).ab.
58.	(search* adj4 literature).ab.
59.	(medline or pubmed or cochrane or embase or psychlit or psyclit or psychinfo or psycinfo or cinahl or science citation index or bids or cancerlit).ab.
60.	cochrane.jw.
61.	((multiple treatment* or indirect or mixed) adj2 comparison*).ti,ab.
62.	or/52-61
63.	32 and (51 or 62)
64.	39 and (51 or 62)
65.	(2016* or 2017*).ed,dc.
66.	63 and 65
67.	64 or 66

1 **Embase (Ovid) search terms**

1.	exp *rheumatoid arthritis/
2.	(rheumatoid adj2 (arthritis or arthrosis)).ti,ab.
3.	(caplan* adj2 syndrome).ti,ab.
4.	(felty* adj2 syndrome).ti,ab.
5.	(rheumatoid adj2 factor).ti,ab.
6.	((inflammatory or idiopathic) adj2 arthritis).ti,ab.
7.	"inflammatory polyarthritis".ti,ab.
8.	or/1-7
9.	limit 8 to English language

10.	letter.pt. or letter/
11.	note.pt.
12.	editorial.pt.
13.	case report/ or case study/
14.	(letter or comment*).ti.
15.	or/10-14
16.	randomized controlled trial/ or random*.ti,ab.
17.	15 not 16
18.	animal/ not human/
19.	nonhuman/
20.	exp Animal Experiment/
21.	exp Experimental Animal/
22.	animal model/
23.	exp Rodent/
24.	(rat or rats or mouse or mice).ti.
25.	or/17-24
26.	9 not 25
27.	*methotrexate/
28.	(Methotrexate or amet?opterin* or mexate or Abitrexate or Met?opterin* or Antifolan or Emt?exate or Enthexate or Farmitrexate or Folex or Ledertrexate or Methoblastin* or Methohexate or Methotrate or Methylaminopterin* or Metotrexate or Mtx or Novatrex or Rheumatrex or maxtrex).ti,ab.
29.	27 or 28
30.	26 and 29
31.	*hydroxychloroquine/ or *hydroxychloroquine sulfate/
32.	(hydroxychloroquin* or Plaquenil or Quinoric or hydroxychlorochin* or oxychlorochin* or oxychloroquin*).ti,ab.
33.	*leflunomide/
34.	(Leflunomide or Arava).ti,ab.
35.	*salazosulfapyridine/
36.	(sulfasalazin* or Salazopyrin* or Sulazin* or asulfidin* or azulfadin* or azulfidin* or colo-pleon or pleon or pyralin* or salazosulfapyridin* or salicylazosulfapyridin* or ucine or ulcol).ti,ab.
37.	or/31-36
38.	26 and 37
39.	random*.ti,ab.
40.	factorial*.ti,ab.
41.	(crossover* or cross over*).ti,ab.
42.	((doubl* or singl*) adj blind*).ti,ab.
43.	(assign* or allocat* or volunteer* or placebo*).ti,ab.
44.	crossover procedure/
45.	single blind procedure/
46.	randomized controlled trial/
47.	double blind procedure/
48.	or/39-47
49.	systematic review/
50.	meta-analysis/

51.	(meta analy* or metanaly* or metaanaly* or meta regression).ti,ab.
52.	((systematic or evidence) adj3 (review* or overview*)).ti,ab.
53.	(reference list* or bibliograph* or hand search* or manual search* or relevant journals).ab.
54.	(search strategy or search criteria or systematic search or study selection or data extraction).ab.
55.	(search* adj4 literature).ab.
56.	(medline or pubmed or cochrane or embase or psychlit or psyclit or psychinfo or psycinfo or cinahl or science citation index or bids or cancerlit).ab.
57.	cochrane.jw.
58.	((multiple treatment* or indirect or mixed) adj2 comparison*).ti,ab.
59.	or/49-58
60.	30 and (48 or 59)
61.	(2016* or 2017*).dc.
62.	60 and 61
63.	38 and (48 or 59)
64.	62 or 63

1 **Cochrane Library (Wiley) search terms**

#1.	[mh "Arthritis, Rheumatoid"]
#2.	(rheumatoid near/2 (arthritis or arthrosis)):ti,ab
#3.	(caplan* near/2 syndrome):ti,ab
#4.	(felty* near/2 syndrome):ti,ab
#5.	(rheumatoid near/2 factor):ti,ab
#6.	((inflammatory or idiopathic) near/2 arthritis):ti,ab
#7.	inflammatory polyarthritis:ti,ab
#8.	(or #1-#7)
#9.	[mh ^Methotrexate]
#10.	(Methotrexate or amet?opterin* or mexate or Abitrexate or Met?opterin* or Antifolan or Emt?exate or Enthexate or Farmitrexate or Folex or Ledertrexate or Methoblastin* or Methohexate or Methotrate or Methylaminopterin* or Metotrexate or Mtx or Novatrex or Rheumatrex or maxtrex):ti,ab
#11.	#8 and #10 Publication Year from 2016 to 2017
#12.	[mh ^Hydroxychloroquine]
#13.	(hydroxychloroquin* or Plaquenil or Quinoric or hydroxychlorochin* or oxychlorochin* or oxychloroquin*):ti,ab
#14.	(Leflunomide or Arava):ti,ab
#15.	[mh ^sulfasalazine]
#16.	(sulfasalazin* or Salazopyrin* or Sulazin* or asulfidin* or azulfadin* or azulfidin* or colo-pleon or pleon or pyralin* or salazosulfapyridin* or salicylazosulfapyridin* or ucine or ulcol):ti,ab
#17.	#12 or #13 or #14 or #15 or #16
#18.	#8 and #17
#19.	#11 or #18

B.12 Health Economics literature search strategy

3 Health economic evidence was identified by conducting a broad search relating to
4 rheumatoid arthritis population in NHS Economic Evaluation Database (NHS EED – this

ceased to be updated after March 2015) and the Health Technology Assessment database (HTA) with no date restrictions. NHS EED and HTA databases are hosted by the Centre for Research and Dissemination (CRD). Additional searches were run on Medline and Embase for health economics studies.

Table 34: Database date parameters and filters used

Database	Dates searched	Search filter used
Medline	2014 – 06 October 2017	Exclusions Health economics studies
Embase	2014– 06 October 2017	Exclusions Health economics studies
Centre for Research and Dissemination (CRD)	HTA - 2001 – 06 October 2017 NHSEED - 2001 – 31 March 2015	None

Medline (Ovid) search terms

1.	exp Arthritis, Rheumatoid/
2.	(rheumatoid adj2 (arthritis or arthrosis)).ti,ab.
3.	(caplan* adj2 syndrome).ti,ab.
4.	(felty* adj2 syndrome).ti,ab.
5.	(rheumatoid adj2 factor).ti,ab.
6.	((inflammatory or idiopathic) adj2 arthritis).ti,ab.
7.	"inflammatory polyarthritis".ti,ab.
8.	or/1-7
9.	limit 8 to English language
10.	letter/
11.	editorial/
12.	news/
13.	exp historical article/
14.	Anecdotes as Topic/
15.	comment/
16.	case report/
17.	(letter or comment*).ti.
18.	or/10-17
19.	randomized controlled trial/ or random*.ti,ab.
20.	18 not 19
21.	animals/ not humans/
22.	Animals, Laboratory/
23.	exp animal experiment/
24.	exp animal model/
25.	exp Rodentia/
26.	(rat or rats or mouse or mice).ti.
27.	or/20-26
28.	9 not 27
29.	Economics/

30.	Value of life/
31.	exp "Costs and Cost Analysis"/
32.	exp Economics, Hospital/
33.	exp Economics, Medical/
34.	Economics, Nursing/
35.	Economics, Pharmaceutical/
36.	exp "Fees and Charges"/
37.	exp Budgets/
38.	budget*.ti,ab.
39.	cost*.ti.
40.	(economic* or pharmaco?economic*).ti.
41.	(price* or pricing*).ti,ab.
42.	(cost* adj2 (effective* or utilit* or benefit* or minimi* or unit* or estimat* or variable*)).ab.
43.	(financ* or fee or fees).ti,ab.
44.	(value adj2 (money or monetary)).ti,ab.
45.	or/29-44
46.	exp models, economic/
47.	*Models, Theoretical/
48.	*Models, Organizational/
49.	markov chains/
50.	monte carlo method/
51.	exp Decision Theory/
52.	(markov* or monte carlo).ti,ab.
53.	econom* model*.ti,ab.
54.	(decision* adj2 (tree* or analy* or model*)).ti,ab.
55.	or/46-54
56.	28 and (45 or 55)

1 **Embase (Ovid) search terms**

1.	exp *rheumatoid arthritis/
2.	(rheumatoid adj2 (arthritis or arthrosis)).ti,ab.
3.	(caplan* adj2 syndrome).ti,ab.
4.	(felty* adj2 syndrome).ti,ab.
5.	(rheumatoid adj2 factor).ti,ab.
6.	((inflammatory or idiopathic) adj2 arthritis).ti,ab.
7.	"inflammatory polyarthritis".ti,ab.
8.	or/1-7
9.	limit 8 to English language
10.	letter.pt. or letter/
11.	note.pt.
12.	editorial.pt.
13.	case report/ or case study/
14.	(letter or comment*).ti.

15.	or/10-14
16.	randomized controlled trial/ or random*.ti,ab.
17.	15 not 16
18.	animal/ not human/
19.	nonhuman/
20.	exp Animal Experiment/
21.	exp Experimental Animal/
22.	animal model/
23.	exp Rodent/
24.	(rat or rats or mouse or mice).ti.
25.	or/17-24
26.	9 not 25
27.	statistical model/
28.	exp economic aspect/
29.	27 and 28
30.	*theoretical model/
31.	*nonbiological model/
32.	stochastic model/
33.	decision theory/
34.	decision tree/
35.	monte carlo method/
36.	(markov* or monte carlo).ti,ab.
37.	econom* model*.ti,ab.
38.	(decision* adj2 (tree* or analy* or model*)).ti,ab.
39.	or/29-38
40.	*health economics/
41.	exp *economic evaluation/
42.	exp *health care cost/
43.	exp *fee/
44.	budget/
45.	funding/
46.	budget*.ti,ab.
47.	cost*.ti.
48.	(economic* or pharmaco?economic*).ti.
49.	(price* or pricing*).ti,ab.
50.	(cost* adj2 (effective* or utilit* or benefit* or minimi* or unit* or estimat* or variable*)).ab.
51.	(financ* or fee or fees).ti,ab.
52.	(value adj2 (money or monetary)).ti,ab.
53.	or/40-52
54.	26 and (39 or 53)

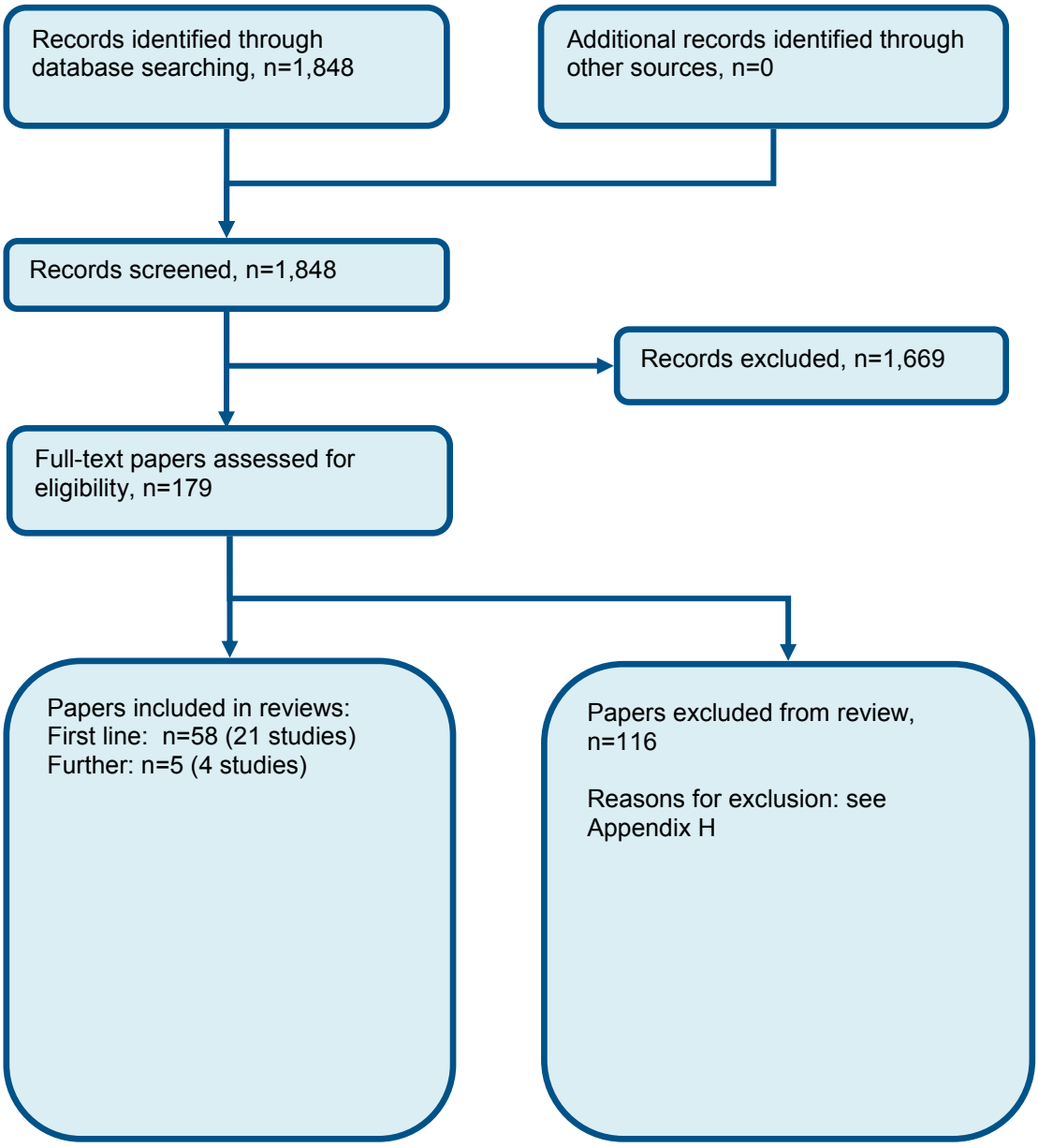
1 **NHS EED and HTA (CRD) search terms**

#1.	MeSH DESCRIPTOR Arthritis, Rheumatoid EXPLODE ALL TREES
#2.	((rheumatoid adj2 (arthritis or arthrosis)))
#3.	((caplan* adj2 syndrome))
#4.	((felty* adj2 syndrome))
#5.	((rheumatoid adj2 factor))
#6.	(((inflammatory or idiopathic) adj2 arthritis))
#7.	("inflammatory polyarthritis")
#8.	#1 OR #2 OR #3 OR #4 OR #5 OR #6 OR #7

2
3

Appendix C: Clinical evidence selection

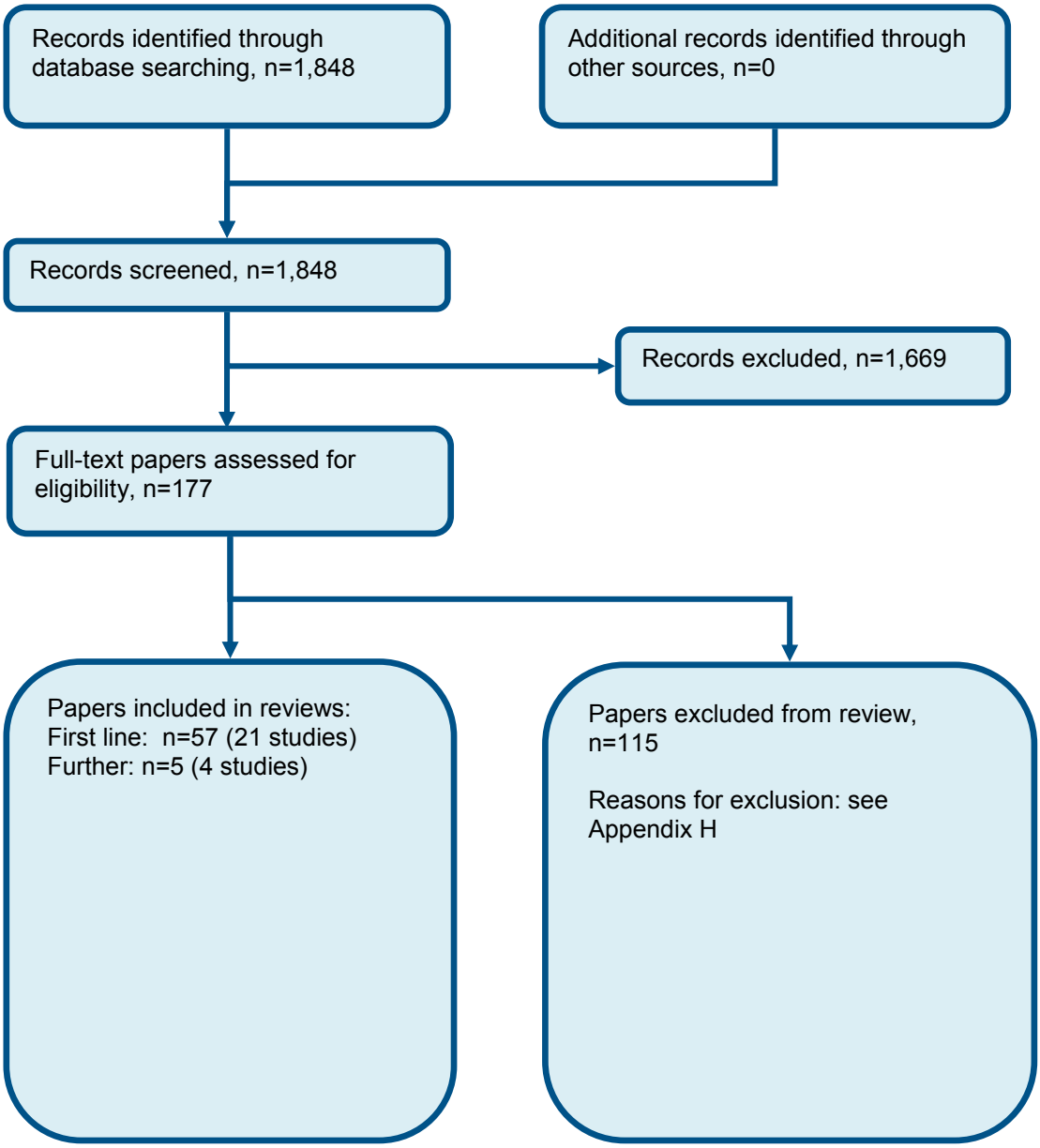
Figure 1: Flow chart of clinical study selection for two reviews of first line and subsequent DMARDs for rheumatoid arthritis



1

2

Figure 2: Flow chart of clinical study selection for two reviews of first line and further DMARDs for rheumatoid arthritis



3

4

Appendix D: Clinical evidence tables

D.1.1 First line DMARDs

Study (subsidiary papers)	Anonymous 1992[7] (Danis 1992[25])
Study type	RCT (Patient randomised; Parallel)
Number of studies (number of participants)	1 (n=122)
Countries and setting	Conducted in Australia; Setting: 14 centres
Line of therapy	1st line
Duration of study	Intervention time: 6 months
Method of assessment of guideline condition	Adequate method of assessment/diagnosis: Fulfilled the criteria for probable, definite or classical RA (Ropes 1958)
Stratum	Overall
Subgroup analysis within study	Not applicable
Inclusion criteria	RA of less than 12 months duration and no evidence of bony erosions in hands and feet
Exclusion criteria	Patients with other significant acute or chronic disease likely to affect ability to participate, patients previously treated with SSZ or other SAARD, patients with history of sensitivity to salicylates or sulfa containing drugs, patients receiving systematic glucocorticoids, patients with significant renal or hepatic disease.
Recruitment/selection of patients	Recruitment from 1 June 1987 to 31 October 1988
Age, gender and ethnicity	Age - Mean (SD): 54 (13). Gender (M:F): NR. Ethnicity: NR
Further population details	
Extra comments	No. tender and swollen joints, mean (SD): 21.5 (12.2) Pain, mm, mean (SD): 32 (20) Ritchie index, mean (SD): 13.3 (9.2) ESR, mm/h, mean (SD): 28 (24)
Indirectness of population	No indirectness: No evidence of bony erosions
Interventions	(n=62) Intervention 1: Monotherapy - Monotherapy - specify. 2g / day (Salazopyrin EN-tabs). Duration 6 months. Concurrent medication/care: "Normal NSAID therapy". Indirectness: No indirectness

	Further details: 1. Dose: Higher dose (sulfasalazine: 2 gm, methotrexate: >15 mg, leflunomide: 20mg, hydroxychloroquine: 400mg) 2. Use of glucocorticoids: Short term glucocorticoids not used (Patients excluded from analysis for protocol violation if glucocorticoids used). (n=60) Intervention 2: Placebo. Matching placebo. Duration 6 months. Concurrent medication/care: "Normal NSAID therapy". Indirectness: No indirectness Further details: 1. Dose: Not applicable 2. Use of glucocorticoids: Short term glucocorticoids not used (As above).
Funding	Study funded by industry ("Supported by Kabi-Pharmacia, Uppsala, Sweden and Sydney, Australia")

RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: MONOTHERAPY - SULFASALAZINE versus PLACEBO

Protocol outcome 1: Pain at 6 months
- Actual outcome: Pain at 6 months; Group 1: mean 19.9 mm (SD 20.79); n=29, Group 2: mean 28.8 mm (SD 20.79); n=36; VAS 0-100 Top=High is poor outcome; Comments: SE of 5.19 calculated from mean (t value). Note: change scores also reported.
Risk of bias: All domain - Very high, Selection - High, Blinding - Low, Incomplete outcome data - Very high, Outcome reporting - Low, Measurement - Low, Crossover - Low, Comments - ITT analysis clearly used as no. analysed in placebo group was 36, which was higher than the number left after withdrawals. Method not specified. ; Indirectness of outcome: No indirectness ; Baseline details: Comparable for age, ESR, pain, morning stiffness, Ritchie index, no. tender/swollen joints; Blinding details: Patient was outcome assessor for outcome; Group 1 Number missing: 33, Reason: 9 - excluded from analysis for various reasons, 14 - adverse drug event, 2 lack of efficacy, 1 lost to follow up, 5 non-compliance, 1 protocol violation, 1 NR; Group 2 Number missing: 25, Reason: 8 - excluded from analysis for various reasons, 4 - adverse drug event, 5 lack of efficacy, 3 lost to follow up, 3 non-compliance, 2 protocol violation

Protocol outcome 2: Withdrawal/discontinuation: adverse events at Longest time period reported
- Actual outcome: Withdrawal: adverse events at 6 months; Group 1: 14/53, Group 2: 4/52
Risk of bias: All domain - Very high, Selection - High, Blinding - High, Incomplete outcome data - High, Outcome reporting - Low, Measurement - Low, Crossover - Low, Comments - ; Indirectness of outcome: No indirectness ; Baseline details: Comparable for age, ESR, pain, morning stiffness, Ritchie index, no. tender/swollen joints; Group 1 Number missing: 19, Reason: 9 - excluded from analysis for various reasons, 2 lack of efficacy, 1 lost to follow up, 5 non-compliance, 1 protocol violation, 1 NR; Group 2 Number missing: 21, Reason: 8 - excluded from analysis for various reasons, 5 lack of efficacy, 3 lost to follow up, 3 non-compliance, 2 protocol violation
- Actual outcome: Withdrawal: inefficacy at 6 months; Group 1: 2/53, Group 2: 5/52
Risk of bias: All domain - Very high, Selection - High, Blinding - High, Incomplete outcome data - Very high, Outcome reporting - Low, Measurement - High, Crossover - Low, Comments - ; Indirectness of outcome: No indirectness ; Baseline details: Comparable for age, ESR, pain, morning stiffness, Ritchie index, no. tender/swollen joints; Group 1 Number missing: 31, Reason: 9 - excluded from analysis for various reasons, 14 - adverse drug event, 1 lost to follow up, 5 non-compliance, 1 protocol violation, 1 NR; Group 2 Number missing: 20, Reason: 8 - excluded from analysis for various reasons, 4 - adverse drug event, 3 lost to follow up, 3 non-compliance, 2 protocol violation

Disease Activity Score at 12 months; Disease Activity Score at 6 months; Quality of life at 12 months; Quality of life at 6 months; Function at 6 months; Function at 12 months; Pain at 12 months; Remission at 6 months; Remission at 12 months; Low disease activity at 6 months; Low disease activity at 12 months; Radiological progression at 12+ months; ACR50 response at 6 months; ACR50 response at 12 months; Adverse events - mortality at 12+ months; Withdrawal/discontinuation: inefficacy at Longest time period reported	
Protocol outcomes not reported by the study	

Study (subsidiary papers)	Anonymous 1995[6] (Tsakonas 2000[159])
Study type	RCT (Patient randomised; Parallel)
Number of studies (number of participants)	1 (n=120)
Countries and setting	Conducted in Canada; Setting: 6 centres in Canada.
Line of therapy	1st line
Duration of study	Intervention time: 36 weeks
Method of assessment of guideline condition	Adequate method of assessment/diagnosis: 1987 ARA criteria
Stratum	Overall
Subgroup analysis within study	Not applicable
Inclusion criteria	Adults with RA for less than 2 years. Persistent synovitis despite treatment with aspirin or NSAIDs for at least 6 weeks. ≥6 actively inflamed joints, 45 minutes or more of morning stiffness, ESR ≥25mm/h.
Exclusion criteria	Ara functional class IV disease, prior therapy with approved or experimental second line agent, use of IA or systemic glucocorticoids within 1 month of entry into study, ophthalmic abnormality, major surgery within 2 months of entry into study, Felty's syndrome, low platelet count, low white blood cell count, low polymorphonuclear leukocyte count, high serum creatinine level, proteinuria, bilirubin, high liver function tests, severe comorbid condition, women who might become pregnant.
Age, gender and ethnicity	Age - Mean (SD): 53. Gender (M:F): 75% female. Ethnicity: Not detailed
Further population details	
Indirectness of population	No indirectness
Interventions	(n=60) Intervention 1: Monotherapy - Monotherapy - specify. Hydroxychloroquine (7mg/kg to maximum of 400mg per day). Smaller initial dose raised to full dose after 2 weeks. Treatment could be stopped for 4 weeks due to adverse events. . Duration 36 weeks. Concurrent medication/care: Current dose of NSAIDs or aspirin maintained. Some analgesics permitted. IA injections of glucocorticoids permitted from week 2 to week 24. . Indirectness: No indirectness Further details: 1. Dose: Higher dose (sulfasalazine: 2 gm, methotrexate: >15 mg, leflunomide: 20mg, hydroxychloroquine: 400mg) 2. Use of glucocorticoids: Short term glucocorticoids used (n=60) Intervention 2: Placebo. Matching number of specially coated placebo tablets. . Duration 36 weeks. Concurrent medication/care: Current dose of NSAIDs or aspirin maintained. Some analgesics permitted. IA injections of glucocorticoids permitted from week 2 to week 24. . Indirectness: No indirectness Further details: 1. Dose: Not applicable 2. Use of glucocorticoids: Short term glucocorticoids used

Funding	Other (Mix of academic and industry funding. Grants from Medical Research Council University-Industry Program, Arthritis Society of Canada, Sanofi-Winthrop Canada.)

RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: MONOTHERAPY - HYDROXYCHLOROQUINE versus PLACEBO

Protocol outcome 1: Quality of life at 12 months
- Actual outcome: Change in global well being at 9 months; Group 1: mean -0.5 (SD 0.86); n=58, Group 2: mean 0.02 (SD 1.12); n=57
Risk of bias: All domain - Low, Selection - Low, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low, Subgroups - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: 2, Reason: ; Group 2 Number missing: 3

Protocol outcome 2: Function at 12 months
- Actual outcome: Change in psychological disability (AIMS) at 9 months; Group 1: mean -0.44 (SD 0.95); n=58, Group 2: mean -0.41 (SD 1.04); n=57; AIMS SD units Top=High is poor outcome
Risk of bias: All domain - Low, Selection - Low, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low, Subgroups - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: 2, Reason: ; Group 2 Number missing: 3

Protocol outcome 3: Withdrawal/discontinuation: adverse events at Longest time period reported
- Actual outcome: Discontinuation due to adverse events at 9 months; Group 1: 1/54, Group 2: 2/46
Risk of bias: All domain - High, Selection - Low, Blinding - Low, Incomplete outcome data - High, Outcome reporting - Low, Measurement - Low, Crossover - Low, Subgroups - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: 6, Reason: ; Group 2 Number missing: 14

Protocol outcome 4: Withdrawal/discontinuation: inefficacy at Longest time period reported
- Actual outcome: Discontinuation due to inefficacy at 9 months; Group 1: 4/57, Group 2: 10/54
Risk of bias: All domain - High, Selection - Low, Blinding - Low, Incomplete outcome data - High, Outcome reporting - Low, Measurement - Low, Crossover - Low, Subgroups - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: 6, Reason: ; Group 2 Number missing: 14

Protocol outcomes not reported by the study	Disease Activity Score at 12 months; Disease Activity Score at 6 months; Quality of life at 6 months; Function at 6 months; Pain at 6 months; Pain at 12 months; Remission at 6 months; Remission at 12 months; Low disease activity at 6 months; Low disease activity at 12 months; Radiological progression at 12+ months; ACR50 response at 6 months; ACR50 response at 12 months; Adverse events - mortality at 12+ months

Study (subsidiary papers)	BeSt study: 12 month outcomes trial: Goekoop-ruiterman 2005-1[48] (Allaart 2007[4], Allaart 2006[5], Van der kooij 2009[169], De vries-bouwstra 2008[30])
Study type	RCT (Patient randomised; Parallel)
Number of studies (number of participants)	1 (n=380)
Countries and setting	Conducted in Netherlands; Setting: Rheumatologists in 18 peripheral and 2 university hospitals.
Line of therapy	1st line
Duration of study	Intervention time: 2 years
Method of assessment of guideline condition	Adequate method of assessment/diagnosis: 1987 ACR criteria
Stratum	Overall
Subgroup analysis within study	Not applicable
Inclusion criteria	Adults with RA with a disease duration ≤2 years and active disease in a least 6 swollen and at least 6 tender joints, and either an ESR ≥28 mm/hour or a global health score of ≥20 mm on VAS (higher is worse).
Exclusion criteria	Previous treatment with DMARDs other than antimalarials, concomitant treatment with an experimental medication, malignancy within 5 years, bone marrow hypoplasia, serum aspartate aminotransferase level >3 times upper normal limit, serum creatinine level >150 µmoles per litre, estimated creatinine clearance <75 ml/minute. Diabetes, alcohol or drug abuse, pregnancy or wish to conceive during study or inadequate contraception.
Recruitment/selection of patients	Recruited from 2000-2002.
Age, gender and ethnicity	Age - Mean (SD): 54. Gender (M:F): 86% women. Ethnicity: Not detailed
Further population details	
Indirectness of population	No indirectness
Interventions	(n=126) Intervention 1: Sequential monotherapy - Sequential monotherapy - specify. Methotrexate at 15mg per week. Increasing to 30mg per week if DAS44 >2.4. If response insufficient therapy went through a sequence: sulfasalazine monotherapy, leflunomide monotherapy, methotrexate with infliximab, gold with methylprednisolone, methotrexate with ciclosporin A and prednisone. Outcomes extracted prior to people beginning treatments biologic treatment. . Duration 2 years. Concurrent medication/care: NSAIDs and intraarticular glucocorticoid injections permitted. Folic acid at 1mg per day during methotrexate treatment. . Indirectness: No indirectness Further details: 1. Dose: Higher dose (sulfasalazine: 2 gm, methotrexate: >15 mg, leflunomide: 20mg, hydroxychloroquine: 400mg) 2. Use of glucocorticoids: Short term glucocorticoids used (n=121) Intervention 2: Step up therapy - Step up therapy - specify. Methotrexate at 15mg per week.

	Increasing to 30mg per week if DAS44 >2.4. If response insufficient therapy went through an additive sequence: Sulfasalazine added, hydroxychloroquine added, prednisone added. If response still insufficient then participant switched to methotrexate with infliximab, methotrexate with ciclosporin A and prednisone, and finally to leflunomide. Outcomes extracted prior to people beginning treatments biologic treatment. . Duration 2 years. Concurrent medication/care: NSAIDs and intraarticular glucocorticoid injections permitted. Folic acid at 1mg per day during methotrexate treatment. . Indirectness: No indirectness Further details: 1. Dose: Higher dose (sulfasalazine: 2 gm, methotrexate: >15 mg, leflunomide: 20mg, hydroxychloroquine: 400mg) 2. Use of glucocorticoids: Short term glucocorticoids used (n=133) Intervention 3: Parallel combination therapy - Parallel combination therapy - specify. Methotrexate at 7.5mg per week, sulfasalazine at 2g per day, prednisone at 60mg per day reduced to 7.5mg per day after 7 weeks. If DAS44 >2.4 then methotrexate increased up to 30mg per week. If response was insufficient then treatment altered to methotrexate with ciclosporin A and prednisone, and then to methotrexate and infliximab, and then to leflunomide monotherapy, and then to gold with methylprednisolone, and finally to azathioprine with prednisone. Outcomes extracted prior to people beginning treatments biologic treatment. . Duration 2 years. Concurrent medication/care: NSAIDs and intraarticular glucocorticoid injections permitted. Folic acid at 1mg per day during methotrexate treatment. . Indirectness: No indirectness Further details: 1. Dose: Higher dose (sulfasalazine: 2 gm, methotrexate: >15 mg, leflunomide: 20mg, hydroxychloroquine: 400mg) 2. Use of glucocorticoids: Short term glucocorticoids used
Funding	Funding not stated

RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: SEQUENTIAL MONOTHERAPY - METHOTREXATE / SULFASALAZINE / LEFLUNOMIDE versus STEP UP THERAPY - METHOTREXATE

Protocol outcome 1: Function at 12 months
- Actual outcome: Change in function (HAQ) score at 12 months; Group 1: mean -0.7 (SD 0.7); n=122, Group 2: mean -0.7 (SD 0.7); n=115; HAQ 0-3 Top=High is poor outcome
Risk of bias: All domain - High, Selection - Low, Blinding - High, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low, Subgroups - Low; Indirectness of outcome: No indirectness ; Baseline details: SvdH score higher in step up group; Group 1 Number missing: 4; Group 2 Number missing: 6

Protocol outcome 2: Radiological progression at 12+ months
- Actual outcome: Change in radiographic score (Sharp van der Heijde) at 12 months; Group 1: mean 9 (SD 17.9); n=122, Group 2: mean 5.2 (SD 8.1); n=115; SvdH 0-448 Top=High is poor outcome
Risk of bias: All domain - High, Selection - Low, Blinding - High, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low, Subgroups - Low; Indirectness of outcome: No indirectness ; Baseline details: SvdH score higher in step up group; Group 1 Number missing: 4; Group 2 Number missing: 6

Protocol outcomes not reported by the study	Disease Activity Score at 12 months; Disease Activity Score at 6 months; Quality of life at 12 months; Quality of life at 6 months; Function at 6 months; Pain at 6 months; Pain at 12 months; Remission at 6 months; Remission at 12 months; Low disease activity at 6 months; Low disease activity at 12 months; ACR50 response at 6 months; ACR50 response at 12 months; Adverse events - mortality at 12+ months; Withdrawal/discontinuation: adverse events at Longest time period reported; Withdrawal/discontinuation: inefficacy at Longest time period reported

Study	BeSt study: 6 month outcomes trial: Goekoop-ruiterman 2005-2[48]
Study type	RCT (Patient randomised; Parallel)
Number of studies (number of participants)	1 (n=380)
Countries and setting	Conducted in Netherlands; Setting: Rheumatologists in 18 peripheral and 2 university hospitals.
Line of therapy	1st line
Duration of study	Intervention time: 2 years
Method of assessment of guideline condition	Adequate method of assessment/diagnosis: 1987 ACR criteria
Stratum	Overall
Subgroup analysis within study	Not applicable
Inclusion criteria	Adults with RA with a disease duration ≤2 years and active disease in a least 6 swollen and at least 6 tender joints, and either an ESR ≥28 mm/hour or a global health score of ≥20 mm on VAS (higher is worse).
Exclusion criteria	Previous treatment with DMARDs other than antimalarials, concomitant treatment with an experimental medication, malignancy within 5 years, bone marrow hypoplasia, serum aspartate aminotransferase level >3 times upper normal limit, serum creatinine level >150 µmoles per litre, estimated creatinine clearance <75 ml/minute. Diabetes, alcohol or drug abuse, pregnancy or wish to conceive during study or inadequate contraception.
Recruitment/selection of patients	Recruited from 2000-2002.
Age, gender and ethnicity	Age - Mean (SD): 54. Gender (M:F): 86% women. Ethnicity: Not detailed
Further population details	
Indirectness of population	No indirectness
Interventions	(n=126) Intervention 1: Monotherapy - Monotherapy - specify. Methotrexate at 15mg per week. Increasing to 30mg per week if DAS44 >2.4. . Duration 6 months. Concurrent medication/care: NSAIDs and intraarticular glucocorticoid injections permitted. Folic acid at 1mg per day during methotrexate treatment. . Indirectness: No indirectness Further details: 1. Dose: Lower dose (sulfasalazine: 1 gm, methotrexate: <=15mg, leflunomide: 10mg, hydroxychloroquine: 200mg) 2. Use of glucocorticoids: Short term glucocorticoids used (n=121) Intervention 2: Monotherapy - Monotherapy - specify. Methotrexate at 15mg per week. Increasing to 30mg per week if DAS44 >2.4. . Duration 6 months. Concurrent medication/care: NSAIDs and intraarticular glucocorticoid injections permitted. Folic acid at 1mg per day during methotrexate treatment. . Indirectness: No indirectness Further details: 1. Dose: Lower dose (sulfasalazine: 1 gm, methotrexate: <=15mg, leflunomide: 10mg,

	hydroxychloroquine: 200mg) 2. Use of glucocorticoids: Short term glucocorticoids used (n=133) Intervention 3: Parallel combination therapy - Parallel combination therapy - specify. Methotrexate at 7.5mg per week, sulfasalazine at 2g per day, prednisone at 60mg per day reduced to 7.5mg per day after 7 weeks. If DAS44 >2.4 then methotrexate increased up to 30mg per week. . Duration 6 months. Concurrent medication/care: NSAIDs and intraarticular glucocorticoid injections permitted. Folic acid at 1mg per day during methotrexate treatment. . Indirectness: No indirectness Further details: 1. Dose: Not applicable 2. Use of glucocorticoids: Short term glucocorticoids used
Funding	Funding not stated
RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: MONOTHERAPY - METHOTREXATE versus PARALLEL COMBINATION THERAPY - METHOTREXATE + SULFASALAZINE Protocol outcome 1: Function at 6 months - Actual outcome: Change in function (HAQ) score at 6 months; Group 1: mean -0.5 (SD 0.7); n=123, Group 2: mean -0.9 (SD 0.7); n=128; HAQ 0-3 Top=High is poor outcome Risk of bias: All domain - High, Selection - Low, Blinding - High, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low, Subgroups - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: 3; Group 2 Number missing: 5	
RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: MONOTHERAPY - METHOTREXATE versus PARALLEL COMBINATION THERAPY - METHOTREXATE + SULFASALAZINE Protocol outcome 1: Function at 6 months - Actual outcome: Change in function (HAQ) score at 6 months; Group 1: mean -0.5 (SD 0.7); n=116, Group 2: mean -0.9 (SD 0.7); n=128; HAQ 0-3 Top=High is poor outcome Risk of bias: All domain - High, Selection - Low, Blinding - High, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low, Subgroups - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: 3; Group 2 Number missing: 5	
Protocol outcomes not reported by the study	Disease Activity Score at 12 months; Disease Activity Score at 6 months; Quality of life at 12 months; Quality of life at 6 months; Function at 12 months; Pain at 6 months; Pain at 12 months; Remission at 6 months; Remission at 12 months; Low disease activity at 6 months; Low disease activity at 12 months; Radiological progression at 12+ months; ACR50 response at 6 months; ACR50 response at 12 months; Adverse events - mortality at 12+ months; Withdrawal/discontinuation: adverse events at Longest time period reported; Withdrawal/discontinuation: inefficacy at Longest time period reported

Study	Clark 1993[22]
Study type	RCT (Patient randomised; Parallel)
Number of studies (number of participants)	1 (n=126)
Countries and setting	Conducted in Mexico; Setting: Outpatient consultation clinic
Line of therapy	1st line
Duration of study	Intervention time: Six months
Method of assessment of guideline condition	Adequate method of assessment/diagnosis: ARA 1987 criteria
Stratum	Overall
Subgroup analysis within study	Not applicable
Inclusion criteria	≤ 5 years since diagnosis, ≥ 18 years of age, onset of RA > 16 years, 5+ actively inflamed joints, unsuccessful treatment with 2+ NSAIDs or salicylates.
Exclusion criteria	Current or previous treatment with second-line drugs or cytotoxic agents, current use of glucocorticoids, RA functional class IV.
Recruitment/selection of patients	Consecutive patients attending the clinic of the Rheumatology Service, Hospital General de Mexico, from June 1989 to August 1991, were enrolled.
Age, gender and ethnicity	Age - Other: Mean, years: HCQ - 39, placebo - 36. Gender (M:F): 10:116. Ethnicity: NR
Further population details	
Extra comments	Duration of disease, mean, months: HCQ - 30, placebo - 28. Functional class 1: HCQ - 80%, placebo - 82%. RF > 1:40 : hCQ - 48%, placebo 49% Pain, mean, mm: HCQ - 46.3, placebo - 40.6 ESR, mean, mm/h: HCQ - 35.7, placebo - 37.5 Radiographic erosions, 0-1: HCQ - 68%, placebo - 80% Radiographic erosions, >5: HCQ - 6%, placebo - 2%.
Indirectness of population	No indirectness
Interventions	(n=65) Intervention 1: Monotherapy - Monotherapy - specify. 400mg/day. Duration 6 months. Concurrent medication/care: NR. Indirectness: No indirectness Further details: 1. Dose: Higher dose (sulfasalazine: 2 gm, methotrexate: >15 mg, leflunomide: 20mg, hydroxychloroquine: 400mg) 2. Use of glucocorticoids: Not stated / Unclear (n=61) Intervention 2: Placebo. Matching placebo identical in shape, taste and colour. Duration 6 months. Concurrent medication/care: NR. Indirectness: No indirectness

	Further details: 1. Dose: Not applicable 2. Use of glucocorticoids: Not stated / Unclear
Funding	Study funded by industry ("in part by Sanofi-Winthrop Company, Mexico City")
RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: MONOTHERAPY - HYDROXYCHLOROQUINE versus PLACEBO Protocol outcome 1: Pain at 6 months - Actual outcome: Change in pain score at 6 months; Group 1: mean -25.8 mm (SD 28.75); n=63, Group 2: mean -6.5 mm (SD 32.25); n=58; VAS 0-100 Top=High is poor outcome Risk of bias: All domain - Very high, Selection - High, Blinding - Low, Incomplete outcome data - High, Outcome reporting - Low, Measurement - Low, Crossover - Low, Comments - Imputation method used (LOCF) not appropriate. ; Indirectness of outcome: No indirectness ; Baseline details: Pain, baseline: HCQ - 46.3mm, placebo - 40.6mm (difference after treatment much greater than difference at baseline); Blinding details: Matching placebo; Group 1 Number missing: 11, Reason: Across both arms: moved - 2pts, pregnancy - 1pt, severe anemia - 1pt, severe depression - 1pt, economic reasons - 5pts, unknown - 15pts. 20 of the 25 missing were included in the ITT analysis using last values carried forward. ; Group 2 Number missing: 14, Reason: Across both arms: moved - 2pts, pregnancy - 1pt, severe anemia - 1pt, severe depression - 1pt, economic reasons - 5pts, unknown - 15pts. 20 of the 25 missing were included in the ITT analysis using last values carried forward.	
Protocol outcomes not reported by the study	Disease Activity Score at 12 months; Disease Activity Score at 6 months; Quality of life at 12 months; Quality of life at 6 months; Function at 6 months; Function at 12 months; Pain at 12 months; Remission at 6 months; Remission at 12 months; Low disease activity at 6 months; Low disease activity at 12 months; Radiological progression at 12+ months; ACR50 response at 6 months; ACR50 response at 12 months; Adverse events - mortality at 12+ months; Withdrawal/discontinuation: adverse events at Longest time period reported; Withdrawal/discontinuation: inefficacy at Longest time period reported

Study (subsidiary papers)	COBRA trial: Boers 1997[13] (Van tuyl 2010[174], Boers 2001[14], Landewe 2004[87], Landewe 2002[88], Boers 1998[12], Verhoeven 2001[175])
Study type	RCT (Patient randomised; Parallel)
Number of studies (number of participants)	1 (n=156)
Countries and setting	Conducted in Belgium, Netherlands; Setting: NR
Line of therapy	1st line
Duration of study	Intervention time: 56 weeks
Method of assessment of guideline condition	Adequate method of assessment/diagnosis: ACR 1987 criteria
Stratum	Overall
Subgroup analysis within study	Stratified then randomised: Stratification by centre prior to randomisation
Inclusion criteria	Define
Exclusion criteria	Define
Recruitment/selection of patients	Patients recruited between May 1993 and May 1995 from 10 centres (nine in the Netherlands, one in Belgium).
Age, gender and ethnicity	Age - Mean (SD): MTX+SSZ - 49.5 (11.9), SSZ - 49.4 (12.3). Gender (M:F): Define. Ethnicity: 99% white
Further population details	
Extra comments	Median (range) disease duration, months: MTX+SSZ - 4 (1-24), SSZ - 4 (1-23) Previous treatment with antimalarials: MTX+SSZ - 21%, SSZ - 24% RF+: MTX+SSZ - 78%, SSZ - 72% Erosions: MTX+SSZ - 74%, SSZ - 79%.
Indirectness of population	No indirectness
Interventions	(n=77) Intervention 1: Step down therapy - Step-down therapy - specify. SSZ 500mg/day increased to 2000mg/day over 3 weeks; MTX 7.5mg / week, tapered to zero over weeks 40-56. If there was a flare, the medication was re-introduced. . Duration 56 weeks. Concurrent medication/care: Prednisolone 60mg, tapered to 7.5mg by week 7, tapered to zero over weeks 29-35. If there was a flare, the medication was re-introduced. NSAIDs and simple analgesics were allowed, discontinuation was actively pursued. A maximum of two intra-articular glucocorticoid injections was allowed in two periods after week 38 of the protocol, but not in the 6 week period preceding independent assessment. Other glucocorticoid interventions were not permitted. All patients received folic acid during MTX or placebo prescription. Vitamin D deficiency was also corrected. . Indirectness: No indirectness Further details: 1. Dose: Not applicable (SSZ - higher dose, MTX - lower dose). 2. Use of glucocorticoids: Short term glucocorticoids used (See above).

	(n=79) Intervention 2: Monotherapy - Monotherapy - specify. 500 mg/day, increased to 2000mg/day over 3 weeks. Matching placebo MTX. . Duration 56 weeks. Concurrent medication/care: Matching placebo prednisolone. NSAIDs and simple analgesics were allowed, discontinuation was actively pursued. A maximum of two intra-articular glucocorticoid injections was allowed in two periods after week 38 of the protocol, but not in the 6 week period preceding independent assessment. Other glucocorticoid interventions were not permitted. All patients received folic acid during MTX or placebo prescription. Vitamin D deficiency was also corrected. . Indirectness: No indirectness Further details: 1. Dose: Higher dose (sulfasalazine: 2 gm, methotrexate: >15 mg, leflunomide: 20mg, hydroxychloroquine: 400mg) 2. Use of glucocorticoids: Short term glucocorticoids not used (Ad hoc use only (see above)).
Funding	Equipment / drugs provided by industry (Trial funded by Ontwikkelingsgeneeskunde, Ziekenfondsraad, the Netherlands (grant number 92-045). SSZ provided by Pharmacia & Upjohn, Uppsala, Sweden.)

RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: STEP-DOWN THERAPY - SSZ+MTX, STEP DOWN TO SSZ versus MONOTHERAPY - SSZ

Protocol outcome 1: Disease Activity Score at 12 months
- Actual outcome: DAS at 56 weeks; Group 1: mean -1.4 (SD 1.2); n=76, Group 2: mean -1.3 (SD 1.4); n=79; Disease Activity Score 0-10 Top=High is poor outcome
Risk of bias: All domain - High, Selection - Low, Blinding - Low, Incomplete outcome data - High, Outcome reporting - Low, Measurement - Low, Crossover - Low, Comments - Data missing due to loss to follow-up were handled by a LOCF. For other missing data, values were interpolated if actual assessments were available at least every 38 weeks. ; Indirectness of outcome: No indirectness ; Baseline details: Difference in % male (SSZ+MTX - 34%, SSZ - 48%). DAS similar at baseline (0.1 difference between groups).; Group 1 Number missing: 7, Reason: 1 ineligible at start, 5 adverse events, 1 loss of efficacy (none lost to follow up); Group 2 Number missing: 23, Reason: 6 adverse events, 12 loss of efficacy, 2 both, 3 other (5 of total lost to follow up)
- Actual outcome: DAS at 28 weeks; Group 1: mean -2.1 (SD 1.2); n=76, Group 2: mean -1.3 (SD 1.2); n=79; Disease Activity Score 0-10 Top=High is poor outcome
Risk of bias: All domain - High, Selection - Low, Blinding - Low, Incomplete outcome data - High, Outcome reporting - Low, Measurement - Low, Crossover - Low, Comments - Data missing due to loss to follow-up were handled by a LOCF. For other missing data, values were interpolated if actual assessments were available at least every 38 weeks. ; Indirectness of outcome: No indirectness ; Baseline details: Difference in % male (SSZ+MTX - 34%, SSZ - 48%). DAS similar at baseline (0.1 difference between groups).; Group 1 Number missing: 2, Reason: 1 ineligible at start, 1 adverse event; Group 2 Number missing: 17, Reason: 5 adverse events, 9 loss of efficacy, 2 both, 1 other (3 of total lost to follow up)

Protocol outcome 2: Function at 6 months
- Actual outcome: Function (MACTAR) at 28 weeks; Group 1: mean 10 (SD 5); n=76,
Risk of bias: All domain - High, Selection - Low, Blinding - Low, Incomplete outcome data - High, Outcome reporting - Low, Measurement - Low,

Crossover - Low, Comments - Data missing due to loss to follow-up were handled by a LOCF. For other missing data, values were interpolated if actual assessments were available at least every 38 weeks. ; Indirectness of outcome: No indirectness ; Baseline details: Difference in % male (SSZ+MTX - 34%, SSZ - 48%). Outcome comparable at baseline (no difference between groups).; Group 1 Number missing: 2, Reason: 1 ineligible at start, 1 adverse events; Group 2 Number missing: 17, Reason: 5 adverse events, 9 loss of efficacy, 2 both, 1 other (3 of total lost to follow up)
- Actual outcome: Function (HAQ) at 28 weeks; Group 1: mean -1.1 (SD 0.8); n=76, Group 2: mean -0.6 (SD 0.6); n=79; Health Assessment Questionnaire 0-3 Top=High is poor outcome
Risk of bias: All domain - High, Selection - Low, Blinding - Low, Incomplete outcome data - High, Outcome reporting - Low, Measurement - Low, Crossover - Low, Comments - Data missing due to loss to follow-up were handled by a LOCF. For other missing data, values were interpolated if actual assessments were available at least every 38 weeks. ; Indirectness of outcome: No indirectness ; Baseline details: Difference in % male (SSZ+MTX - 34%, SSZ - 48%). Outcome comparable at baseline (0.1 difference between groups).; Group 1 Number missing: 2, Reason: 1 ineligible at start, 1 adverse events; Group 2 Number missing: 17, Reason: 5 adverse events, 9 loss of efficacy, 2 both, 1 other (3 of total lost to follow up)

Protocol outcome 3: Function at 12 months
- Actual outcome: Function (MACTAR) at 56 weeks; Group 1: mean 7 (SD 7); n=76,
Risk of bias: All domain - High, Selection - Low, Blinding - Low, Incomplete outcome data - High, Outcome reporting - Low, Measurement - Low, Crossover - Low, Comments - Data missing due to loss to follow-up were handled by a LOCF. For other missing data, values were interpolated if actual assessments were available at least every 38 weeks. ; Indirectness of outcome: No indirectness ; Baseline details: Difference in % male (SSZ+MTX - 34%, SSZ - 48%). Outcome comparable at baseline (no difference between groups).; Group 1 Number missing: 7, Reason: 1 ineligible at start, 5 adverse events, 1 loss of efficacy (none lost to follow up); Group 2 Number missing: 23, Reason: 6 adverse events, 12 loss of efficacy, 2 both, 3 other (5 of total lost to follow up)
- Actual outcome: Function (HAQ) at 56 weeks; Group 1: mean -0.8 (SD 0.8); n=76, Group 2: mean -0.6 (SD 0.7); n=79; Health Assessment Questionnaire 0-3 Top=High is poor outcome
Risk of bias: All domain - High, Selection - Low, Blinding - Low, Incomplete outcome data - High, Outcome reporting - Low, Measurement - Low, Crossover - Low, Comments - Data missing due to loss to follow-up were handled by a LOCF. For other missing data, values were interpolated if actual assessments were available at least every 38 weeks. ; Indirectness of outcome: No indirectness ; Baseline details: Difference in % male (SSZ+MTX - 34%, SSZ - 48%). Outcome comparable at baseline (0.1 difference between groups).; Group 1 Number missing: 7, Reason: 1 ineligible at start, 5 adverse events, 1 loss of efficacy (none lost to follow up); Group 2 Number missing: 23, Reason: 6 adverse events, 12 loss of efficacy, 2 both, 3 other (5 of total lost to follow up)

Protocol outcome 4: Pain at 12 months
- Actual outcome: Pain (VAS) at 56 weeks; Group 1: mean -23 mm (SD 29); n=76, Group 2: mean -25 mm (SD 28); n=79; Visual Analogue Scale 0-100 Top=High is poor outcome
Risk of bias: All domain - High, Selection - Low, Blinding - Low, Incomplete outcome data - High, Outcome reporting - Low, Measurement - Low, Crossover - Low, Comments - Data missing due to loss to follow-up were handled by a LOCF. For other missing data, values were interpolated if actual assessments were available at least every 38 weeks. ; Indirectness of outcome: No indirectness ; Baseline details: Difference in % male (SSZ+MTX - 34%, SSZ - 48%). Outcome comparable at baseline (1.0 difference between groups).; Group 1 Number missing: 7, Reason: 1 ineligible at start, 5 adverse events, 1 loss of efficacy (none lost to follow up); Group 2 Number missing: 23, Reason: 6 adverse events, 12 loss of efficacy, 2 both, 3 other (5 of total lost to follow up)

Protocol outcome 5: Pain at 6 months
- Actual outcome: Pain (VAS) at 28 weeks; Group 1: mean -34 mm (SD 25); n=76, Group 2: mean -20 mm (SD 30); n=79; Visual Analogue Scale 0-100 Top=High is poor outcome
Risk of bias: All domain - High, Selection - Low, Blinding - Low, Incomplete outcome data - High, Outcome reporting - Low, Measurement - Low, Crossover - Low, Comments - Data missing due to loss to follow-up were handled by a LOCF. For other missing data, values were interpolated if actual assessments were available at least every 38 weeks. ; Indirectness of outcome: No indirectness ; Baseline details: Difference in % male (SSZ+MTX - 34%, SSZ - 48%). Outcome comparable at baseline (1.0 difference between groups).; Group 1 Number missing: 2, Reason: 1 ineligible at start, 1 adverse events; Group 2 Number missing: 17, Reason: 5 adverse events, 9 loss of efficacy, 2 both, 1 other (3 of total lost to follow up)

Protocol outcome 6: Remission at 12 months
- Actual outcome: ACR remission at 56 weeks; Group 1: 1/70, Group 2: 3/56; Comments: Persistent remission at 56 weeks (not any remission over course of study)
Risk of bias: All domain - High, Selection - Low, Blinding - Low, Incomplete outcome data - High, Outcome reporting - Low, Measurement - Low, Crossover - Low, Comments - ; Indirectness of outcome: Serious indirectness, Comments: Remission not measured using DAS or other similar disease activity measure; Baseline details: Difference in % male (SSZ+MTX - 34%, SSZ - 48%). ; Group 1 Number missing: 7, Reason: 1 ineligible at start, 5 adverse events, 1 loss of efficacy (none lost to follow up); Group 2 Number missing: 23, Reason: 6 adverse events, 12 loss of efficacy, 2 both, 3 other (5 of total lost to follow up)

Protocol outcome 7: ACR50 response at 6 months
- Actual outcome: ACR50 response at 28 weeks? (unclear); Group 1: 37/75, Group 2: 21/62; Comments: Time point unclear. From context, appears to be 28 week data.
Risk of bias: All domain - Very high, Selection - Low, Blinding - Low, Incomplete outcome data - High, Outcome reporting - High, Measurement - Low, Crossover - Low, Comments - Time point outcome reported at unclear; Indirectness of outcome: No indirectness; Baseline details: Difference in % male (SSZ+MTX - 34%, SSZ - 48%). ; Group 1 Number missing: 2, Reason: 1 ineligible at start, 1 adverse events; Group 2 Number missing: 17, Reason: 5 adverse events, 9 loss of efficacy, 2 both, 1 other (3 of total lost to follow up)

Protocol outcome 8: Withdrawal/discontinuation: adverse events at Longest time period reported
- Actual outcome: Discontinuation: adverse events at 56 weeks; Group 1: 5/75, Group 2: 8/64
Risk of bias: All domain - High, Selection - Low, Blinding - Low, Incomplete outcome data - High, Outcome reporting - Low, Measurement - Low, Crossover - Low, Comments - ; Indirectness of outcome: No indirectness ; Baseline details: Difference in % male (SSZ+MTX - 34%, SSZ - 48%). ; Group 1 Number missing: 2, Reason: 1 ineligible at start, 1 loss of efficacy (none lost to follow up); Group 2 Number missing: 15, Reason: 12 loss of efficacy, 3 other (4 of total lost to follow up)

Protocol outcome 9: Withdrawal/discontinuation: inefficacy at Longest time period reported
- Actual outcome: Discontinuation: inefficacy at 56 weeks; Group 1: 1/71, Group 2: 14/70
Risk of bias: All domain - High, Selection - Low, Blinding - Low, Incomplete outcome data - High, Outcome reporting - Low, Measurement - Low, Crossover - Low, Comments - ; Indirectness of outcome: No indirectness ; Baseline details: Difference in % male (SSZ+MTX - 34%, SSZ - 48%). ; Group

1 Number missing: 6, Reason: 1 ineligible at start, 5 adverse events (none lost to follow up); Group 2 Number missing: 9, Reason: 6 adverse events, 3 other (3 of total lost to follow up)	
Protocol outcomes not reported by the study	Disease Activity Score at 6 months; Quality of life at 12 months; Quality of life at 6 months; Remission at 6 months; Low disease activity at 6 months; Low disease activity at 12 months; Radiological progression at 12+ months; ACR50 response at 12 months; Adverse events - mortality at 12+ months

Study	Davis 1991[27]
Study type	RCT (Patient randomised; Parallel)
Number of studies (number of participants)	1 (n=104)
Countries and setting	Conducted in United Kingdom; Setting: NR
Line of therapy	1st line
Duration of study	Intervention time: 12 months
Method of assessment of guideline condition	Adequate method of assessment/diagnosis: 4 or more ARA criteria
Stratum	Overall
Subgroup analysis within study	Stratified then randomised: Stratification for presence or absence of erosions
Inclusion criteria	Presence of palpable synovitis but limited to hands, wrists and feet, ESR < 30mm/h and CRP < 2 mg/L.
Exclusion criteria	Previous use of disease suppressive therapy or oral glucocorticoids.
Recruitment/selection of patients	NR
Age, gender and ethnicity	Age - Median (IQR): HCQ - 46 (18), placebo - 46 (20). Gender (M:F): 36:67. Ethnicity: NR
Further population details	
Extra comments	Median (IQR) disease duration, months: HCQ - 17 (22), placebo - 12 (30) +ve Latex (>1:40): HCQ - 69%, placebo - 51% Erosive: HCQ - 61%, placebo - 55%.
Indirectness of population	No indirectness: Described as "mild" RA population
Interventions	(n=51) Intervention 1: Monotherapy - Monotherapy - specify. 400mg / day. Duration 12 months. Concurrent medication/care: NSAIDs were maintained at a stable dose in tolerant patients. Diclofenac was used where possible. . Indirectness: No indirectness Further details: 1. Dose: Higher dose (sulfasalazine: 2 gm, methotrexate: >15 mg, leflunomide: 20mg, hydroxychloroquine: 400mg) 2. Use of glucocorticoids: Short term glucocorticoids not used (n=53) Intervention 2: Placebo. Matching tablets. Duration 12 months. Concurrent medication/care: NSAIDs were maintained at a stable dose in tolerant patients. Diclofenac was used where possible. . Indirectness: No indirectness Further details: 1. Dose: Not applicable 2. Use of glucocorticoids: Short term glucocorticoids not used
Funding	Equipment / drugs provided by industry (Active and placebo medication provided by Sterling-Winthrop)

RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: MONOTHERAPY - HYDROXYCHLOROQUINE versus PLACEBO Protocol outcome 1: Withdrawal/discontinuation: inefficacy at Longest time period reported - Actual outcome: Withdrawal: inefficacy at 12 months; Group 1: 8/51, Group 2: 18/53 Risk of bias: All domain - High, Selection - High, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Baseline details: Difference in disease duration, % +ve Latex and % erosive (HCQ group worse on all characteristics) ; Blinding details: Matching placebo; Group 1 Number missing: 0; Group 2 Number missing: 0	
Protocol outcomes not reported by the study	Disease Activity Score at 12 months; Disease Activity Score at 6 months; Quality of life at 12 months; Quality of life at 6 months; Function at 6 months; Function at 12 months; Pain at 6 months; Pain at 12 months; Remission at 6 months; Remission at 12 months; Low disease activity at 6 months; Low disease activity at 12 months; Radiological progression at 12+ months; ACR50 response at 6 months; ACR50 response at 12 months; Adverse events - mortality at 12+ months; Withdrawal/discontinuation: adverse events at Longest time period reported

Study	Den uyl 2014[31]
Study type	RCT (Patient randomised; Parallel)
Number of studies (number of participants)	1 (n=164)
Countries and setting	Conducted in Netherlands, Unknown
Line of therapy	1st line
Duration of study	Intervention + follow up: 2 years
Method of assessment of guideline condition	Adequate method of assessment/diagnosis: 1987 ACR criteria
Stratum	Overall
Subgroup analysis within study	Not applicable
Inclusion criteria	Adults with currently active RA, for 2 years or less. Active RA defined as at least 6 swollen or tender joints and either ESR ≥28 mm/h or global health score ≥20 on 0-100 VAS.
Exclusion criteria	Previous treatment with glucocorticoids or DMARD other than antimalarial agents, uncontrolled diabetes, heart failure, uncontrolled hypertension, ALT or AST more than 3 times upper limit of normal, reduced renal function, contraindications to glucocorticoids, positive tubercilin skin test.
Recruitment/selection of patients	Recruited from March 2008 to March 2011.
Age, gender and ethnicity	Age - Mean (SD): 52. Gender (M:F): 56% female. Ethnicity: Not detailed
Further population details	
Indirectness of population	No indirectness
Interventions	(n=81) Intervention 1: Parallel combination therapy - Parallel combination therapy - specify. COBRA therapy. Methotrexate (7.5mg per week), sulfasalazine (1g per day increased to 2g per day after 1 week), prednisolone (60mg per day, tapered to 7.5mg per day by week 6). Treatment adjusted if DAS44 was not less than 1.6. Increase MTX dose to 25mg per week after 13 weeks. . Duration 1 year. Concurrent medication/care: Folic acid 5mg per week. Daily calcium/vitamin supplementation. NSAID and IA glucocorticoid treatment permitted. . Indirectness: No indirectness Further details: 1. Dose: Higher dose (sulfasalazine: 2 gm, methotrexate: >15 mg, leflunomide: 20mg, hydroxychloroquine: 400mg) 2. Use of glucocorticoids: Short term glucocorticoids used (n=83) Intervention 2: Monotherapy - Monotherapy - specify. COBRA-light therapy. Methotrexate (10mg per week rising to 25mg per week by week 9), prednisolone (30mg per day, tapered to 7.5mg per day by week 6). Parenteral methotrexate considered after 13 weeks if DAS44 was not less than 1.6.. Duration 1 year. Concurrent medication/care: Folic acid 5mg per week. Daily calcium/vitamin supplementation. NSAID and IA glucocorticoid treatment permitted. . Indirectness: No indirectness

	Further details: 1. Dose: Higher dose (sulfasalazine: 2 gm, methotrexate: >15 mg, leflunomide: 20mg, hydroxychloroquine: 400mg) 2. Use of glucocorticoids: Short term glucocorticoids used
Funding	Study funded by industry (Performed within framework of project T1-106 of the Dutch Top Institute Pharma and with an unrestricted grant from Pfizer.)

RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: PARALLEL COMBINATION THERAPY - METHOTREXATE + SULFASALAZINE versus MONOTHERAPY - METHOTREXATE

Protocol outcome 1: Disease Activity Score at 6 months
- Actual outcome: Change in Disease Activity Score (DAS) at 26 weeks; Group 1: mean -2.5 (SD 1.21); n=81, Group 2: mean -2.18 (SD 1.1); n=81; DAS44 0-10 Top=High is poor outcome
Risk of bias: All domain - High, Selection - Low, Blinding - High, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low, Subgroups - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: 0, Reason: ; Group 2 Number missing: 2

Protocol outcome 2: Function at 6 months
- Actual outcome: Change in function (HAQ) at 26 weeks; Group 1: mean -0.8 (SD 0.6); n=81, Group 2: mean -0.8 (SD 0.7); n=81; HAQ 0-3 Top=High is poor outcome
Risk of bias: All domain - High, Selection - Low, Blinding - High, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low, Subgroups - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: 0, Reason: ; Group 2 Number missing: 2

Protocol outcome 3: Pain at 6 months
- Actual outcome: Change in pain (VAS) at 26 weeks; Group 1: mean -32 (SD 30); n=81, Group 2: mean -34 (SD 30); n=81
Risk of bias: All domain - High, Selection - Low, Blinding - High, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low, Subgroups - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: 0, Reason: ; Group 2 Number missing: 2

Protocol outcome 4: Remission at 6 months
- Actual outcome: ACR/EULAR Boolean remission at 26 weeks; Group 1: 13/81, Group 2: 16/81
Risk of bias: All domain - High, Selection - Low, Blinding - High, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low, Subgroups - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: 0, Reason: ; Group 2 Number missing: 2

Protocol outcome 5: ACR50 response at 6 months
- Actual outcome: ACR50 response at 26 weeks; Group 1: 46/81, Group 2: 50/81
Risk of bias: All domain - High, Selection - Low, Blinding - High, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low, Subgroups - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: 0, Reason: ; Group 2 Number missing: 2

Protocol outcome 6: Withdrawal/discontinuation: adverse events at Longest time period reported
- Actual outcome: Discontinuation due to adverse events at 26 weeks; Group 1: 2/81, Group 2: 1/78

Risk of bias: All domain - Low, Selection - Low, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low, Subgroups - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: 1, Reason: ; Group 2 Number missing: 5 Protocol outcome 7: Withdrawal/discontinuation: inefficacy at Longest time period reported - Actual outcome: Discontinuation due to inefficacy at 26 weeks; Group 1: 0/79, Group 2: 0/77 Risk of bias: All domain - Low, Selection - Low, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low, Subgroups - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: 2, Reason: ; Group 2 Number missing: 6	
Protocol outcomes not reported by the study	Disease Activity Score at 12 months; Quality of life at 12 months; Quality of life at 6 months; Function at 12 months; Pain at 12 months; Remission at 12 months; Low disease activity at 6 months; Low disease activity at 12 months; Radiological progression at 12+ months; ACR50 response at 12 months; Adverse events - mortality at 12+ months

Study	Dougados 1999[33]
Study type	RCT (Patient randomised; Parallel)
Number of studies (number of participants)	1 (n=209)
Countries and setting	Conducted in Finland, France, Germany
Line of therapy	1st line
Duration of study	Intervention time: 52 weeks
Method of assessment of guideline condition	Adequate method of assessment/diagnosis: People fulfilling ACR criteria for the diagnosis of RA
Stratum	Overall
Subgroup analysis within study	Not applicable
Inclusion criteria	People with active RA. Disease duration less than 1 year.
Exclusion criteria	Previous non analgesic or NSAID treatment for RA. Contraindications for study medications.
Recruitment/selection of patients	Outpatients fulfilling study criteria
Age, gender and ethnicity	Age - Mean (SD): 51. Gender (M:F): Define. Ethnicity: Not detailed
Further population details	
Indirectness of population	No indirectness
Interventions	(n=68) Intervention 1: Monotherapy - Monotherapy - specify. Sulfasalazine (1g per day rising to 2g per day from day 9 in 500mg tablets). After week 16 dose could rise to 3g per day if efficacy inadequate. Placebo MTX tablets 3 times per week or 6 times per week if dose increased at 16 weeks. . Duration 52 weeks. Concurrent medication/care: Not detailed. Indirectness: No indirectness Further details: 1. Dose: Higher dose (sulfasalazine: 2 gm, methotrexate: >15 mg, leflunomide: 20mg, hydroxychloroquine: 400mg) 2. Use of glucocorticoids: Short term glucocorticoids not used (n=69) Intervention 2: Monotherapy - Monotherapy - specify. Methotrexate (7.5mg per week in 3 2.5mg tablets). After week 16 dose could rise to 15mg per week if efficacy inadequate. Placebo SASP tablets each day matching possible SASP dose. . Duration 52 weeks. Concurrent medication/care: Not detailed. Indirectness: No indirectness Further details: 1. Dose: Higher dose (sulfasalazine: 2 gm, methotrexate: >15 mg, leflunomide: 20mg, hydroxychloroquine: 400mg) 2. Use of glucocorticoids: Short term glucocorticoids not used (n=68) Intervention 3: Parallel combination therapy - Parallel combination therapy - specify. Methotrexate (7.5mg per week in 3 2.5mg tablets) and Sulfasalazine (1g per day rising to 2g per day from day 9 in 500mg tablets). After week 16 MTX dose could rise to 15mg per week and SASP dose to 3g per day if efficacy

	inadequate. MTX was started and SASP either continued or discontinued. . Duration 52 weeks. Concurrent medication/care: Not detailed. Indirectness: No indirectness Further details: 1. Dose: Higher dose (sulfasalazine: 2 gm, methotrexate: >15 mg, leflunomide: 20mg, hydroxychloroquine: 400mg) 2. Use of glucocorticoids: Short term glucocorticoids not used
Funding	Study funded by industry (Study supported in part by a grant from Pharmacia Upjohn)

RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: MONOTHERAPY - SULFASALAZINE versus MONOTHERAPY - METHOTREXATE

Protocol outcome 1: Withdrawal/discontinuation: adverse events at Longest time period reported
- Actual outcome: Discontinuation due to adverse events at 52 weeks; Group 1: 10/57, Group 2: 7/61
Risk of bias: All domain - Very high, Selection - High, Blinding - Low, Incomplete outcome data - High, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Baseline details: Time since onset longer in MTX group; Group 1 Number missing: 11; Group 2 Number missing: 8

Protocol outcome 2: Withdrawal/discontinuation: inefficacy at Longest time period reported
- Actual outcome: Discontinuation due to inefficacy at 52 weeks; Group 1: 7/54, Group 2: 5/59
Risk of bias: All domain - Very high, Selection - High, Blinding - Low, Incomplete outcome data - High, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Baseline details: Time since onset longer in MTX group; Group 1 Number missing: 14; Group 2 Number missing: 10

RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: MONOTHERAPY - SULFASALAZINE versus PARALLEL COMBINATION THERAPY - METHOTREXATE + SULFASALAZINE

Protocol outcome 1: Withdrawal/discontinuation: adverse events at Longest time period reported
- Actual outcome: Discontinuation due to adverse events at 52 weeks; Group 1: 10/57, Group 2: 9/60
Risk of bias: All domain - Very high, Selection - High, Blinding - Low, Incomplete outcome data - High, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: 11; Group 2 Number missing: 8

Protocol outcome 2: Withdrawal/discontinuation: inefficacy at Longest time period reported
- Actual outcome: Discontinuation due to inefficacy at 52 weeks; Group 1: 7/54, Group 2: 3/54
Risk of bias: All domain - Very high, Selection - High, Blinding - Low, Incomplete outcome data - High, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: 14; Group 2 Number missing: 14

RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: MONOTHERAPY - METHOTREXATE versus PARALLEL COMBINATION THERAPY - METHOTREXATE + SULFASALAZINE

Protocol outcome 1: Withdrawal/discontinuation: adverse events at Longest time period reported - Actual outcome: Discontinuation due to adverse events at 52 weeks; Group 1: 7/61, Group 2: 9/60 Risk of bias: All domain - Very high, Selection - High, Blinding - Low, Incomplete outcome data - High, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Baseline details: Time since onset longer in MTX group; Group 1 Number missing: 8; Group 2 Number missing: 8 Protocol outcome 2: Withdrawal/discontinuation: inefficacy at Longest time period reported - Actual outcome: Discontinuation due to inefficacy at 52 weeks; Group 1: 5/59, Group 2: 3/54 Risk of bias: All domain - Very high, Selection - High, Blinding - Low, Incomplete outcome data - High, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Baseline details: Time since onset longer in MTX group; Group 1 Number missing: 10; Group 2 Number missing: 14	
Protocol outcomes not reported by the study	Disease Activity Score at 12 months; Disease Activity Score at 6 months; Quality of life at 12 months; Quality of life at 6 months; Function at 6 months; Function at 12 months; Pain at 6 months; Pain at 12 months; Remission at 6 months; Remission at 12 months; Low disease activity at 6 months; Low disease activity at 12 months; Radiological progression at 12+ months; ACR50 response at 6 months; ACR50 response at 12 months; Adverse events - mortality at 12+ months

Study	Ferraccioli 2002[40]
Study type	RCT (Patient randomised; Parallel)
Number of studies (number of participants)	1 (n=84)
Countries and setting	Conducted in Italy; Setting: Rheumatology Unit, University of Udine
Line of therapy	1st line
Duration of study	Intervention time: 3 years
Method of assessment of guideline condition	Adequate method of assessment/diagnosis: ACR criteria
Stratum	Overall
Subgroup analysis within study	Not applicable
Inclusion criteria	Active disease (at least 3 of the following criteria for at least 3 months: ESR > 30 mm/h or CRP > 20 mg/L; > 6 swollen joints (of 66) or > 9 tender joints (of 68); moderate or severe pain on verbal scale as none, mild, moderate or severe; receiving prednisone at 5mg/day). All patients at least one erosion at baseline and all had received at least a 4 month course of antimalarials.
Exclusion criteria	Age < 17 or > 70 years; comorbidities that might preclude any of the therapeutic approaches; previous treatment with immune suppressants; possible pregnancy or breastfeeding; psychiatric or neurological disease; hypertension under treatment.
Recruitment/selection of patients	Recruitment between June 1993 and June 1995
Age, gender and ethnicity	Age - Mean (SD): MTX - 59 (7.7), SSZ - 59 (15). Gender (M:F): 12:72. Ethnicity: NR
Further population details	
Extra comments	Disease duration, years, mean (SD): MTX - 1.2 (0.8), SSZ - 2.0 (1.0) Swollen joint count, mean (SD): MTX - 10 (12), SSZ - 9 (11) Tender joint count, mean (SD): MTX - 12 (13), SSZ - 10 (11) Pain, VAS, cm, mean (SD): MTX - 6.1 (0.9), SSZ - 6.3 (0.9) ESR, mm/h, mean (SD): MTX - 52 (30), SSZ - 43 (29) RF+: MTX - 73%, SSZ - 55% Prednisone, previous: MTX - 71%, SSZ - 76% (current use % same. Mean dose 5mg/day)
Indirectness of population	Serious indirectness: All patients had previously received at least a 4 month course of antimalarials
Interventions	(n=42) Intervention 1: Monotherapy - Monotherapy - specify. 10mg/week, after 8 weeks the dose was increased monthly by 5mg, up to 20 mg/week. Duration 6 months. Concurrent medication/care: Attempts to decrease or stop the daily prednisone dose were performed throughout the study period. Paracetamol and NSAIDs were allowed concurrently. . Indirectness: No indirectness Further details: 1. Dose: Higher dose (sulfasalazine: 2 gm, methotrexate: >15 mg, leflunomide: 20mg,

	hydroxychloroquine: 400mg) 2. Use of steroids: Short term steroids used (Ad hoc, as above.). Comments: After 6 months patients who had not shown ACR50 improvement had CsA added to their therapy. As this drug is out of scope, only data up to 6 months has been included in the review. (n=42) Intervention 2: Monotherapy - Monotherapy - specify. 1g/day, increased by 500mg each week for 5 weeks to reach 3g/day. Duration 6 months. Concurrent medication/care: Attempts to decrease or stop the daily prednisone dose were performed throughout the study period. Paracetamol and NSAIDs were allowed concurrently. . Indirectness: No indirectness Further details: 1. Dose: 2. Use of steroids: Comments: After 6 months patients in the comparator arm had an out of scope drug added to their therapy. Therefore, only data up to 6 months has been included in the review.
Funding	Academic or government funding ("Supported by University of Udine")
RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: MONOTHERAPY - MTX versus MONOTHERAPY - SSZ Protocol outcome 1: ACR50 response at 6 months - Actual outcome: ACR50 response at 6 months; Group 1: 24/42, Group 2: 14/37 Risk of bias: All domain - Very high, Selection - High, Blinding - High, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Baseline details: Difference in disease duration (MTX 1.2 yr, SSZ 2.0 yr), RF+ status (MTX 73%, SSZ 55%); Blinding details: Assessors were blinded to treatment allocation, but outcome involves patient-reported measures and they were not blinded. Paper mentions that patients were allocated randomly for the first 6 months "and then managed in an open fashion". ; Group 1 Number missing: 0; Group 2 Number missing: 5, Reason: Lost to follow up	
Protocol outcomes not reported by the study	Disease Activity Score at 12 months; Disease Activity Score at 6 months; Quality of life at 12 months; Quality of life at 6 months; Function at 6 months; Function at 12 months; Pain at 6 months; Pain at 12 months; Remission at 6 months; Remission at 12 months; Low disease activity at 6 months; Low disease activity at 12 months; Radiological progression at 12+ months; ACR50 response at 12 months; Adverse events - mortality at 12+ months; Withdrawal/discontinuation: adverse events at Longest time period reported; Withdrawal/discontinuation: inefficacy at Longest time period reported

Study (subsidiary papers)	FIN-RACo trial: Mottonen 1999[108] (Rantalaiho 2013[132], Korpela 2004[77], Neva 2000[115], Puolakka 2005[128], Puolakka 2004[129], Rantalaiho 2009[130], Rantalaiho 2010[131], Eklund 2007[35], Karstila 2010[74], Laivoranta-nyman 2006[86], Mustila 2011[110], Makinen 2007[98])
Study type	RCT (Patient randomised; Parallel)
Number of studies (number of participants)	1 (n=199)
Countries and setting	Conducted in Finland; Setting: NR
Line of therapy	1st line
Duration of study	Intervention time: 2 years
Method of assessment of guideline condition	Adequate method of assessment/diagnosis: ARA 1987 criteria
Stratum	Overall
Subgroup analysis within study	Stratified then randomised: Stratified by RF+ status prior to randomisation
Inclusion criteria	Age between 18-65 years, duration of symptoms < 2 years, active disease with 3+ swollen joints and 3+ of the following: ESR ≥ 28mm/h or CRP > 19 mg/L, morning stiffness of ≥ 29 min, > 5 swollen and > 10 tender joints.
Exclusion criteria	Previous use of DMARDs, use of glucocorticoids within previous 2 weeks, serious comorbidity, suspected inability to comply with protocol, hypersensitivity to any study medication, history of cancer, pregnant women, women of childbearing age not using reliable contraception.
Recruitment/selection of patients	Patients recruited between April 1993 and May 1995 at 18 hospitals.
Age, gender and ethnicity	Age - Mean (range): SSZ+MTX+HCQ - 47 (23-65), SSZ - 48 (20-65). Gender (M:F): 74:121. Ethnicity: NR
Further population details	
Extra comments	Mean (range) disease duration, months: SSZ+MTX+HCQ - 7.3 (2-22), SSZ - 8.6 (2-23) RF+: SSZ+MTX+HCQ - 70%, SSZ - 66% DAS28, mean (SD): overall - 5.6 (1.0) HAQ, mean (SD): SSZ+MTX+HCQ - 0.9 (0.6), SSZ - 0.9 (0.6). Erosions: SSZ+MTX+HCQ - 48%, SSZ - 53%.
Indirectness of population	No indirectness
Interventions	(n=99) Intervention 1: Parallel combination therapy - Parallel combination therapy - specify. SSZ 500mg twice daily, MTX 7.5mg/week, HCQ 300mg/day. If clinical improvement at 3 months was under 50% in at least 2 of 3 criteria at 3 months (swollen joints, tender joints, ESR or CRP), the dose of MTX was increased to 10mg/week. Drug doses were tapered if the patient reached remission.. Duration 6 months. Concurrent medication/care: Prednisolone 5mg/day. If clinical improvement at 3 months was under 50% in at least 2 of 3 criteria at 3 months (swollen joints, tender joints, ESR or CRP), the dose of prednisolone was increased to

	7.5mg/day. Drug doses were tapered if the patient reached remission. . Indirectness: No indirectness Further details: 1. Dose: Lower dose (sulfasalazine: 1 gm, methotrexate: <=15mg, leflunomide: 10mg, hydroxychloroquine: 200mg) (MTX and SSZ lower dose for first 6 months; HCQ moderate). 2. Use of glucocorticoids: Short term glucocorticoids used (See above). Comments: Data up to 6 months only have been included in the review due to out of scope drugs used in comparison group by 12 months. (n=100) Intervention 2: Monotherapy - Monotherapy - specify. 2g/day, increased to 3g/day at 3 months, if clinically indicated.. Duration 6 months. Concurrent medication/care: Use of oral prednisolone up to 10mg was allowed in patients with continuously active disease, at the discretion of the treating physician. . Indirectness: No indirectness Further details: 1. Dose: 2. Use of glucocorticoids: Comments: Subsequent steps in treatment strategy involved replacement of SSZ with MTX from 6 months, and then with Azathioprine from 9 months, followed by other DMARDs. Data up to 6 months only have been included in the review due to out of scope drugs used after 9 months and outcome data sought at 6 and 12 months.
Funding	Academic or government funding (Supported by Finnish Society for Rheumatology, the Rheumatism Research Foundation in Finland, Medical Research Foundation of Turku University Central Hospital, and the Finnish Office for Health Care Technology Assessment, Finland.)

RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: PARALLEL COMBINATION THERAPY - SSZ+MTX+HCQ versus MONOTHERAPY - SSZ

Protocol outcome 1: Remission at 6 months
- Actual outcome: DAS28 < 2.6 at 6 months; Group 1: 52/79, Group 2: 33/90
Risk of bias: All domain - Very high, Selection - High, Blinding - High, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Baseline details: DS28 baseline (continuous): SSZ+MTX+HCQ - 5.4 (0.9), SSZ - 5.7 (1.1); Blinding details: Clearly stated to be open label. ; Group 1 Number missing: 20, Reason: NR - only patients with complete data on remission and good treatment response at 6, 12 and 24 months were analysed; Group 2 Number missing: 10, Reason: NR - only patients with complete data on remission and good treatment response at 6, 12 and 24 months were analysed

Protocol outcome 2: Withdrawal/discontinuation: adverse events at Longest time period reported
- Actual outcome: Withdrawal: adverse events at 6 months; Group 1: 0/94, Group 2: 0/96
Risk of bias: All domain - Very high, Selection - High, Blinding - High, Incomplete outcome data - High, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Baseline details: See population panel; Blinding details: Clearly stated to be open label. ; Group 1 Number missing: 5, Reason: 3 refused, 1 protocol violation, 1 intercurrent illness; Group 2 Number missing: 4, Reason: 3 refused, 1 protocol violation

Protocol outcome 3: Withdrawal/discontinuation: inefficacy at Longest time period reported - Actual outcome: Withdrawal: inefficacy at 6 months; Group 1: 0/94, Group 2: 0/96 Risk of bias: All domain - Very high, Selection - High, Blinding - High, Incomplete outcome data - High, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Baseline details: See population panel; Blinding details: Clearly stated to be open label. ; Group 1 Number missing: 5, Reason: 3 refused, 1 protocol violation, 1 intercurrent illness; Group 2 Number missing: 4, Reason: 3 refused, 1 protocol violation	
Protocol outcomes not reported by the study	Disease Activity Score at 12 months; Disease Activity Score at 6 months; Quality of life at 12 months; Quality of life at 6 months; Function at 6 months; Function at 12 months; Pain at 6 months; Pain at 12 months; Remission at 12 months; Low disease activity at 6 months; Low disease activity at 12 months; Radiological progression at 12+ months; ACR50 response at 6 months; ACR50 response at 12 months; Adverse events - mortality at 12+ months

Study	Ghosh 2008[46]
Study type	RCT (Patient randomised; Parallel)
Number of studies (number of participants)	1 (n=110)
Countries and setting	Conducted in India; Setting: Not detailed
Line of therapy	1st line
Duration of study	Intervention time: 6 months
Method of assessment of guideline condition	Adequate method of assessment/diagnosis: 1987 criteria
Stratum	Overall
Subgroup analysis within study	Not applicable
Inclusion criteria	People with RA with disease duration for less than 6 months. No treatment with DMARDs before inception.
Exclusion criteria	None detailed
Recruitment/selection of patients	Not detailed
Age, gender and ethnicity	Age - Mean (range): Age at onset: 36 (13-57). Gender (M:F): 1/4.5 ratio. Ethnicity: Not detailed
Further population details	
Extra comments	.
Indirectness of population	No indirectness
Interventions	(n=56) Intervention 1: Parallel combination therapy - Parallel combination therapy - specify. Methotrexate (10mg once per week) and hydroxychloroquine (200mg twice per day). People who required glucocorticoid treatment or dose escalation of DMARD treatment due to flare were excluded. . Duration 6 months. Concurrent medication/care: Folic acid (5mg once per day). Analgesics taken as required. . Indirectness: No indirectness Further details: 1. Dose: Lower dose (sulfasalazine: 1 gm, methotrexate: <=15mg, leflunomide: 10mg, hydroxychloroquine: 200mg) 2. Use of glucocorticoids: Short term glucocorticoids not used (n=54) Intervention 2: Parallel combination therapy - Parallel combination therapy - specify. Sulfasalazine (500mg three times per day) + hydroxychloroquine (200mg twice per day). People who required glucocorticoid treatment or does escalation of DMARD treatment due to flare were excluded. Duration 6 months. Concurrent medication/care: Analgesics taken as required. Indirectness: No indirectness Further details: 1. Dose: Lower dose (sulfasalazine: 1 gm, methotrexate: <=15mg, leflunomide: 10mg, hydroxychloroquine: 200mg) 2. Use of glucocorticoids: Short term glucocorticoids not used
Funding	No funding (None)

RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: PARALLEL COMBINATION THERAPY - METHOTREXATE + HYDROXYCHLOROQUINE versus PARALLEL COMBINATION THERAPY - SULFASALAZINE + HYDROXYCHLOROQUINE

Protocol outcome 1: Disease Activity Score at 6 months
- Actual outcome: Disease Activity Score at 6 months; Group 1: mean 4.4 (SD 1.77); n=56, Group 2: mean 3.6 (SD 1.43); n=54; DAS28 2-10 Top=High is poor outcome
Risk of bias: All domain - Very high, Selection - High, Blinding - High, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low, Subgroups - Low; Indirectness of outcome: No indirectness ; Baseline details: 0.6 higher DAS28 at baseline for sulfasalazine group. ; Group 1 Number missing: ; Group 2 Number missing:

Protocol outcome 2: Remission at 6 months
- Actual outcome: Disease Activity Score 28 ≤3 at 6 months; Group 1: 14/56, Group 2: 20/54
Risk of bias: All domain - Very high, Selection - High, Blinding - High, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low, Subgroups - Low; Indirectness of outcome: No indirectness ; Baseline details: 0.6 higher DAS28 at baseline for sulfasalazine group. ; Group 1 Number missing: ; Group 2 Number missing:

Protocol outcomes not reported by the study	Disease Activity Score at 12 months; Quality of life at 12 months; Quality of life at 6 months; Function at 6 months; Function at 12 months; Pain at 6 months; Pain at 12 months; Remission at 12 months; Low disease activity at 6 months; Low disease activity at 12 months; Radiological progression at 12+ months; ACR50 response at 6 months; ACR50 response at 12 months; Adverse events - mortality at 12+ months; Withdrawal/discontinuation: adverse events at Longest time period reported; Withdrawal/discontinuation: inefficacy at Longest time period reported

Study (subsidiary papers)	Haagsma 1997[55] (Haagsma 1999[54], Van gestel 1998[170])
Study type	RCT (Patient randomised; Parallel)
Number of studies (number of participants)	1 (n=105)
Countries and setting	Conducted in Netherlands; Setting: 6 peripheral or 1 academic clinics
Line of therapy	1st line
Duration of study	Intervention time: 52 weeks
Method of assessment of guideline condition	Adequate method of assessment/diagnosis: ACR criteria
Stratum	Overall
Subgroup analysis within study	Not applicable
Inclusion criteria	People ≥18 years with active (DAS≥3) RA for less than 1 year. Positive rheumatoid factor and/or HLA-DR4 and/or HLA-DR1 positivity. No RA treatment except analgesics and NSAIDs.
Exclusion criteria	People with contraindications to sulfasalazine and methotrexate were excluded.
Recruitment/selection of patients	Consecutive people who attended six peripheral and one academic clinic.
Age, gender and ethnicity	Age - Mean (SD): 57. Gender (M:F): 37 / 68. Ethnicity: NR
Further population details	
Extra comments	.
Indirectness of population	No indirectness
Interventions	(n=34) Intervention 1: Monotherapy - Monotherapy - specify. Sulfasalazine (1g per day rising to 2g per day from day 10 in 500mg tablets). After week 16 dose could rise to 3g per day if efficacy inadequate. Placebo MTX tablets 3 times per week or 6 times per week if dose increased at 16 weeks. If higher dose was not effective after 8 weeks then participant withdrawn from study. . Duration 52 weeks. Concurrent medication/care: NSAID therapy at a dose that was preferable not altered. No systematically administered glucocorticoids permitted. . Indirectness: No indirectness Further details: 1. Dose: Higher dose (sulfasalazine: 2 gm, methotrexate: >15 mg, leflunomide: 20mg, hydroxychloroquine: 400mg) 2. Use of glucocorticoids: Short term glucocorticoids used (Systemic glucocorticoid treatment not permirtted but local glucocorticoid treatment permitted). (n=35) Intervention 2: Monotherapy - Monotherapy - specify. Methotrexate (7.5mg per week in 3 2.5mg tablets). After week 16 dose could rise to 15mg per week if efficacy inadequate. Placebo SASP tablets each day matching possible SASP dose. If higher dose was not effective after 8 weeks then participant withdrawn from study. . Duration 52 weeks. Concurrent medication/care: NSAID therapy at a dose that was preferable not altered. No systematically administered glucocorticoids permitted. . Indirectness: No indirectness

	Further details: 1. Dose: Higher dose (sulfasalazine: 2 gm, methotrexate: >15 mg, leflunomide: 20mg, hydroxychloroquine: 400mg) 2. Use of glucocorticoids: Short term glucocorticoids used (Systemic glucocorticoid treatment not permirtted but local glucocorticoid treatment permitted). (n=36) Intervention 3: Parallel combination therapy - Parallel combination therapy - specify. Methotrexate (7.5mg per week in 3 2.5mg tablets) and Sulfasalazine (1g per day rising to 2g per day from day 9 in 500mg tablets). After week 16 MTX dose could rise to 15mg per week and SASP dose to 3g per day if efficacy inadequate. Stated to be a step-down-bridge strategy. If higher dose was not effective after 8 weeks then participant withdrawn from study. . Duration 52 weeks. Concurrent medication/care: NSAID therapy at a dose that was preferable not altered. No systematically administered glucocorticoids permitted. . Indirectness: No indirectness Further details: 1. Dose: Higher dose (sulfasalazine: 2 gm, methotrexate: >15 mg, leflunomide: 20mg, hydroxychloroquine: 400mg) 2. Use of glucocorticoids: Short term glucocorticoids used (Systemic glucocorticoid treatment not permirtted but local glucocorticoid treatment permitted).
Funding	Study funded by industry (Study partly financed by Pharmacia AB. Methotrexate tablets and placebo provided by Pharmachemie BV.)

RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: MONOTHERAPY - SULFASALAZINE versus MONOTHERAPY - METHOTREXATE

Protocol outcome 1: Disease Activity Score at 12 months
- Actual outcome: DAS change from baseline at 52 weeks; Group 1: mean -1.8 (SD 1.2); n=22, Group 2: mean -2 (SD 1.03); n=33
Risk of bias: All domain - Very high, Selection - High, Blinding - High, Incomplete outcome data - High, Outcome reporting - Low, Measurement - Low, Crossover - Low, Subgroups - Low; Indirectness of outcome: No indirectness; Baseline details: Similar for age, gender, disease duration, Rh factor, DAS, ESR, HAQ; Group 1 Number missing: 12, Reason: 9 AEs and 3 inefficacy; Group 2 Number missing: 2, Reason: 2 AEs

Protocol outcome 2: Disease Activity Score at 6 months
- Actual outcome: DAS change over first 12 weeks at 12 weeks; Group 1: mean -1.1 (SD 0.48); n=22, Group 2: mean -1 (SD 0.59); n=33
Risk of bias: All domain - Very high, Selection - High, Blinding - High, Incomplete outcome data - High, Outcome reporting - Low, Measurement - Low, Crossover - Low, Subgroups - Low; Indirectness of outcome: No indirectness; Baseline details: Similar for age, gender, disease duration, Rh factor, DAS, ESR, HAQ; Group 1 Number missing: 12, Reason: 9 AEs and 3 inefficay; Group 2 Number missing: 2, Reason: 2 AEs

Protocol outcome 3: Function at 12 months
- Actual outcome: Function (HAQ) score change from baseline at 52 weeks; Group 1: mean -0.32 (SD 0.51); n=22, Group 2: mean -0.46 (SD 0.63); n=33; HAQ 0-3 Top=High is poor outcome
Risk of bias: All domain - Very high, Selection - High, Blinding - High, Incomplete outcome data - High, Outcome reporting - Low, Measurement - Low, Crossover - Low, Subgroups - Low; Indirectness of outcome: No indirectness; Group 1 Number missing: 11, Reason: 9 AEs and 2 inefficacy; Group 2

Number missing: 2, Reason: 2 AEs

Protocol outcome 4: Pain at 12 months
- Actual outcome: Pain (VAS) score change from baseline at 52 weeks; Group 1: mean -25.2 (SD 26.8); n=22, Group 2: mean -25.1 (SD 22.72); n=33; VAS 100mm 0-100 Top=High is poor outcome
Risk of bias: All domain - Very high, Selection - High, Blinding - Low, Incomplete outcome data - High, Outcome reporting - Low, Measurement - Low, Crossover - Low, Subgroups - Low; Indirectness of outcome: No indirectness; Group 1 Number missing: 11, Reason: 9 AEs and 2 inefficay; Group 2 Number missing: 2, Reason: 2 AEs

Protocol outcome 5: Pain at 6 months
- Actual outcome: Pain (VAS) score change over first 12 weeks at 12 weeks; Group 1: mean -18.1 (SD 16.87); n=22, Group 2: mean -12.3 (SD 19.64); n=33; VAS 100mm 0-100 Top=High is poor outcome
Risk of bias: All domain - Very high, Selection - High, Blinding - Low, Incomplete outcome data - High, Outcome reporting - Low, Measurement - Low, Crossover - Low, Subgroups - Low, Comments - ; Indirectness of outcome: No indirectness ; Group 1 Number missing: 11, Reason: 9 AEs and 2 inefficacy; Group 2 Number missing: 2, Reason: 2 AEs

Protocol outcome 6: Withdrawal/discontinuation: adverse events at Longest time period reported
- Actual outcome: Discontinuation due to adverse events at 52 weeks; Group 1: 9/31, Group 2: 2/35
Risk of bias: All domain - Very high, Selection - High, Blinding - Low, Incomplete outcome data - High, Outcome reporting - Low, Measurement - Low, Crossover - Low, Subgroups - Low; Indirectness of outcome: No indirectness; Group 1 Number missing: 11, Reason: 9 AEs and 2 inefficacy; Group 2 Number missing: 2, Reason: 2 AEs

Protocol outcome 7: Withdrawal/discontinuation: inefficacy at Longest time period reported
- Actual outcome: Discontinuation due to inefficacy at 52 weeks; Group 1: 3/25, Group 2: 0/33
Risk of bias: All domain - Very high, Selection - High, Blinding - Low, Incomplete outcome data - High, Outcome reporting - Low, Measurement - Low, Crossover - Low, Subgroups - Low; Indirectness of outcome: No indirectness; Group 1 Number missing: 11, Reason: 9 AEs and 2 inefficacy; Group 2 Number missing: 2, Reason: 2 AEs

RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: MONOTHERAPY - SULFASALAZINE versus PARALLEL COMBINATION THERAPY - METHOTREXATE + SULFASALAZINE

Protocol outcome 1: Disease Activity Score at 12 months
- Actual outcome: DAS change from baseline at 52 weeks; Group 1: mean -1.8 (SD 1.2); n=22, Group 2: mean -2.3 (SD 1.12); n=30; DAS 2-10 Top=High is poor outcome
Risk of bias: All domain - Very high, Selection - High, Blinding - High, Incomplete outcome data - High, Outcome reporting - Low, Measurement - Low, Crossover - Low, Subgroups - Low; Indirectness of outcome: No indirectness; Baseline details: Similar for age, gender, disease duration, Rh factor. Small difference in DAS, HAQ and ESR. ; Group 1 Number missing: 12, Reason: 9 AEs and 3 inefficacy; Group 2 Number missing: 6, Reason: 2 AEs

Protocol outcome 2: Disease Activity Score at 6 months
- Actual outcome: DAS change over first 12 weeks at 12 weeks; Group 1: mean -1.1 (SD 0.48); n=22, Group 2: mean -1.1 (SD 0.56); n=30; DAS 2-10 Top=High is poor outcome
Risk of bias: All domain - Very high, Selection - High, Blinding - High, Incomplete outcome data - High, Outcome reporting - Low, Measurement - Low, Crossover - Low, Subgroups - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: 12, Reason: 9 AEs and 3 inefficacy; Group 2 Number missing: 6, Reason: 2 AEs

Protocol outcome 3: Function at 12 months
- Actual outcome: Function (HAQ) score change from baseline at 52 weeks; Group 1: mean -0.32 (SD 0.51); n=22, Group 2: mean -0.51 (SD 0.7); n=30; HAQ 0-3 Top=High is poor outcome
Risk of bias: All domain - Very high, Selection - High, Blinding - High, Incomplete outcome data - High, Outcome reporting - Low, Measurement - Low, Crossover - Low, Subgroups - Low; Indirectness of outcome: No indirectness; Group 1 Number missing: 11, Reason: 9 AEs and 2 inefficay; Group 2 Number missing: 6, Reason: 5 AEs and 1 inefficacy

Protocol outcome 4: Pain at 12 months
- Actual outcome: Pain (VAS) score change from baseline at 52 weeks; Group 1: mean -25.2 (SD 26.8); n=22, Group 2: mean -25.1 (SD 24.17); n=30; VAS 100mm 0-100 Top=High is poor outcome
Risk of bias: All domain - Very high, Selection - High, Blinding - Low, Incomplete outcome data - High, Outcome reporting - Low, Measurement - Low, Crossover - Low, Subgroups - Low; Indirectness of outcome: No indirectness; Group 1 Number missing: 11, Reason: 9 AEs and 2 inefficacy; Group 2 Number missing: 6, Reason: 5 AEs and 1 inefficacy

Protocol outcome 5: Pain at 6 months
- Actual outcome: Pain (VAS) score change over first 12 weeks at 12 weeks; Group 1: mean -18.1 (SD 16.87); n=22, Group 2: mean -13.1 (SD 20.14); n=30; VAS 100mm 0-100 Top=High is poor outcome
Risk of bias: All domain - Very high, Selection - High, Blinding - Low, Incomplete outcome data - High, Outcome reporting - Low, Measurement - Low, Crossover - Low, Subgroups - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: 11, Reason: 9 AEs and 2 inefficacy; Group 2 Number missing: 6, Reason: 5 AEs and 1 inefficacy

Protocol outcome 6: Withdrawal/discontinuation: adverse events at Longest time period reported
- Actual outcome: Discontinuation due to adverse events at 52 weeks; Group 1: 9/31, Group 2: 5/35
Risk of bias: All domain - Very high, Selection - High, Blinding - Low, Incomplete outcome data - High, Outcome reporting - Low, Measurement - Low, Crossover - Low, Subgroups - Low; Indirectness of outcome: No indirectness; Group 1 Number missing: 11, Reason: 9 AEs and 2 inefficacy; Group 2 Number missing: 6, Reason: 5 AEs and 1 inefficacy

Protocol outcome 7: Withdrawal/discontinuation: inefficacy at Longest time period reported
- Actual outcome: Discontinuation due to inefficacy at 52 weeks; Group 1: 3/25, Group 2: 1/31
Risk of bias: All domain - Very high, Selection - High, Blinding - Low, Incomplete outcome data - High, Outcome reporting - Low, Measurement - Low, Crossover - Low, Subgroups - Low, Comments - ; Indirectness of outcome: No indirectness ; Group 1 Number missing: 11, Reason: 9 AEs and 2

inefficacy; Group 2 Number missing: 6, Reason: 5 AEs and 1 inefficacy

RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: MONOTHERAPY - METHOTREXATE versus PARALLEL COMBINATION THERAPY - METHOTREXATE + SULFASALAZINE

Protocol outcome 1: Disease Activity Score at 12 months
- Actual outcome: DAS change from baseline at 52 weeks; Group 1: mean -2 (SD 1.03); n=33, Group 2: mean -2.3 (SD 1.12); n=30; DAS 2-10 Top=High is poor outcome
Risk of bias: All domain - Very high, Selection - High, Blinding - High, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low, Subgroups - Low; Indirectness of outcome: No indirectness; Group 1 Number missing: 2, Reason: 2 AEs ; Group 2 Number missing: 6, Reason: 5AEs and 1 inefficacy

Protocol outcome 2: Disease Activity Score at 6 months
- Actual outcome: DAS change over first 12 weeks at 12 weeks; Group 1: mean -1 (SD 0.59); n=33, Group 2: mean -1.1 (SD 0.56); n=30
Risk of bias: All domain - Very high, Selection - High, Blinding - High, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low, Subgroups - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: 2, Reason: 2 AEs ; Group 2 Number missing: 6, Reason: 5AEs and 1 inefficacy

Protocol outcome 3: Function at 12 months
- Actual outcome: Function (HAQ) score change from baseline at 52 weeks; Group 1: mean -0.46 (SD 0.63); n=33, Group 2: mean -0.51 (SD 0.7); n=30; HAQ 0-3 Top=High is poor outcome
Risk of bias: All domain - Very high, Selection - High, Blinding - High, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low, Subgroups - Low; Indirectness of outcome: No indirectness; Group 1 Number missing: 2, Reason: 2 AEs; Group 2 Number missing: 6, Reason: 5 AEs and 1 inefficacy

Protocol outcome 4: Pain at 12 months
- Actual outcome: Pain (VAS) score change from baseline at 52 weeks; Group 1: mean -25.1 (SD 22.42); n=33, Group 2: mean -25.1 (SD 24.17); n=30; VAS 100mm 0-100 Top=High is poor outcome
Risk of bias: All domain - High, Selection - High, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low, Subgroups - Low; Indirectness of outcome: No indirectness; Group 1 Number missing: 2, Reason: 2 AEs; Group 2 Number missing: 6, Reason: 5 AEs and 1 inefficacy

Protocol outcome 5: Pain at 6 months
- Actual outcome: Pain (VAS) score change over first 12 weeks at 12 weeks; Group 1: mean -12.3 (SD 19.64); n=33, Group 2: mean -13.1 (SD 20.14); n=30; VAS 100mm 0-100 Top=High is poor outcome
Risk of bias: All domain - High, Selection - High, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low, Subgroups - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: 2, Reason: 2 AEs; Group 2 Number missing: 6, Reason: 5 AEs and 1 inefficacy

Protocol outcome 6: Withdrawal/discontinuation: adverse events at Longest time period reported - Actual outcome: Discontinuation due to adverse events at 52 weeks; Group 1: 2/35, Group 2: 5/35 Risk of bias: All domain - High, Selection - High, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low, Subgroups - Low; Indirectness of outcome: No indirectness; Group 1 Number missing: 2, Reason: 2 AEs; Group 2 Number missing: 6, Reason: 5 AEs and 1 inefficacy Protocol outcome 7: Withdrawal/discontinuation: inefficacy at Longest time period reported - Actual outcome: Discontinuation due to inefficacy at 52 weeks; Group 1: 0/33, Group 2: 1/31 Risk of bias: All domain - High, Selection - High, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low, Subgroups - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: 2, Reason: 2 AEs; Group 2 Number missing: 6, Reason: 5 AEs and 1 inefficacy	
Protocol outcomes not reported by the study	Quality of life at 12 months; Quality of life at 6 months; Function at 6 months; Remission at 6 months; Remission at 12 months; Low disease activity at 6 months; Low disease activity at 12 months; Radiological progression at 12+ months; ACR50 response at 6 months; ACR50 response at 12 months; Adverse events - mortality at 12+ months

Study	Hannonen 1993[57]
Study type	RCT (Patient randomised; Parallel)
Number of studies (number of participants)	1 (n=80)
Countries and setting	Conducted in Sweden; Setting: Single centre
Line of therapy	1st line
Duration of study	Intervention time: 48 weeks
Method of assessment of guideline condition	Adequate method of assessment/diagnosis: ACR criteria for definite RA
Stratum	Overall:
Subgroup analysis within study	Not applicable
Inclusion criteria	Duration of symptomatic disease < 12 months, never treated with DMARDs, stable dose of NSAIDs for at least previous 2 weeks, at least 2 of the following 3 criteria: ESR > 20mm/h, 6+ (of 30) joints with active RA, duration of morning stiffness > 45mins.
Exclusion criteria	Other severe systemic diseases or previous allergic reaction to salicylates or sulfonamides. Originally, intention was to exclude patients with joint erosions, but 30 patients with some minor radiographic changes at baseline were included.
Recruitment/selection of patients	Consecutive patients with RA in the Medical Department of the Jvyaskyla Central Hospital
Age, gender and ethnicity	Age - Mean (range): SSZ - 52.1 (22-78), placebo - 50.5 (23-74). Gender (M:F): 28:50. Ethnicity: NR
Further population details	
Extra comments	Disease duration, months, mean (range): SSZ - 4.7 (2-12), placebo - 5.5 (2-12) RF+: SSZ - 66%, placebo - 68% Functional class I: SSZ - 11%, placebo - 8%; class II: SSZ - 84%, placebo - 93%. . No. of swollen joints, mean (SD): SSZ - 6.8 (3.3), placebo - 5.3 (3.3) Ritchie articular index, mean (SD): SSZ - 10.6 (5.2), placebo - 9.1 (4.2) Patient's global assessment, mean (SD): SSZ - 2.9 (0.8), placebo - 2.8 (0.7) Pain, mm, mean (SD): SSZ - 37 (20), placebo - 33 (18) ESR, mm/h, mean (SD): SSZ - 37.7 (21.3), placebo - 39.0 (18.9) CRP, mg/liter, mean (SD): SSZ - 26.7 (30.3), placebo -23.6 (25.7)
Indirectness of population	No indirectness
Interventions	(n=40) Intervention 1: Monotherapy - Monotherapy - specify. Starting dose of 500mg / day, increased by 500mg each week to total dose of 2g / day. In case of intolerance, the dosage was temporarily decreased. . Duration 48 weeks. Concurrent medication/care: Simultaneous treatment with NSAIDs, low-dose prednisolone (up to 7.5 mg/day) and local injections of glucocorticoids into the joints was permitted.

	Indirectness: No indirectness Further details: 1. Dose: Higher dose (sulfasalazine: 2 gm, methotrexate: >15 mg, leflunomide: 20mg, hydroxychloroquine: 400mg) 2. Use of glucocorticoids: Short term glucocorticoids used (glucocorticoids permitted but not prescribed routinely). (n=40) Intervention 2: Placebo. Identical tablet and dose escalation regime. Duration 48 weeks. Concurrent medication/care: Simultaneous treatment with NSAIDs, low-dose prednisolone (up to 7.5 mg/day) and local injections of glucocorticoids into the joints was permitted. Indirectness: No indirectness Further details: 1. Dose: Not applicable 2. Use of glucocorticoids: Short term glucocorticoids used (As above).
Funding	Study funded by industry ("Supported by Kabi-Pharmacia, Uppsala, Sweden")
RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: MONOTHERAPY - SULFASALAZINE versus PLACEBO Protocol outcome 1: Radiological progression at 12+ months - Actual outcome: Radiographic progression at 44-60 weeks; Group 1: mean 3.5 (SD 10.04); n=36, Risk of bias: All domain - High, Selection - High, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low, Comments - Missing data - patients who withdrew from the study were asked to obtain follow up radiographs at 48 weeks. 1 patient included in analysis was data at 24 weeks due to pregnancy at 48 weeks. ; Indirectness of outcome: No indirectness ; Baseline details: See population panel. Comparable for radiographic damage at baseline (SSZ -1.9, placebo - 2.1) ; Blinding details: Matched placebo. Outcome assessor also blinded. ; Group 1 Number missing: 4, Reason: 1 death, 2 withdrawn for protocol violations, 1 unknown; Group 2 Number missing: 3, Reason: 1 death, 1 lost to follow up, 1 unknown Protocol outcome 2: Adverse events - mortality at 12+ months - Actual outcome: Mortality at 48 weeks; Group 1: 1/38, Group 2: 1/40 Risk of bias: All domain - High, Selection - High, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low, Comments - ; Indirectness of outcome: No indirectness ; Baseline details: See population panel. ; Blinding details: Matched placebo. ; Group 1 Number missing: 2, Reason: 2 withdrawn for protocol violations; Group 2 Number missing: 1, Reason: 1 lost to follow up	
Protocol outcomes not reported by the study	Disease Activity Score at 12 months; Disease Activity Score at 6 months; Quality of life at 12 months; Quality of life at 6 months; Function at 6 months; Function at 12 months; Pain at 6 months; Pain at 12 months; Remission at 6 months; Remission at 12 months; Low disease activity at 6 months; Low disease activity at 12 months; ACR50 response at 6 months; ACR50 response at 12 months; Withdrawal/discontinuation: adverse events at Longest time period reported; Withdrawal/discontinuation: inefficacy at Longest time period reported

Study	Jaimes-Hernandez 2012[67]
Study type	RCT (Patient randomised; Parallel)
Number of studies (number of participants)	1 (n=85)
Countries and setting	Conducted in Mexico
Line of therapy	1st line
Duration of study	Intervention time: 52 weeks
Method of assessment of guideline condition	Adequate method of assessment/diagnosis: 1987 ACR criteria
Stratum	Overall
Subgroup analysis within study	Not applicable
Inclusion criteria	Adults with active RA. Active RA defined as >5 swollen joints and painful joints, morning stiffness for more than 30 minutes, ESR ≥20 mm/h. Any previous treatment with DMARDs was suspended for at least 1 month (3 months for methotrexate or leflunomide) prior to enrollment. Normal count of white blood cells, haemoglobin concentration of > 12g/dl, Albumin levels ≥3.5 g/d, normal liver function test. Negative pregnancy test.
Exclusion criteria	History of high alcohol consumption.
Age, gender and ethnicity	Age - Mean (SD): 42. Gender (M:F): 87% female. Ethnicity: No detailed
Further population details	
Indirectness of population	No indirectness
Interventions	(n=43) Intervention 1: Monotherapy - Monotherapy - specify. Leflunomide (starting at 100mg per day and reduced to 100mg per week after 3 days). Placebo utilised to achieve blinding. Treatment discontinued if participants did not achieve ACR20 improvement by week 16. . Duration 52 weeks. Concurrent medication/care: Use of glucocorticoid treatment allowed though regular dose prednisolone or equivalent not exceeding 10mg daily for the shortest possible time. . Indirectness: No indirectness Further details: 1. Dose: Lower dose (sulfasalazine: 1 gm, methotrexate: <=15mg, leflunomide: 10mg, hydroxychloroquine: 200mg) 2. Use of glucocorticoids: Short term glucocorticoids used (n=42) Intervention 2: Monotherapy - Monotherapy - specify. Methotrexate (10mg per week). Placebo utilised to achieve blinding. Treatment discontinued if participants did not achieve ACR20 improvement by week 16. . Duration 52 weeks. Concurrent medication/care: Use of glucocorticoid treatment allowed though regular dose prednisolone or equivalent not exceeding 10mg daily for the shortest possible time. . Indirectness: No indirectness Further details: 1. Dose: Lower dose (sulfasalazine: 1 gm, methotrexate: <=15mg, leflunomide: 10mg, hydroxychloroquine: 200mg) 2. Use of glucocorticoids: Short term glucocorticoids used

Funding	Other (Study and researchers had "no financial relationship" with the pharmaceutical industry)

RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: MONOTHERAPY - LEFLUNOMIDE versus MONOTHERAPY - METHOTREXATE

Protocol outcome 1: Disease Activity Score at 12 months
- Actual outcome: Change in Disease Activity Score (DAS28) at 52 weeks; Group 1: mean -2.38 (SD 2.5); n=31, Group 2: mean -1.93 (SD 2.5); n=32; DAS28 2-10 Top=High is poor outcome; Comments: Use GIV and mean difference and SE in Revman. SE=0.63
Risk of bias: All domain - High, Selection - Low, Blinding - Low, Incomplete outcome data - High, Outcome reporting - Low, Measurement - Low, Crossover - Low, Subgroups - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: 12, Reason: 4 lost to follow-up, 6 EAs, 2 inefficacy; Group 2 Number missing: 10, Reason: 4 lost to follow-up, 2 EAs, 4 inefficacy

Protocol outcome 2: Function at 12 months
- Actual outcome: Change in function (HAQ-Di) at 52 weeks; Group 1: mean -0.73 (SD 0.58); n=31,
Risk of bias: All domain - High, Selection - Low, Blinding - Low, Incomplete outcome data - High, Outcome reporting - Low, Measurement - Low, Crossover - Low, Subgroups - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: 12, Reason: 4 lost to follow-up, 6 EAs, 2 inefficacy; Group 2 Number missing: 10, Reason: 4 lost to follow-up, 2 EAs, 4 inefficacy

Protocol outcome 3: Remission at 12 months
- Actual outcome: EULAR DAS28 <2.6 points at 52 weeks; Group 1: 11/31, Group 2: 11/32
Risk of bias: All domain - High, Selection - Low, Blinding - Low, Incomplete outcome data - High, Outcome reporting - Low, Measurement - Low, Crossover - Low, Subgroups - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: 12, Reason: 4 lost to follow-up, 6 EAs, 2 inefficacy; Group 2 Number missing: 10, Reason: 4 lost to follow-up, 2 EAs, 4 inefficacy

Protocol outcome 4: Withdrawal/discontinuation: adverse events at Longest time period reported
- Actual outcome: Discontinuation due to adverse events at 52 weeks; Group 1: 6/37, Group 2: 2/34
Risk of bias: All domain - High, Selection - Low, Blinding - Low, Incomplete outcome data - High, Outcome reporting - Low, Measurement - Low, Crossover - Low, Subgroups - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: 6, Reason: 4 lost to follow-up, 2 inefficacy; Group 2 Number missing: 8, Reason: 4 lost to follow-up, 4 inefficacy

Protocol outcome 5: Withdrawal/discontinuation: inefficacy at Longest time period reported
- Actual outcome: Discontinuation due to inefficacy at 52 weeks; Group 1: 2/33, Group 2: 4/36
Risk of bias: All domain - High, Selection - Low, Blinding - Low, Incomplete outcome data - High, Outcome reporting - Low, Measurement - Low, Crossover - Low, Subgroups - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: 10, Reason: 4 lost to follow-up, 6 EAs, ; Group 2 Number missing: 6, Reason: 4 lost to follow-up, 2 EAs,

Protocol outcomes not reported by the study	Disease Activity Score at 6 months; Quality of life at 12 months; Quality of life at 6 months; Function at 6 months; Pain at 6 months; Pain at 12 months; Remission at 6 months; Low disease activity at 6 months; Low disease activity at 12 months; Radiological progression at 12+ months; ACR50 response at 6 months; ACR50 response at 12 months; Adverse events - mortality at 12+ months

Study	Lisbona mp 2012[96]
Study type	RCT (Patient randomised; Parallel)
Number of studies (number of participants)	1 (n=78)
Countries and setting	Conducted in Spain
Line of therapy	1st line
Duration of study	Intervention time: 16 weeks
Method of assessment of guideline condition	Method of assessment /diagnosis not stated: Early RA
Stratum	Overall
Subgroup analysis within study	Not applicable
Inclusion criteria	People with early RA (symptom duration for less than 1 year). No previous DMARD or biologic therapy.
Exclusion criteria	None detailed
Age, gender and ethnicity	Age - Mean (SD): Not detailed. Gender (M:F): Not detailed. Ethnicity: Not detailed
Further population details	
Indirectness of population	No indirectness
Interventions	(n=41) Intervention 1: Monotherapy - Monotherapy - specify. Methotrexate (12.5mg per week rising to 20-25mg per week if symptoms persist. . Duration 16 weeks. Concurrent medication/care: Low dose glucocorticosteroid and NSAID treatment permitted when doses stable during study period. . Indirectness: No indirectness Further details: 1. Dose: Higher dose (sulfasalazine: 2 gm, methotrexate: >15 mg, leflunomide: 20mg, hydroxychloroquine: 400mg) 2. Use of glucocorticoids: Short term glucocorticoids used (n=37) Intervention 2: Monotherapy - Monotherapy - specify. Leflunomide (20mg per day). . Duration 16 weeks. Concurrent medication/care: Low dose glucocorticoid and NSAID treatment permitted when doses stable during study. Indirectness: No indirectness Further details: 1. Dose: Higher dose (sulfasalazine: 2 gm, methotrexate: >15 mg, leflunomide: 20mg, hydroxychloroquine: 400mg) 2. Use of glucocorticoids: Short term glucocorticoids used
Funding	Funding not stated
RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: MONOTHERAPY - METHOTREXATE versus MONOTHERAPY - LEFLUNOMIDE	

Protocol outcome 1: Disease Activity Score at 6 months - Actual outcome: Change in Disease Activity Score (DAS28) at 16 weeks; Group 1: mean -1.46 (SD 1.6); n=33, Group 2: mean -0.87 (SD 1.22); n=29; DAS28 2-10 Top=High is poor outcome Risk of bias: All domain - Very high, Selection - High, Blinding - High, Incomplete outcome data - High, Outcome reporting - Low, Measurement - Low, Crossover - Low, Subgroups - Low; Indirectness of outcome: No indirectness ; Baseline details: Not detailed; Group 1 Number missing: 8, Reason: Moved residence, declined to participate, loss of compliance of treatment, pregnancy desire; Group 2 Number missing: 4, Reason: Move residence, declined to participate, loss of compliance, pregnancy desire Protocol outcome 2: Function at 6 months - Actual outcome: Change in Health Assessment Questionnaire (HAQ) at 16 weeks; Group 1: mean -0.242 (SD 0.543); n=33, Group 2: mean -0.235 (SD 0.374); n=29; HAQ 0-3 Top=High is poor outcome Risk of bias: All domain - Very high, Selection - High, Blinding - High, Incomplete outcome data - High, Outcome reporting - Low, Measurement - Low, Crossover - Low, Subgroups - Low; Indirectness of outcome: No indirectness ; Baseline details: Not detailed; Group 1 Number missing: 8, Reason: Moved residence, declined to participate, loss of compliance of treatment, pregnancy desire; Group 2 Number missing: 4, Reason: Move residence, declined to participate, loss of compliance, pregnancy desire Protocol outcome 3: Pain at 6 months - Actual outcome: Change in VAS pain score at 16 weeks; Group 1: mean -13.2 (SD 18.1); n=33, Group 2: mean -9.6 (SD 20.5); n=29; VAS 0-100 Top=High is poor outcome Risk of bias: All domain - Very high, Selection - High, Blinding - High, Incomplete outcome data - High, Outcome reporting - Low, Measurement - Low, Crossover - Low, Subgroups - Low; Indirectness of outcome: No indirectness ; Baseline details: Not detailed; Group 1 Number missing: 8, Reason: Moved residence, declined to participate, loss of compliance of treatment, pregnancy desire; Group 2 Number missing: 4, Reason: Move residence, declined to participate, loss of compliance, pregnancy desire	
Protocol outcomes not reported by the study	Disease Activity Score at 12 months; Quality of life at 12 months; Quality of life at 6 months; Function at 12 months; Pain at 12 months; Remission at 6 months; Remission at 12 months; Low disease activity at 6 months; Low disease activity at 12 months; Radiological progression at 12+ months; ACR50 response at 6 months; ACR50 response at 12 months; Adverse events - mortality at 12+ months; Withdrawal/discontinuation: adverse events at Longest time period reported; Withdrawal/discontinuation: inefficacy at Longest time period reported

Study (subsidiary papers)	Nuver-zwart 1989[118] (Van der heijde 2000[166], Van der heijde 1989[164], Van der heijde 1990[165], Van der heijde 1990[167])
Study type	RCT (Patient randomised; Parallel)
Number of studies (number of participants)	1 (n=60)
Countries and setting	Conducted in Sweden
Line of therapy	1st line
Duration of study	Intervention time: 48 weeks
Method of assessment of guideline condition	Adequate method of assessment/diagnosis: 1987 ACR criteria
Stratum	Overall
Subgroup analysis within study	Not applicable
Inclusion criteria	People aged 16-75 years old with definite or classical RA. Active disease defined as at least 3 of the following (≥7 painful or tender joints in motion, ≥4 swollen joints, morning stiffness for at least 1 hour, ESR >28mm/1st h, anaemia) not adequately controlled by NSAIDs.
Exclusion criteria	People with serious complicating illnesses or previous reactions to sulphonamides or salicylates. People with a desire for children and previous treatment with second line medication.
Recruitment/selection of patients	From 5 participating clinics.
Age, gender and ethnicity	Age - Mean (SD): 53. Gender (M:F): 38 female, 22 male. Ethnicity: Not detailed
Further population details	
Indirectness of population	No indirectness
Interventions	(n=30) Intervention 1: Monotherapy - Monotherapy - specify. Hydroxychloroquine (200mg twice per day for 6 months and then 200mg once per day). Double dummy technique to ensure blinding. . Duration 48 weeks. Concurrent medication/care: glucocorticoid treatment not permitted 3 months previous to trial or during the trial. NSAID dose kept stable throughout the study. . Indirectness: No indirectness Further details: 1. Dose: Higher dose (sulfasalazine: 2 gm, methotrexate: >15 mg, leflunomide: 20mg, hydroxychloroquine: 400mg) 2. Use of glucocorticoids: Short term glucocorticoids not used (n=30) Intervention 2: Monotherapy - Monotherapy - specify. Sulfasalazine (500mg per day increased to 2g per day after 2 weeks). Double dummy technique to ensure blinding. . Duration 48 weeks. Concurrent medication/care: glucocorticoid treatment not permitted 3 months previous to trial or during the trial. NSAID dose kept stable throughout the study. . Indirectness: No indirectness Further details: 1. Dose: Higher dose (sulfasalazine: 2 gm, methotrexate: >15 mg, leflunomide: 20mg, hydroxychloroquine: 400mg) 2. Use of glucocorticoids: Short term glucocorticoids not used

Funding	Study funded by industry (Supported by a grant from Pharmacia Sweden)

RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: MONOTHERAPY - HYDROXYCHLOROQUINE versus MONOTHERAPY - SULFASALAZINE

Protocol outcome 1: Pain at 12 months
- Actual outcome: Pain (VAS) at 48 weeks; Group 1: mean 33 (SD 23.4); n=29, Group 2: mean 32.8 (SD 28); n=28; VAS 0-100 Top=High is poor outcome
Risk of bias: All domain - High, Selection - High, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low, Subgroups - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: 1; Group 2 Number missing: 2

Protocol outcome 2: Pain at 6 months
- Actual outcome: Pain (VAS) at 24 weeks; Group 1: mean 25.2 (SD 19.8); n=29, Group 2: mean 31.6 (SD 25.9); n=28; VAS 0-100 Top=High is poor outcome
Risk of bias: All domain - High, Selection - High, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low, Subgroups - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: 1; Group 2 Number missing: 2

Protocol outcome 3: Radiological progression at 12+ months
- Actual outcome: Change in radiological progressions (SvdH score) at 48 weeks; Group 1: mean 17.3 (SD 22.67); n=29,
Risk of bias: All domain - High, Selection - High, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low, Subgroups - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: 1; Group 2 Number missing: 2

Protocol outcome 4: Withdrawal/discontinuation: adverse events at Longest time period reported
- Actual outcome: Discontinuation due to adverse events at 48 weeks; Group 1: 1/19, Group 2: 4/25
Risk of bias: All domain - Very high, Selection - High, Blinding - Low, Incomplete outcome data - High, Outcome reporting - Low, Measurement - Low, Crossover - Low, Subgroups - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: 11; Group 2 Number missing: 5

Protocol outcome 5: Withdrawal/discontinuation: inefficacy at Longest time period reported
- Actual outcome: Discontinuation due to inefficacy at 48 weeks; Group 1: 9/27, Group 2: 3/24
Risk of bias: All domain - High, Selection - High, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low, Subgroups - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: 3; Group 2 Number missing: 6

Protocol outcomes not reported by the study	Disease Activity Score at 12 months; Disease Activity Score at 6 months; Quality of life at 12 months; Quality of life at 6 months; Function at 12 months; Function at 6 months; Remission at 12 months; Remission at 6 months; Low disease activity at 12 months; Low disease activity at 6 months; ACR50 response at 6 months; ACR50 response at 12 months; Adverse events - mortality at 12+ months

Study	Saunders 2008[137]
Study type	RCT (Patient randomised; Parallel)
Number of studies (number of participants)	1 (n=96)
Countries and setting	Conducted in United Kingdom; Setting: 3 NHS teaching hospitals in Glasgow, Scotland.
Line of therapy	1st line
Duration of study	Intervention time: 1 year
Method of assessment of guideline condition	Unclear method of assessment/diagnosis: Unclear of criteria for diagnosis
Stratum	Overall
Subgroup analysis within study	Not applicable
Inclusion criteria	People 18 to 80 years old with active RA as defined by DAS28 >5.1. Disease duration <5 years. No previous DMARD treatment except for hydroxychloroquine.
Exclusion criteria	Concurrent liver, renal, hematologic, severe respiratory disease. People who are pregnant or unwilling to use effective contraception.
Recruitment/selection of patients	Recruited from February 2003 to March 2005.
Age, gender and ethnicity	Age - Mean (SD): 55. Gender (M:F): 77% female. Ethnicity: Not detailed
Further population details	
Indirectness of population	No indirectness
Interventions	(n=49) Intervention 1: Parallel combination therapy - Parallel combination therapy - specify. Triple therapy: methotrexate (7.5mg per week), sulfasalazine (1g per day), hydroxychloroquine (200mg per day). If DAS28 ≥3.2 then sequential dose rises: MTX increased up to 25mg per week, next SSZ increased to 40mg/kg per day, then HCQ increased to 400mg per day. . Duration 1 year. Concurrent medication/care: IA glucocorticoid injections permitted. 5mg per week folic acid when using MTX. . Indirectness: No indirectness Further details: 1. Dose: Higher dose (sulfasalazine: 2 gm, methotrexate: >15 mg, leflunomide: 20mg, hydroxychloroquine: 400mg) 2. Use of glucocorticoids: Short term glucocorticoids used (n=47) Intervention 2: Step up therapy - Step up therapy - specify. Sulfasalazine (40mg/kg per day). After 3 months of DAS28 ≥3.2 methotrexate (7.5mg per week increased to maximum 25mg per week if required). If disease activity persistent then hydroxychloroquine (400mg per day) added. . Duration 1 year. Concurrent medication/care: IA glucocorticoid injections permitted. 5mg per week folic acid when using MTX. . Indirectness: No indirectness Further details: 1. Dose: Higher dose (sulfasalazine: 2 gm, methotrexate: >15 mg, leflunomide: 20mg, hydroxychloroquine: 400mg) 2. Use of glucocorticoids: Short term glucocorticoids used

Funding	Other (Dr Saunders received speaking fees from Wyeth, Merck, Dohme. Dr Porter received speaking and consulting fees from Abbott, Roche, Bristol-Myers Squibb and consulting fees from Wyeth.)

RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: STEP UP THERAPY - SULFASALAZINE + METHOTREXATE + HYDROXYCHLOROQUINE versus PARALLEL COMBINATION THERAPY - METHOTREXATE + SULFSALAZINE + HYDROXYCHLOROQUINE

Protocol outcome 1: Disease Activity Score at 12 months
- Actual outcome: Change in Disease Activity Score (DAS28) at 12 months; Group 1: mean -4 (SD 1.8); n=44, Group 2: mean -3.3 (SD 1.6); n=47; DAS28 2-10 Top=High is poor outcome
Risk of bias: All domain - High, Selection - Low, Blinding - High, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low, Subgroups - Low; Indirectness of outcome: No indirectness ; Blinding details: High due to participant influence on DAS28 and not blinded; Group 1 Number missing: 3; Group 2 Number missing: 2

Protocol outcome 2: Quality of life at 12 months
- Actual outcome: Change in health related quality of life (SF-36) at 12 months; Group 1: mean 10 (SD 11); n=44, Group 2: mean 9 (SD 13); n=47; SF-36 0-100 Top=High is good outcome
Risk of bias: All domain - High, Selection - Low, Blinding - High, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low, Subgroups - Low; Indirectness of outcome: No indirectness ; Blinding details: High due to participant influence and not blinded; Group 1 Number missing: 3; Group 2 Number missing: 2

Protocol outcome 3: Function at 12 months
- Actual outcome: Change in function (HAQ) at 12 months; Group 1: mean -0.9 (SD 0.7); n=44, Group 2: mean -0.8 (SD 0.7); n=47; HAQ 0-3 Top=High is poor outcome
Risk of bias: All domain - High, Selection - Low, Blinding - High, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low, Subgroups - Low; Indirectness of outcome: No indirectness ; Blinding details: High due to participant influence and not blinded; Group 1 Number missing: 3; Group 2 Number missing: 2

Protocol outcome 4: Pain at 12 months
- Actual outcome: Change in pain score (VAS) at 12 months; Group 1: mean -42 (SD 32); n=44, Group 2: mean -43 (SD 34); n=47; VAS 0-100 Top=High is poor outcome
Risk of bias: All domain - High, Selection - Low, Blinding - High, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low, Subgroups - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: 3; Group 2 Number missing: 2

Protocol outcome 5: Remission at 12 months
- Actual outcome: EULAR remission (DAS28 <2.6) at 12 months; Group 1: 21/47, Group 2: 16/49
Risk of bias: All domain - High, Selection - Low, Blinding - High, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low, Subgroups - Low; Indirectness of outcome: No indirectness ; Blinding details: High due to participant influence on DAS28 and not

blinded; Group 1 Number missing: ; Group 2 Number missing: Protocol outcome 6: Low disease activity at 12 months - Actual outcome: EULAR good response (DAS28 <3.2) at 12 months; Group 1: 28/47, Group 2: 20/49 Risk of bias: All domain - High, Selection - Low, Blinding - High, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low, Subgroups - Low; Indirectness of outcome: No indirectness ; Blinding details: High due to participant influence on DAS28 and not blinded; Group 1 Number missing: ; Group 2 Number missing: Protocol outcome 7: Radiological progression at 12+ months - Actual outcome: Change in radiographic progression (Sharp score) at 12 months; Group 1: mean 6 (SD 5.3); n=44, Risk of bias: All domain - Low, Selection - Low, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low, Subgroups - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: 3; Group 2 Number missing: 2 Protocol outcome 8: ACR50 response at 12 months - Actual outcome: ACR50 response at 12 months; Group 1: 28/47, Group 2: 25/49 Risk of bias: All domain - High, Selection - Low, Blinding - High, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low, Subgroups - Low; Indirectness of outcome: No indirectness ; Blinding details: High due to participant influence and not blinded; Group 1 Number missing: ; Group 2 Number missing:	
Protocol outcomes not reported by the study	Disease Activity Score at 6 months; Quality of life at 6 months; Function at 6 months; Pain at 6 months; Remission at 6 months; Low disease activity at 6 months; ACR50 response at 6 months; Adverse events - mortality at 12+ months; Withdrawal/discontinuation: adverse events at Longest time period reported; Withdrawal/discontinuation: inefficacy at Longest time period reported

Study	Tascioglu 2003[152]
Study type	RCT (Patient randomised; Parallel)
Number of studies (number of participants)	1 (n=70)
Countries and setting	Conducted in Turkey
Line of therapy	1st line
Duration of study	Intervention time: 52 weeks
Method of assessment of guideline condition	Adequate method of assessment/diagnosis: 1987 ACR criteria
Stratum	Overall
Subgroup analysis within study	Not applicable
Inclusion criteria	People ≥18 years old with active RA with disease duration for less than 1 year. Active was defined as at least 3 of the following criteria: >6 swollen joints, >9 tender joints, ESR >20 mm/hr in men or >30 mm/hr in women, morning stiffness ≥1 hour.
Exclusion criteria	Previous medication treatment for RA other than analgesics or NSAIDs. Hepatic, renal, hematologic, pulmonary, cardiovascular disease. Malignancy, peptic ulcers, presence of chronic infection, history of allergy to study medication, pregnancy or breast feeding. White blood cell count <3000 mm³ or polymorphonuclear count <1500 mm³ or platelet count <100000 mm³. Liver enzyme levels at least twice the limit of normal.
Recruitment/selection of patients	Not detailed
Age, gender and ethnicity	Age - Mean (SD): 46. Gender (M:F): 9 / 46 for participants completing the study. Ethnicity: Not detailed
Further population details	
Indirectness of population	No indirectness
Interventions	(n=35) Intervention 1: Monotherapy - Monotherapy - specify. Open label methotrexate. 7.5mg per week in three tablets taken as a single dose. Participants excluded from the study if treatment not effective after 12 weeks or if serious adverse events occurred. . Duration 52 weeks. Concurrent medication/care: NSAID usage not altered during study. Analgesic treatment permitted. No systemic or intraarticular corticosteroid use permitted. . Indirectness: No indirectness Further details: 1. Dose: Lower dose (sulfasalazine: 1 gm, methotrexate: <=15mg, leflunomide: 10mg, hydroxychloroquine: 200mg) 2. Use of steroids: Short term steroids not used (n=35) Intervention 2: Parallel combination therapy - Parallel combination therapy - specify. Open label methotrexate (MTS) and sulfasalazine (SSZ). MTX: 7.5mg per week in three tablets taken as a single dose. SSZ: 1g daily rising to 2g daily from week 2. Participants excluded from the study if treatment not effective

	after 12 weeks or if serious adverse events occurred. . Duration 52 weeks. Concurrent medication/care: NSAID usage not altered during study. Analgesic treatment permitted. No systemic or intraarticular corticosteroid use permitted. . Indirectness: No indirectness Further details: 1. Dose: Not applicable (Dose levels differ between treatments). 2. Use of steroids: Short term steroids not used
Funding	Funding not stated

RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: MONOTHERAPY - METHOTREXATE versus PARALLEL COMBINATION THERAPY - METHOTREXATE + SULFASALAZINE

Protocol outcome 1: Function at 6 months
- Actual outcome: Function (HAQ) score at 6 months; Group 1: mean 0.91 (SD 0.02); n=28, Group 2: mean 1.05 (SD 0.03); n=27; Health Assessment Questionnaire (HAQ) 0-3 Top=High is poor outcome
Risk of bias: All domain - Very high, Selection - High, Blinding - High, Incomplete outcome data - High, Outcome reporting - High, Measurement - Low, Crossover - Low, Subgroups - Low; Indirectness of outcome: No indirectness ; Baseline details: HAQ 0.14 better in MTX+SSZ group at baseline. ; Group 1 Number missing: 7, Reason: Unclear exactly how many. Fewer than 8. ; Group 2 Number missing: 8, Reason: Unclear exactly how many. Fewer than 9.

Protocol outcome 2: Function at 12 months
- Actual outcome: Function (HAQ) score at 12 months; Group 1: mean 0.89 (SD 0.02); n=28, Group 2: mean 0.99 (SD 0.02); n=27; Health Assessment Questionnaire 0-3 Top=High is poor outcome
Risk of bias: All domain - Very high, Selection - High, Blinding - High, Incomplete outcome data - High, Outcome reporting - High, Measurement - Low, Crossover - Low, Subgroups - Low; Indirectness of outcome: No indirectness ; Baseline details: HAQ 0.14 better in MTX+SSZ group at baseline. ; Group 1 Number missing: 7, Reason: 3 withdrawn due to inefficacy, 2 withdrew due to adverse events, 2 lost to follow up; Group 2 Number missing: 8, Reason: 2 withdrawn due to inefficacy, 3 withdrew due to adverse events, 3 lost to follow up

Protocol outcome 3: Pain at 12 months
- Actual outcome: Pain (VAS) at 12 months; Group 1: mean 24.64 (SD 7.85); n=28, Group 2: mean 28 (SD 5.89); n=27; visual analogue scale 0-100 Top=High is poor outcome
Risk of bias: All domain - Very high, Selection - High, Blinding - High, Incomplete outcome data - High, Outcome reporting - Low, Measurement - Low, Crossover - Low, Subgroups - Low; Indirectness of outcome: No indirectness ; Baseline details: HAQ 0.14 better in MTX+SSZ group at baseline. ; Group 1 Number missing: 7, Reason: 3 withdrawn due to inefficacy, 2 withdrew due to adverse events, 2 lost to follow up; Group 2 Number missing: 8, Reason: 2 withdrawn due to inefficacy, 3 withdrew due to adverse events, 3 lost to follow up

Protocol outcome 4: Pain at 6 months
- Actual outcome: Pain (VAS) at 6 months; Group 1: mean 29.32 (SD 8.32); n=28, Group 2: mean 27.79 (SD 8.69); n=27; visual analogue scale 0-100 Top=High is poor outcome
Risk of bias: All domain - Very high, Selection - High, Blinding - High, Incomplete outcome data - High, Outcome reporting - Low, Measurement - Low,

Crossover - Low, Subgroups - Low; Indirectness of outcome: No indirectness ; Baseline details: HAQ 0.14 better in MTX+SSZ group at baseline. ; Group 1 Number missing: 7, Reason: Unclear exactly how many. Fewer than 8. ; Group 2 Number missing: 8, Reason: Unclear exactly how many. Fewer than 9. Protocol outcome 5: Withdrawal/discontinuation: adverse events at Longest time period reported - Actual outcome: Discontinuation due to adverse events at 12 months; Group 1: 2/30, Group 2: 3/30 Risk of bias: All domain - Very high, Selection - High, Blinding - Low, Incomplete outcome data - High, Outcome reporting - Low, Measurement - Low, Crossover - Low, Subgroups - Low; Indirectness of outcome: No indirectness ; Baseline details: HAQ 0.14 better in MTX+SSZ group at baseline. ; Group 1 Number missing: 5, Reason: 3 withdrawn due to inefficacy, 2 lost to follow up; Group 2 Number missing: 5, Reason: 2 withdrawn due to inefficacy, 3 lost to follow up Protocol outcome 6: Withdrawal/discontinuation: inefficacy at Longest time period reported - Actual outcome: Discontinuation due to inefficacy at 12 months; Group 1: 3/31, Group 2: 2/30 Risk of bias: All domain - Very high, Selection - High, Blinding - Low, Incomplete outcome data - High, Outcome reporting - Low, Measurement - Low, Crossover - Low, Subgroups - Low; Indirectness of outcome: No indirectness ; Baseline details: HAQ 0.14 better in MTX+SSZ group at baseline. ; Group 1 Number missing: 4, Reason: 2 withdrew due to adverse events, 2 lost to follow up; Group 2 Number missing: 6, Reason: 3 withdrew due to adverse events, 3 lost to follow up	
Protocol outcomes not reported by the study	Disease Activity Score at 12 months; Disease Activity Score at 6 months; Quality of life at 12 months; Quality of life at 6 months; Remission at 6 months; Remission at 12 months; Low disease activity at 6 months; Low disease activity at 12 months; Radiological progression at 12+ months; ACR50 response at 6 months; ACR50 response at 12 months; Adverse events - mortality at 12+ months

Study (subsidiary papers)	tREACH trial: De jong 2013[28] (De rotte 2014[29], Kuijper 2016[83])
Study type	RCT (Patient randomised; Parallel)
Number of studies (number of participants)	1 (n=281)
Countries and setting	Conducted in Netherlands; Setting: 8 rheumatology centres.
Line of therapy	1st line
Duration of study	Intervention + follow up: 2 years
Method of assessment of guideline condition	Adequate method of assessment/diagnosis: 1987 ACR criteria depending on outcome
Stratum	Overall
Subgroup analysis within study	Not applicable
Inclusion criteria	Overall trial population was adults with arthritis of 1 or more joints for less than 1 year. Results extracted for those with RA via 1987 ACR criteria.
Exclusion criteria	Diagnosed with a crystal arthropathy, (post)infectious arthritis, autoimmune disorder other than RA. Receiving DMARD therapy or glucocorticoids within pervious 3 months. Contraindications for study medication (chronic liver disease, excessive alcohol and drug use, pregnancy, laboratory abnormalities.
Age, gender and ethnicity	Age - Mean (SD): 54. Gender (M:F): 63% female. Ethnicity: Not detailed
Further population details	
Indirectness of population	No indirectness
Interventions	(n=69) Intervention 1: Parallel combination therapy - Parallel combination therapy - specify. Methotrexate (25mg per week), Sulfasalazine (2g per day), Hydroxychloroquine (400mg per day). Intramuscular glucocorticoid treatment with 120mg methylprednisolone or 80mg triamcinolone. . Duration 3 months. Concurrent medication/care: Concurrent treatment with NSAIDs permitted. IA glucocorticoid injections permitted twice per 3 months. 10mg folic acid per week. . Indirectness: No indirectness Further details: 1. Dose: Higher dose (sulfasalazine: 2 gm, methotrexate: >15 mg, leflunomide: 20mg, hydroxychloroquine: 400mg) 2. Use of glucocorticoids: Short term glucocorticoids used (n=57) Intervention 2: Parallel combination therapy - Parallel combination therapy - specify. Methotrexate (25mg per week), Sulfasalazine (2g per day), Hydroxychloroquine (400mg per day). Oral tapering scheme for glucocorticoid treatment beginning at 15mg per day and tapering to 2.5mg per day by week 10.. Duration 3 months. Concurrent medication/care: Concurrent treatment with NSAIDs permitted. IA glucocorticoid injections permitted twice per 3 months. 10mg folic acid per week.. Indirectness: No indirectness Further details: 1. Dose: Higher dose (sulfasalazine: 2 gm, methotrexate: >15 mg, leflunomide: 20mg, hydroxychloroquine: 400mg) 2. Use of glucocorticoids: Short term glucocorticoids used

	(n=63) Intervention 3: Monotherapy - Monotherapy - specify. Methotrexate (25mg per week). Oral tapering scheme for glucocorticoid treatment beginning at 15mg per day and tapering to 2.5mg per day by week 10.. Duration 3 months. Concurrent medication/care: Concurrent treatment with NSAIDs permitted. IA glucocorticoid injections permitted twice per 3 months. 10mg folic acid per week.. Indirectness: No indirectness Further details: 1. Dose: Higher dose (sulfasalazine: 2 gm, methotrexate: >15 mg, leflunomide: 20mg, hydroxychloroquine: 400mg) 2. Use of glucocorticoids: Short term glucocorticoids used
Funding	Study funded by industry (Funded by an unrestricted grant from Wyeth Pharmaceuticals)

RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: PARALLEL COMBINATION THERAPY - METHOTREXATE + SULFASALAZINE + HYDROXYCHLOROQUINE versus MONOTHERAPY - METHOTREXATE

Protocol outcome 1: Disease Activity Score at 6 months
- Actual outcome: Change in DAS at 3 months; Group 1: mean -1.55 (SD 0.9); n=65, Group 2: mean -1.41 (SD 1); n=59
Risk of bias: All domain - High, Selection - Low, Blinding - High, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low, Subgroups - Low; Indirectness of outcome: No indirectness ; Baseline details: Higher erosion number in treatment group. Higher CR in comparator group. ; Group 1 Number missing: 4; Group 2 Number missing: 8

Protocol outcome 2: Function at 6 months
- Actual outcome: Change in function (HAQ) at 3 months; Group 1: mean -0.47 (SD 0.54); n=54, Group 2: mean -0.42 (SD 0.52); n=52; HAQ 0-3 Top=High is poor outcome
Risk of bias: All domain - Very high, Selection - Low, Blinding - High, Incomplete outcome data - High, Outcome reporting - Low, Measurement - Low, Crossover - Low, Subgroups - Low; Indirectness of outcome: No indirectness ; Baseline details: Higher erosion number in treatment group. Higher CR in comparator group. ; Group 1 Number missing: 15; Group 2 Number missing: 11

Protocol outcome 3: Pain at 6 months
- Actual outcome: Median pain (VAS) at 3 months;
Risk of bias: All domain - High, Selection - Low, Blinding - High, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low, Subgroups - Low; Indirectness of outcome: No indirectness ; Baseline details: Higher erosion number in treatment group. Higher CR in comparator group. ; Group 1 Number missing: 4; Group 2 Number missing: 4

Protocol outcome 4: Remission at 6 months
- Actual outcome: Remission (DAS<1.6) at 3 months; Group 1: 28/65, Group 2: 19/59
Risk of bias: All domain - High, Selection - Low, Blinding - High, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low, Subgroups - Low; Indirectness of outcome: No indirectness ; Baseline details: Higher erosion number in treatment group. Higher CR in comparator group. ; Group 1 Number missing: 4; Group 2 Number missing: 4

RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: PARALLEL COMBINATION THERAPY - METHOTREXATE + SULFASALAZINE + HYDROXYCHLOROQUINE versus MONOTHERAPY - METHOTREXATE Protocol outcome 1: Disease Activity Score at 6 months - Actual outcome: Change in DAS at 3 months; Group 1: mean -1.77 (SD 1.04); n=55, Group 2: mean -1.41 (SD 1); n=59 Risk of bias: All domain - High, Selection - Low, Blinding - High, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low, Subgroups - Low; Indirectness of outcome: No indirectness ; Baseline details: Higher CR in comparator group. ; Group 1 Number missing: 4; Group 2 Number missing: 4 Protocol outcome 2: Function at 6 months - Actual outcome: Change in function (HAQ) at 3 months; Group 1: mean -0.47 (SD 0.55); n=47, Group 2: mean -0.42 (SD 0.52); n=52; HAQ 0-3 Top=High is poor outcome Risk of bias: All domain - Very high, Selection - Low, Blinding - High, Incomplete outcome data - High, Outcome reporting - Low, Measurement - Low, Crossover - Low, Subgroups - Low; Indirectness of outcome: No indirectness ; Baseline details: Higher CR in comparator group. ; Group 1 Number missing: 10; Group 2 Number missing: 11 Protocol outcome 3: Pain at 6 months - Actual outcome: Median pain (VAS) at 3 months; Risk of bias: All domain - High, Selection - Low, Blinding - High, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low, Subgroups - Low; Indirectness of outcome: No indirectness ; Baseline details: Higher CR in comparator group. ; Group 1 Number missing: 4; Group 2 Number missing: 4 Protocol outcome 4: Remission at 6 months - Actual outcome: Remission (DAS<1.6) at 3 months; Group 1: 24/55, Group 2: 19/59 Risk of bias: All domain - High, Selection - Low, Blinding - High, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low, Subgroups - Low; Indirectness of outcome: No indirectness ; Baseline details: Higher CR in comparator group. ; Group 1 Number missing: 4; Group 2 Number missing: 4	
Protocol outcomes not reported by the study	Disease Activity Score at 12 months; Quality of life at 12 months; Quality of life at 6 months; Function at 12 months; Pain at 12 months; Remission at 12 months; Low disease activity at 6 months; Low disease activity at 12 months; Radiological progression at 12+ months; ACR50 response at 6 months; ACR50 response at 12 months; Adverse events - mortality at 12+ months; Withdrawal/discontinuation: adverse events at Longest time period reported; Withdrawal/discontinuation: inefficacy at Longest time period reported

Study (subsidiary papers)	Van jaarsveld 2000[171] (Van jaarsveld 20001[72], Verstappen 2003[181])
Study type	RCT (Patient randomised; Parallel)
Number of studies (number of participants)	1 (n=231)
Countries and setting	Conducted in Netherlands; Setting: Six rheumatological centres in Utrecht (1 university hospital and 5 general hospitals)
Line of therapy	1st line
Duration of study	Intervention time: 2 years
Method of assessment of guideline condition	Adequate method of assessment/diagnosis: ARA 1987 revised criteria
Stratum	Overall
Subgroup analysis within study	Not applicable:
Inclusion criteria	Disease duration < 1 year
Exclusion criteria	age , 17 years; comorbid conditions that might interfere with one of the therapeutic strategies (such as malignancy, cardiac, respiratory, hepatic, and renal insufficiency); previous or current treatment with SAARDs, glucocorticoids, cytotoxic or immunosuppressive drugs; possible pregnancy or breastfeeding; psychiatric or mental disturbances that make adherence to study protocol unlikely.
Recruitment/selection of patients	Since 1990 all patients with RA from the six centres were asked to participate
Age, gender and ethnicity	Age - Other: Mean (10-90 centiles): HCQ - 56 (37-74), MTX - 57 (37-73). Gender (M:F): 90:141. Ethnicity: NR
Further population details	
Extra comments	RF+: HCQ - 67%, MTX - 65% HAQ, mean (10-90 centiles): HCQ - 1.4 (0.5-2.5), MTX - 1.3 (0.3-2.4) Pain, mm, mean (10-90 centiles): HCQ - 46 (9-86), MTX - 44 (9-92) Radiological damage (0-448), mean (10-90 centiles): HCQ - 2 (0-12), MTX - 2 (0-13) .
Indirectness of population	No indirectness
Interventions	(n=118) Intervention 1: Monotherapy - Monotherapy - specify. 400mg/day, with dose adjustment due to adverse reactions. Replacement with auranofin (6-9mg/day) if adverse reaction made discontinuation inevitable in the view of the attending doctor. If the patient fulfilled the remission criteria at three subsequent visits (6 months), the dosage was halved. . Duration 1 year. Concurrent medication/care: Use of NSAIDs and analgesics was allowed. Oral and IA injections of glucocorticoids were avoided. . Indirectness: Serious indirectness; Indirectness comment: Replacement with out of scope drug in case of adverse reaction Further details: 1. Dose: Higher dose (sulfasalazine: 2 gm, methotrexate: >15 mg, leflunomide: 20mg,

	hydroxychloroquine: 400mg) 2. Use of glucocorticoids: Short term glucocorticoids not used (As above). Comments: After 1 year, patients without improvement of at least 50% had HCQ replaced by auranofin. For that reason, only data up to 1 year has been included in this review. (n=113) Intervention 2: Monotherapy - Monotherapy - specify. 7.5-15mg/weekly. Replacement with SSZ (2-3g/day) if adverse reaction made discontinuation inevitable in the view of the attending doctor. If the patient fulfilled the remission criteria at three subsequent visits (6 months), the dosage was halved. . Duration 1 year. Concurrent medication/care: Use of NSAIDs and analgesics was allowed. Oral and IA injections of glucocorticoids were avoided. . Indirectness: No indirectness Further details: 1. Dose: Lower dose (sulfasalazine: 1 gm, methotrexate: <=15mg, leflunomide: 10mg, hydroxychloroquine: 200mg) 2. Use of glucocorticoids: Short term glucocorticoids not used (See above). Comments: After 1 year, patients without improvement of at least 50% had MTX replaced by SSZ. In the comparator arm, an out of scope drug was used after 1 year for patients with inadequate response. For that reason, only data up to 1 year has been included in this review.
Funding	Academic or government funding ("Grant support: The Dutch League against Rheumatism")

RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: MONOTHERAPY - HCQ versus MONOTHERAPY - MTX

Protocol outcome 1: Function at 12 months
- Actual outcome: Function (HAQ) at 12 months; Group 1: mean -0.3 (SD 0.79); n=107, Group 2: mean -0.4 (SD 0.52); n=105; Health Assessment Questionnaire 0-3 Top=High is poor outcome
Risk of bias: All domain - Very high, Selection - High, Blinding - High, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low, Comments - ITT used for patients who discontinued strategy, patients lost to follow up excluded from analysis. ; Indirectness of outcome: No indirectness ; Baseline details: Difference in outcome of 0.1 at baseline same magnitude as difference at follow up; Blinding details: Open label trial; Group 1 Number missing: 23, Reason: 11 lost to follow up and excluded from analysis (reasons overall only), 12 discontinued strategy due to ineffectiveness (treatment not in accordance with protocol); Group 2 Number missing: 19, Reason: 8 lost to follow up and excluded from analysis (reasons overall only), 11 discontinued strategy (4 for ineffectiveness, 4 for adverse reaction, 1 for both, 2 other) (treatment not in accordance with protocol)

Protocol outcome 2: Pain at 12 months
- Actual outcome: Pain (VAS) at 12 months; Group 1: mean -21 (SD 32); n=107, Group 2: mean -24 (SD 26); n=105; Visual Analogue Scale 0-100 Top=High is poor outcome
Risk of bias: All domain - Very high, Selection - High, Blinding - High, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low, Comments - ITT used for patients who discontinued strategy, patients lost to follow up excluded from analysis. ; Indirectness of outcome: No indirectness ; Baseline details: Difference in outcome of 2 at baseline less than magnitude of difference at follow up (3); Blinding details: Open label trial; Group 1 Number missing: 23, Reason: 11 lost to follow up and excluded from analysis (reasons overall only), 12 discontinued strategy (treatment not in accordance with protocol); Group 2 Number missing: 19, Reason: 8 lost to follow up and excluded from analysis (reasons overall only), 11 discontinued strategy (4 for ineffectiveness, 4 for adverse reaction, 1 for both, 2 other) (treatment not in accordance with protocol)

Protocol outcome 3: Remission at 12 months
- Actual outcome: ACR remission at 12 months; Group 1: 17/107, Group 2: 25/105; Comments: Remission defined as: morning stiffness ≤ 15 mins, pain score ≤ 10 mm, joint score ≤ 1, ESR ≤ 30mm/h
Risk of bias: All domain - Very high, Selection - High, Blinding - High, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low, Comments - ITT used for patients who discontinued strategy, patients lost to follow up excluded from analysis. ; Indirectness of outcome: Serious indirectness, Comments: Does not use DAS or similar score; Baseline details: See pop panel; Blinding details: Open label trial; Group 1 Number missing: 23, Reason: 11 lost to follow up and excluded from analysis (reasons overall only), 12 discontinued strategy due to ineffectiveness (treatment not in accordance with protocol); Group 2 Number missing: 19, Reason: 8 lost to follow up and excluded from analysis (reasons overall only), 11 discontinued strategy (4 for ineffectiveness, 4 for adverse reaction, 1 for both, 2 other) (treatment not in accordance with protocol)

Protocol outcome 4: Withdrawal/discontinuation: adverse events at Longest time period reported
- Actual outcome: Discontinuation of strategy: adverse events at 12 months; Group 1: 0/107, Group 2: 5/105
Risk of bias: All domain - Very high, Selection - High, Blinding - High, Incomplete outcome data - High, Outcome reporting - Low, Measurement - Low, Crossover - Low, Comments - ITT used for patients who discontinued strategy, patients lost to follow up excluded from analysis. ; Indirectness of outcome: No indirectness; Baseline details: See pop panel; Blinding details: Open label trial; Group 1 Number missing: 23, Reason: 11 lost to follow up and excluded from analysis (reasons overall only), 12 discontinued strategy due to ineffectiveness (treatment not in accordance with protocol); Group 2 Number missing: 14, Reason: 8 lost to follow up and excluded from analysis (reasons overall only), 6 discontinued strategy (4 for ineffectiveness, 2 other) (treatment not in accordance with protocol)

Protocol outcome 5: Withdrawal/discontinuation: inefficacy at Longest time period reported
- Actual outcome: Discontinuation of strategy: inefficacy at 12 months; Group 1: 12/107, Group 2: 5/105
Risk of bias: All domain - Very high, Selection - High, Blinding - High, Incomplete outcome data - High, Outcome reporting - Low, Measurement - Low, Crossover - Low, Comments - ITT used for patients who discontinued strategy, patients lost to follow up excluded from analysis. ; Indirectness of outcome: No indirectness ; Baseline details: See pop panel; Blinding details: Open label trial; Group 1 Number missing: 11, Reason: 11 lost to follow up and excluded from analysis (reasons overall only); Group 2 Number missing: 14, Reason: 8 lost to follow up and excluded from analysis (reasons overall only), 6 discontinued strategy (4 for adverse events, 2 other) (treatment not in accordance with protocol)

Protocol outcomes not reported by the study	Disease Activity Score at 12 months; Disease Activity Score at 6 months; Quality of life at 12 months; Quality of life at 6 months; Function at 6 months; Pain at 6 months; Remission at 6 months; Low disease activity at 6 months; Low disease activity at 12 months; Radiological progression at 12+ months; ACR50 response at 6 months; ACR50 response at 12 months; Adverse events - mortality at 12+ months

Study (subsidiary papers)	Verschueren 2016[177] (Verschueren 2015[176], Verschueren 2015[178])
Study type	RCT (Patient randomised; Parallel)
Number of studies (number of participants)	1 (n=289)
Countries and setting	Conducted in Belgium
Line of therapy	1st line
Duration of study	Intervention time: 2 years
Method of assessment of guideline condition	Adequate method of assessment/diagnosis: ACR 1987 criteria
Stratum	Poor-prognosis disease
Subgroup analysis within study	Not applicable
Inclusion criteria	People with RA with disease duration ≤1 year and DMARD/glucocorticoid unexperienced. Defined as "high risk" due to erosions, rheumatoid factor, ACPA, disease activity.
Exclusion criteria	People with contraindications to intensive treatment with glucocorticoids.
Recruitment/selection of patients	Recruited in 13 Flemish rheumatology centres.
Age, gender and ethnicity	Age - Mean (SD): 52. Gender (M:F): 66% female. Ethnicity: Not detailed
Further population details	
Indirectness of population	No indirectness
Interventions	(n=98) Intervention 1: Parallel combination therapy - Parallel combination therapy - specify. COBRA Classic: methotrexate (15mg per week), sulfasalazine (2g per day). MTX increased to 20mg per week if DAS ≤3.2 at week 8. Then, SSZ increased to 3g per day if DAS ≤3.2 at week 16. Duration 2 years. Concurrent medication/care: Oral prednisone in a step-down scheme (60mg to 7.5mg). Prophylactic treatment with folic acid, calcium and vitamin D prescribed. IM or IA glucocorticoid injections are allowed once per 8 weeks but not in 4 weeks before W16, Q28, W40 or W52. . Indirectness: No indirectness Further details: 1. Dose: Higher dose (sulfasalazine: 2 gm, methotrexate: >15 mg, leflunomide: 20mg, hydroxychloroquine: 400mg) 2. Use of glucocorticoids: Short term glucocorticoids used (n=98) Intervention 2: Step up therapy - Step up therapy - specify. COBRA Slim: methotrexate (15mg per week). MTX increased to 20mg per week if DAS ≤3.2 at week 8. Then, addition of Leflunomide (10mg per day) if DAS ≤3.2 at week 16. . Duration 2 years. Concurrent medication/care: Oral prednisone in a step-down scheme (60mg to 7.5mg). Prophylactic treatment with folic acid, calcium and vitamin D prescribed. IM or IA glucocorticoids injections are allowed once per 8 weeks but not in 4 weeks before W16, Q28, W40 or W52. . Indirectness: No indirectness Further details: 1. Dose: Not applicable (MTX dose could be high but LEF dose was low). 2. Use of

	glucocorticoids: Short term glucocorticoids used (n=93) Intervention 3: Parallel combination therapy - Parallel combination therapy - specify. COBRA Avant Garde: methotrexate (15mg per week), leflunomide (10mg per day). MTX increased to 20mg per week if DAS ≤3.2 at week 8. Then, LEF increased to 20mg per day if DAS ≤3.2 at week 16. . Duration 2 years. Concurrent medication/care: Oral prednisone in a step-down scheme (60mg to 7.5mg). Prophylactic treatment with folic acid, calcium and vitamin D prescribed. IM or IA glucocorticoids injections are allowed once per 8 weeks but not in 4 weeks before W16, Q28, W40 or W52. . Indirectness: No indirectness Further details: 1. Dose: Higher dose (sulfasalazine: 2 gm, methotrexate: >15 mg, leflunomide: 20mg, hydroxychloroquine: 400mg) 2. Use of glucocorticoids: Short term glucocorticoids used
Funding	Other

RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: PARALLEL COMBINATION THERAPY - METHOTREXATE + SULFASALAZINE versus STEP UP THERAPY: METHOTREXATE + LEFLUNOMIDE

Protocol outcome 1: Disease Activity Score at 12 months
- Actual outcome for Poor-prognosis disease: Change in Disease Activity Score (DAS28) at 12 months; Group 1: mean -2.5 (SD 1.5); n=90, Group 2: mean -2.3 (SD 1.4); n=89; DAS28 2-10 Top=High is poor outcome
Risk of bias: All domain - Very high, Selection - High, Blinding - High, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low, Subgroups - Low, Other 1 - High; Indirectness of outcome: No indirectness ; Group 1 Number missing: 8; Group 2 Number missing: 9

Protocol outcome 2: Disease Activity Score at 6 months
- Actual outcome for Poor-prognosis disease: Change in Disease Activity Score (DAS28) at week 16; Group 1: mean -2.8 (SD 1.2); n=98, Group 2: mean -2.6 (SD 1.2); n=98; DAS28 2-10 Top=High is poor outcome
Risk of bias: All domain - Very high, Selection - High, Blinding - High, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low, Subgroups - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: ; Group 2 Number missing:

Protocol outcome 3: Function at 6 months
- Actual outcome for Poor-prognosis disease: Change in function (HAQ) at 16 weeks; Group 1: mean -0.8 (SD 0.6); n=98, Group 2: mean -0.6 (SD 0.6); n=98; HAQ 0-3 Top=High is poor outcome
Risk of bias: All domain - Very high, Selection - High, Blinding - High, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low, Subgroups - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: ; Group 2 Number missing:

Protocol outcome 4: Function at 12 months
- Actual outcome for Poor-prognosis disease: Change in function (HAQ) at 12 months; Group 1: mean -0.7 (SD 0.7); n=90, Group 2: mean -0.5 (SD 0.7); n=89; HAQ 0-3 Top=High is poor outcome
Risk of bias: All domain - Very high, Selection - High, Blinding - High, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low,

Crossover - Low, Subgroups - Low, Other 1 - High; Indirectness of outcome: No indirectness ; Group 1 Number missing: 8; Group 2 Number missing: 9

Protocol outcome 5: Remission at 6 months
- Actual outcome for Poor-prognosis disease: Remission (DAS28 <2.6) at 16 weeks; Group 1: 69/98, Group 2: 72/98
Risk of bias: All domain - Very high, Selection - High, Blinding - High, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low, Subgroups - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: ; Group 2 Number missing:

Protocol outcome 6: Remission at 12 months
- Actual outcome for Poor-prognosis disease: Remission (DAS28 <2.6) at 12 months; Group 1: 63/98, Group 2: 59/98
Risk of bias: All domain - Very high, Selection - High, Blinding - High, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low, Subgroups - Low, Other 1 - High; Indirectness of outcome: No indirectness ; Group 1 Number missing: ; Group 2 Number missing:

Protocol outcome 7: Low disease activity at 6 months
- Actual outcome for Poor-prognosis disease: Low disease activity (DAS28 ≤3.2) at 16 weeks; Group 1: 83/98, Group 2: 85/98
Risk of bias: All domain - Very high, Selection - High, Blinding - High, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low, Subgroups - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: ; Group 2 Number missing:

Protocol outcome 8: Low disease activity at 12 months
- Actual outcome for Poor-prognosis disease: Low disease activity (DAS28 ≤3.2) at 12 months; Group 1: 74/98, Group 2: 74/98
Risk of bias: All domain - Very high, Selection - High, Blinding - High, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low, Subgroups - Low, Other 1 - High; Indirectness of outcome: No indirectness ; Group 1 Number missing: ; Group 2 Number missing:

Protocol outcome 9: Radiological progression at 12+ months
- Actual outcome for Poor-prognosis disease: Change in radiological progression (SvdH) at 12 months; Group 1: mean -0.3 (SD 0.5); n=90,
Risk of bias: All domain - Very high, Selection - High, Blinding - High, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low, Subgroups - Low, Other 1 - High; Indirectness of outcome: No indirectness ; Group 1 Number missing: 8; Group 2 Number missing: 9

Protocol outcome 10: Withdrawal/discontinuation: adverse events at Longest time period reported
- Actual outcome for Poor-prognosis disease: Discontinuation due to adverse events at 16 weeks; Group 1: 2/93, Group 2: 1/97
Risk of bias: All domain - Very high, Selection - High, Blinding - Low, Incomplete outcome data - High, Outcome reporting - Low, Measurement - Low, Crossover - Low, Subgroups - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: 5; Group 2 Number missing: 1

Protocol outcome 11: Withdrawal/discontinuation: inefficacy at Longest time period reported
- Actual outcome for Poor-prognosis disease: Discontinuation due to inefficacy at 16 weeks; Group 1: 2/93, Group 2: 0/96
Risk of bias: All domain - Very high, Selection - High, Blinding - Low, Incomplete outcome data - High, Outcome reporting - Low, Measurement - Low, Crossover - Low, Subgroups - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: 5; Group 2 Number missing: 2

RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: PARALLEL COMBINATION THERAPY - METHOTREXATE +

SULFASALAZINE versus PARALLEL COMBINATION THERAPY - METHOTREXATE + LEFLUNOMIDE

Protocol outcome 1: Disease Activity Score at 12 months
- Actual outcome for Poor-prognosis disease: Change in Disease Activity Score (DAS28) at 12 months; Group 1: mean -2.5 (SD 1.5); n=90, Group 2: mean -2.3 (SD 1.5); n=85; DAS28 2-10 Top=High is poor outcome
Risk of bias: All domain - Very high, Selection - High, Blinding - High, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low, Subgroups - Low, Other 1 - High; Indirectness of outcome: No indirectness ; Baseline details: Higher symptom duration, ESR, CRP in comparator group; Group 1 Number missing: 8; Group 2 Number missing: 8

Protocol outcome 2: Disease Activity Score at 6 months
- Actual outcome for Poor-prognosis disease: Change in Disease Activity Score (DAS28) at week 16; Group 1: mean -2.8 (SD 1.2); n=98, Group 2: mean -2.4 (SD 1.3); n=94
Risk of bias: All domain - Very high, Selection - High, Blinding - High, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low, Subgroups - Low; Indirectness of outcome: No indirectness ; Baseline details: Higher symptom duration, ESR, CRP in comparator group; Group 1 Number missing: ; Group 2 Number missing:

Protocol outcome 3: Function at 6 months
- Actual outcome for Poor-prognosis disease: Change in function (HAQ) at 16 weeks; Group 1: mean -0.8 (SD 0.6); n=98, Group 2: mean -0.7 (SD 0.6); n=94
Risk of bias: All domain - Very high, Selection - High, Blinding - High, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low, Subgroups - Low; Indirectness of outcome: No indirectness ; Baseline details: Higher symptom duration, ESR, CRP in comparator group; Group 1 Number missing: ; Group 2 Number missing:

Protocol outcome 4: Function at 12 months
- Actual outcome for Poor-prognosis disease: Change in function (HAQ) at 12 months; Group 1: mean -0.7 (SD 0.7); n=90, Group 2: mean -0.6 (SD 0.7); n=85
Risk of bias: All domain - Very high, Selection - High, Blinding - High, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low, Subgroups - Low, Other 1 - High; Indirectness of outcome: No indirectness ; Baseline details: Higher symptom duration, ESR, CRP in comparator group; Group 1 Number missing: 8; Group 2 Number missing: 8

Protocol outcome 5: Remission at 6 months
- Actual outcome for Poor-prognosis disease: Remission (DAS28 <2.6) at 16 weeks; Group 1: 69/98, Group 2: 64/94
Risk of bias: All domain - Very high, Selection - High, Blinding - High, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low, Subgroups - Low; Indirectness of outcome: No indirectness ; Baseline details: Higher symptom duration, ESR, CRP in comparator group; Group 1 Number missing: ; Group 2 Number missing:

Protocol outcome 6: Remission at 12 months
- Actual outcome for Poor-prognosis disease: Remission (DAS28 <2.6) at 12 months; Group 1: 63/98, Group 2: 58/93

Risk of bias: All domain - Very high, Selection - High, Blinding - High, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low, Subgroups - Low, Other 1 - High; Indirectness of outcome: No indirectness ; Baseline details: Higher symptom duration, ESR, CRP in comparator group; Group 1 Number missing: ; Group 2 Number missing:

Protocol outcome 7: Low disease activity at 6 months
- Actual outcome for Poor-prognosis disease: Low disease activity (DAS28 ≤3.2) at 16 weeks; Group 1: 83/98, Group 2: 82/94
Risk of bias: All domain - Very high, Selection - High, Blinding - High, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low, Subgroups - Low; Indirectness of outcome: No indirectness ; Baseline details: Higher symptom duration, ESR, CRP in comparator group; Group 1 Number missing: ; Group 2 Number missing:

Protocol outcome 8: Low disease activity at 12 months
- Actual outcome for Poor-prognosis disease: Low disease activity (DAS28 ≤3.2) at 12 months; Group 1: 73/98, Group 2: 74/93
Risk of bias: All domain - Very high, Selection - High, Blinding - High, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low, Subgroups - Low, Other 1 - High; Indirectness of outcome: No indirectness ; Baseline details: Higher symptom duration, ESR, CRP in comparator group; Group 1 Number missing: ; Group 2 Number missing:

Protocol outcome 9: Radiological progression at 12+ months
- Actual outcome for Poor-prognosis disease: Change in radiological progression (SvdH) at 12 months; Group 1: mean 0.3 (SD 0.5); n=90,
Risk of bias: All domain - Very high, Selection - High, Blinding - High, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low, Subgroups - Low, Other 1 - High; Indirectness of outcome: No indirectness ; Baseline details: Higher symptom duration, ESR, CRP in comparator group; Group 1 Number missing: 8; Group 2 Number missing: 8

Protocol outcome 10: Withdrawal/discontinuation: adverse events at Longest time period reported
- Actual outcome for Poor-prognosis disease: Discontinuation due to adverse events at 16 weeks; Group 1: 2/93, Group 2: 0/91
Risk of bias: All domain - Very high, Selection - High, Blinding - Low, Incomplete outcome data - High, Outcome reporting - Low, Measurement - Low, Crossover - Low, Subgroups - Low; Indirectness of outcome: No indirectness ; Baseline details: Higher symptom duration, ESR, CRP in comparator group; Group 1 Number missing: 5; Group 2 Number missing: 3

Protocol outcome 11: Withdrawal/discontinuation: inefficacy at Longest time period reported
- Actual outcome for Poor-prognosis disease: Discontinuation due to inefficacy at 16 weeks; Group 1: 2/93, Group 2: 1/92
Risk of bias: All domain - Very high, Selection - High, Blinding - Low, Incomplete outcome data - High, Outcome reporting - Low, Measurement - Low, Crossover - Low, Subgroups - Low; Indirectness of outcome: No indirectness ; Baseline details: Higher symptom duration, ESR, CRP in comparator group; Group 1 Number missing: 5; Group 2 Number missing: 1

RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: STEP UP THERAPY: METHOTREXATE + LEFLUNOMIDE versus PARALLEL COMBINATION THERAPY - METHOTREXATE + LEFLUNOMIDE

Protocol outcome 1: Disease Activity Score at 12 months

- Actual outcome for Poor-prognosis disease: Change in Disease Activity Score (DAS28) at 12 months; Group 1: mean -2.3 (SD 1.4); n=89, Group 2: mean -2.3 (SD 1.5); n=85; DAS28 2-10 Top=High is poor outcome
Risk of bias: All domain - Very high, Selection - High, Blinding - High, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low, Subgroups - Low, Other 1 - High; Indirectness of outcome: No indirectness ; Baseline details: Higher symptom duration, ESR, CRP in comparator group; Group 1 Number missing: 9; Group 2 Number missing: 8

Protocol outcome 2: Disease Activity Score at 6 months
- Actual outcome for Poor-prognosis disease: Change in Disease Activity Score (DAS28) at week 16; Group 1: mean -2.6 (SD 1.2); n=98, Group 2: mean -2.4 (SD 1.3); n=94; DAS28 2-10 Top=High is poor outcome
Risk of bias: All domain - Very high, Selection - High, Blinding - High, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low, Subgroups - Low; Indirectness of outcome: No indirectness ; Baseline details: Higher symptom duration, ESR, CRP in comparator group; Group 1 Number missing: ; Group 2 Number missing:

Protocol outcome 3: Function at 6 months
- Actual outcome for Poor-prognosis disease: Change in function (HAQ) at 16 weeks; Group 1: mean -0.6 (SD 0.6); n=98, Group 2: mean -0.7 (SD 0.6); n=94; HAQ 0-3 Top=High is poor outcome
Risk of bias: All domain - Very high, Selection - High, Blinding - High, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low, Subgroups - Low; Indirectness of outcome: No indirectness ; Baseline details: Higher symptom duration, ESR, CRP in comparator group; Group 1 Number missing: ; Group 2 Number missing:

Protocol outcome 4: Function at 12 months
- Actual outcome for Poor-prognosis disease: Change in function (HAQ) at 12 months; Group 1: mean -0.5 (SD 0.7); n=89, Group 2: mean -0.6 (SD 0.7); n=85; HAQ 0-3 Top=High is poor outcome
Risk of bias: All domain - Very high, Selection - High, Blinding - High, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low, Subgroups - Low, Other 1 - High; Indirectness of outcome: No indirectness ; Baseline details: Higher symptom duration, ESR, CRP in comparator group; Group 1 Number missing: 9; Group 2 Number missing: 8

Protocol outcome 5: Remission at 6 months
- Actual outcome for Poor-prognosis disease: Remission (DAS28 <2.6) at 16 weeks; Group 1: 72/98, Group 2: 64/94
Risk of bias: All domain - Very high, Selection - High, Blinding - High, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low, Subgroups - Low; Indirectness of outcome: No indirectness ; Baseline details: Higher symptom duration, ESR, CRP in comparator group; Group 1 Number missing: ; Group 2 Number missing:

Protocol outcome 6: Remission at 12 months
- Actual outcome for Poor-prognosis disease: Remission (DAS28 <2.6) at 12 months; Group 1: 59/98, Group 2: 58/93
Risk of bias: All domain - Very high, Selection - High, Blinding - High, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low, Subgroups - Low, Other 1 - High; Indirectness of outcome: No indirectness ; Baseline details: Higher symptom duration, ESR, CRP in comparator group; Group 1 Number missing: ; Group 2 Number missing:

Protocol outcome 7: Low disease activity at 6 months - Actual outcome for Poor-prognosis disease: Low disease activity (DAS28 ≤3.2) at 16 weeks; Group 1: 85/98, Group 2: 82/94 Risk of bias: All domain - Very high, Selection - High, Blinding - High, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low, Subgroups - Low; Indirectness of outcome: No indirectness ; Baseline details: Higher symptom duration, ESR, CRP in comparator group; Group 1 Number missing: ; Group 2 Number missing: Protocol outcome 8: Low disease activity at 12 months - Actual outcome for Poor-prognosis disease: Low disease activity (DAS28 ≤3.2) at 12 months; Group 1: 74/98, Group 2: 74/93 Risk of bias: All domain - Very high, Selection - High, Blinding - High, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low, Subgroups - Low, Other 1 - High; Indirectness of outcome: No indirectness ; Baseline details: Higher symptom duration, ESR, CRP in comparator group; Group 1 Number missing: ; Group 2 Number missing: Protocol outcome 9: Radiological progression at 12+ months - Actual outcome for Poor-prognosis disease: Change in radiological progression (SvdH) at 12 months; Group 1: mean -0.4 (SD 1.1); n=89, Risk of bias: All domain - Very high, Selection - High, Blinding - High, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low, Subgroups - Low, Other 1 - High; Indirectness of outcome: No indirectness ; Baseline details: Higher symptom duration, ESR, CRP in comparator group; Group 1 Number missing: 9; Group 2 Number missing: 8 Protocol outcome 10: Withdrawal/discontinuation: adverse events at Longest time period reported - Actual outcome for Poor-prognosis disease: Discontinuation due to adverse events at 16 weeks; Group 1: 1/97, Group 2: 0/91 Risk of bias: All domain - Very high, Selection - High, Blinding - Low, Incomplete outcome data - High, Outcome reporting - Low, Measurement - Low, Crossover - Low, Subgroups - Low; Indirectness of outcome: No indirectness ; Baseline details: Higher symptom duration, ESR, CRP in comparator group; Group 1 Number missing: 5; Group 2 Number missing: 1 Protocol outcome 11: Withdrawal/discontinuation: inefficacy at Longest time period reported - Actual outcome for Poor-prognosis disease: Discontinuation due to inefficacy at 16 weeks; Group 1: 0/96, Group 2: 1/92 Risk of bias: All domain - Very high, Selection - High, Blinding - Low, Incomplete outcome data - High, Outcome reporting - Low, Measurement - Low, Crossover - Low, Subgroups - Low; Indirectness of outcome: No indirectness ; Baseline details: Higher symptom duration, ESR, CRP in comparator group; Group 1 Number missing: 2; Group 2 Number missing: 1	
Protocol outcomes not reported by the study	Quality of life at 12 months; Quality of life at 6 months; Pain at 6 months; Pain at 12 months; ACR50 response at 6 months; ACR50 response at 12 months; Adverse events - mortality at 12+ months

D.1.21 Failed DMARDs

Study	Leflunomide failed trial: Dougados 2005[34]
Study type	RCT (Patient randomised; Parallel)
Number of studies (number of participants)	1 (n=106)
Countries and setting	Conducted in Multiple countries; Setting: 24 week, double blind phase of a multi-centre, international RELIEF study, which followed an initial 24 week open label phase. The study was carried out in 162 centres in 14 countries across Europe, South America, Australia, and New Zealand.
Line of therapy	Mixed line
Duration of study	Other: Patients randomised to double blind phase for 24 weeks if initial 24 weeks of leflunomide had failed
Method of assessment of guideline condition	Adequate method of assessment/diagnosis
Stratum	LFN failed:
Subgroup analysis within study	Not applicable
Inclusion criteria	Male or female patients aged 18-75 years with active RA as defined by a DAS28>3.2, and with a functional classification of I, II, or III according to the American Rheumatology Association (ARA) criteria were included in the main study. Women of childbearing potential and men were required to use adequate contraception throughout the study. Patients with inadequate DAS28 response to leflunomide in the initial open label phase of the study were eligible for entry into the double blind phase.
Exclusion criteria	Patients of ARA functional class IV were not eligible for inclusion. Women who were pregnant or breastfeeding were also excluded.
Recruitment/selection of patients	In the initial open label phase of the study, after a 1-2 week screening period and interruption of any other DMARD for at least a month, patients received a leflunomide loading dose of 100mg once daily for the first 3 days followed by maintenance dose of 20mg once daily thereafter. Patients who were non-responders to leflunomide at the end of the first open label phase were randomly allocated to a further 24 weeks' treatment with either leflunide plus sulfasalazine or sulfasalazine plus placebo. Patients who were good or moderate responders in the first open label phase entered a second open label phase of 24 weeks leflunomide monotherapy, the results of which are not presented here. The protocol required treatment with other DMARDs to be discontinued at least 4 weeks before enrolment in the initial phase of the study.
Age, gender and ethnicity	Age - Mean (SD): monotherapy (SSZ): 55.4; parallel therapy (SSZ+LFN): 56.3. Gender (M:F): 1/2. Ethnicity: not specified but multi-centre, international study
Further population details	1. Disease duration: Not stated / Unclear

Extra comments	Before starting on Leflunomide in the first open label phase 66.1% of patients in the LFN+SSZ group and 68.0% in the SSZ+placebo group had already used other DMARDs (mean number of DMARDS: 1.7 and 1.3 respectively) previously.
Indirectness of population	No indirectness
Interventions	(n=56) Intervention 1: Parallel combination therapy - Parallel combination therapy - specify. Patients who were non-responders to leflunomide monotherapy at the end of the 24 weeks open label phase and randomly allocated to the parallel combination therapy received leflunomide (20mg once daily) plus sulfasalazine (2g once daily starting at 0.5g increasing in weekly steps of 0.5g) . Duration 24 weeks. Concurrent medication/care: Stable doses of non-glucocorticoid anti-inflammatory drugs or oral glucocorticoids (max 10mg prednisone or glucocorticoid equivalent) were permitted as concomitant drugs. Intra-articular injections of glucocorticoids (max 60mg prednisone or equivalent) were to be avoided if possible, and were not permitted within the 4 weeks preceding the assessment. Analgesics were allowed, but were not to be taken in the 6 hours before joint examination.. Indirectness: No indirectness Further details: 1. Dose: Higher dose (sulfasalazine: 2 gm, methotrexate: >15 mg, leflunomide: 20mg, hydroxychloroquine: 400mg) (LFN (20mg) + SSZ (2g)). 2. Use of steroids: Not stated / Unclear (Stable doses of non-glucocorticoid anti-inflammatory drugs or oral glucocorticoids (max 10mg prednisone or glucocorticoid equivalent) were permitted as concomitant drugs. Intra-articular injections of glucocorticoids (max 60mg prednisone or equivalent) were to be avoided if possible, and were not permitted within the 4 weeks preceding the assessment.). (n=50) Intervention 2: Monotherapy - Monotherapy - specify. Patients who were non-responders to leflunomide monotherapy at the end of the 24 weeks open label phase and randomly allocated to the monotherapy group received sulfasalazine (2g once daily starting at 0.5g increasing in weekly steps of 0.5g) plus placebo. . Duration 24 weeks. Concurrent medication/care: Stable doses of non-glucocorticoid anti-inflammatory drugs or oral glucocorticoids (max 10mg prednisone or glucocorticoid equivalent) were permitted as concomitant drugs. Intra-articular injections of glucocorticoids (max 60mg prednisone or equivalent) were to be avoided if possible, and were not permitted within the 4 weeks preceding the assessment. Analgesics were allowed, but were not to be taken in the 6 hours before joint examination. . Indirectness: No indirectness Further details: 1. Dose: Higher dose (sulfasalazine: 2 gm, methotrexate: >15 mg, leflunomide: 20mg, hydroxychloroquine: 400mg) (SSZ (2g) + placebo). 2. Use of glucocorticoids: Not stated / Unclear (Stable doses of non-glucocorticoid anti-inflammatory drugs or oral glucocorticoids (max 10mg prednisone or glucocorticoid equivalent) were permitted as concomitant drugs. Intra-articular injections of glucocorticoids (max 60mg prednisone or equivalent) were to be avoided if possible, and were not permitted within the 4 weeks preceding the assessment.).

Funding	Study funded by industry (Aventis Pharma)

RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: PARALLEL COMBINATION THERAPY - LFN+SSZ versus MONOTHERAPY - SSZ

Protocol outcome 1: Function at 6 months
- Actual outcome: HAQ (change from baseline/end of 24 week open label phase) at 24 weeks; Group 1: mean -0.09 (SD 0.32); n=56, Group 2: mean -0.02 (SD 0.36); n=50; Health Assessment Questionnaire 0-100 Top=High is poor outcome
Risk of bias: All domain - Very high, Selection - Low, Blinding - High, Incomplete outcome data - Very high, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: 32, Reason: adverse events, inefficacy, wish to withdraw; Group 2 Number missing: 27, Reason: adverse events, inefficacy, wish to withdraw

Protocol outcome 2: Pain at 6 months
- Actual outcome: Pain intensity assessment (mm) (change from baseline/end of 24 week open label phase) at 24 weeks; Group 1: mean -9.21 (SD 24.91); n=56, Group 2: mean -8.32 (SD 21.74); n=50
Risk of bias: All domain - Very high, Selection - Low, Blinding - High, Incomplete outcome data - Very high, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: 32, Reason: adverse events, inefficacy, wish to withdraw; Group 2 Number missing: 27, Reason: adverse events, inefficacy, wish to withdraw

Protocol outcome 3: ACR50 response at 6 months
- Actual outcome: ACR50 responses at 24 weeks; Group 1: 5/56, Group 2: 0/50
Risk of bias: All domain - Very high, Selection - Low, Blinding - High, Incomplete outcome data - Very high, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: 32, Reason: adverse events, inefficacy, wish to withdraw; Group 2 Number missing: 27, Reason: adverse events, inefficacy, wish to withdraw

Protocol outcome 4: Withdrawal/discontinuation: adverse events at Longest time period reported
- Actual outcome: Withdrawal due to adverse events at 24 weeks; Group 1: 26/56, Group 2: 18/50
Risk of bias: All domain - High, Selection - Low, Blinding - High, Incomplete outcome data - High, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: 6, Reason: lack of efficacy or not wishing to continue; Group 2 Number missing: 9, Reason: lack of efficacy or not wishing to continue

Protocol outcome 5: Withdrawal/discontinuation: inefficacy at Longest time period reported
- Actual outcome: Withdrawal due to inefficacy at 24 weeks; Group 1: 3/56, Group 2: 4/50
Risk of bias: All domain - Very high, Selection - Low, Blinding - High, Incomplete outcome data - Very high, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: 29, Reason: adverse event or not wishing to continue; Group 2 Number missing: 23, Reason: adverse event or not wishing to continue

Protocol outcomes not reported by the study	Disease Activity Score at 12 months; Disease Activity Score at 6 months; Quality of life at 12 months; Quality of life at 6 months; Function at 12 months; Pain at 12 months; Remission at 6 months; Remission at 12 months; Low disease activity at 6 months; Low disease activity at 12 months; ACR50 response at 12 months; Radiological progression at 12+ months; Adverse events - mortality at 12+ months

Study	Methotrexate failures in BeSt trial trial: Van der kooij 2007[168]
Study type	RCT (Patient randomised; Parallel)
Number of studies (number of participants)	1 (n=138)
Countries and setting	Conducted in Netherlands; Setting: The BeSt study was conducted by rheumatologists participating in 18 peripheral and 2 university hospitals in the western part of the Netherlands.
Line of therapy	Mixed line
Duration of study	Intervention time: 2 years
Method of assessment of guideline condition	Adequate method of assessment/diagnosis
Stratum	MTX failed
Subgroup analysis within study	Not applicable
Inclusion criteria	BeSt study overall: Patients with disease duration of ≤2 years, aged ≥18 years, and have active disease with ≥6 of 66 swollen joints, ≥6 of 68 tender joints, and either an erythrocyte sedimentation rate (ESR) ≥28 mm/hour or a global health score of ≥20 mm on a 0-100 mm visual analogue scale. Sub-analysis: subset of patients from group 1 and group 2 of the BeSt study who failed MTX (persistent DAS>2.4)
Exclusion criteria	BeSt study overall: previous treatment with DMARDs other than antimalarials, concomitant treatment with an experimental drug, a malignancy within the last 5 years, bone marrow hypoplasia, a serum aspartate aminotransferase or alanine aminotransferase (ALT) level >3x the upper limit of normal, a serum creatinine level >150 µmoles/liter or an estimated creatinine clearance <75 ml/minute, diabetes mellitus, alcohol or drug abuse, concurrent pregnancy, wish to conceive during the study period, or inadequate contraception.
Recruitment/selection of patients	Patients with early RA (ACR1987) were recruited between April 2000 and August 2002.
Age, gender and ethnicity	Age - Mean (SD): 54 (13). Gender (M:F): 1/3. Ethnicity: not mentioned but study took place in the Netherlands
Further population details	1. Disease duration: early RA (<= 2 years) (≤2 years).
Extra comments	All patients were DMARD naive at the start of the BeSt trial.
Indirectness of population	No indirectness
Interventions	(n=69) Intervention 1: Sequential monotherapy - Sequential monotherapy - specify. All patients started therapy with methotrexate (MTX) 7.5mg/week, after 4 weeks instantly increased to 15mg/week, in combination with folic acid (1 mg/day). In the case of DAS>2.4 after 3 months, MTX was increased to 25 mg/week (or the highest tolerated dose). Patients with persistingDAS >2.4 on MTX 25 mg/week proceeded to next treatment steps (1 month overlap when switching from one single DMARD to the next). In the case of drug adverse events, the responsible drug was tapered to the lowest tolerable dose or discontinued if not

	tolerated at all. In this case, patients in the sequential monotherapy group proceeded to the next step in the treatment protocol. If a DAS ≤2.4 was achieved and maintained for ≥6 months, medication was tapered to a single DMARD in maintenance dose: 2 g/day for SSZand 10 mg every other day for LFN. If the DAS increased to >2.4 after tapering to maintenance dose, the last effective dose of the last tapered drug was resumed. If DAS remained >2.4, the patient proceeded to the next treatment steps. Next steps after failure of MTX for sequential monotherapy group: SSZ monotherapy (2-3 g/day), LFN monotherapy (20 mg/day). Assessments were performed by a research nurse every 3 months.. Duration up to 2 years. Concurrent medication/care: Concomitant treatment with non-glucocorticoid anti-inflammatory drugs and intra-articular injections with glucocorticoids were permitted. Other parenteral glucocorticoids were not allowed. The use of DMARDs or oral glucocorticoids was only permitted as dictated by the treatment protocol. All patients received 1 mg/day folic acid during the treatment with MTX.. Indirectness: No indirectness Further details: 1. Dose: Higher dose (sulfasalazine: 2 gm, methotrexate: >15 mg, leflunomide: 20mg, hydroxychloroquine: 400mg) (Step 1: SSZ 2-3g/day; if failed then Step 2: LFN 20 mg/day). 2. Use of s: Short term glucocorticoids not used (Concomitant treatment with non-steroidal glucocorticoid anti-inflammatory drugs and intra-articular injections with glucocorticoids were permitted. Other parenteral glucocorticoids were not allowed. The use of DMARDs or oral glucocorticoids was only permitted as dictated by the treatment protocol.). (n=69) Intervention 2: Step up therapy - Step up therapy - specify. All patients started therapy with methotrexate (MTX) 7.5mg/week, after 4 weeks instantly increased to 15mg/week, in combination with folic acid (1 mg/day). In the case of DAS>2.4 after 3 months, MTX was increased to 25 mg/week (or the highest tolerated dose). Patients with persisting DAS >2.4 on MTX 25 mg/week proceeded to next treatment steps (1 month overlap when switching from one single DMARD to the next). In the case of drug adverse events, the responsible drug was tapered to the lowest tolerable dose or discontinued if not tolerated at all. In this case patients in the step-up group continued with the other drugs in the combination. If a DAS ≤2.4 was achieved and maintained for ≥6 months, medication was tapered to maintenance dose: 10 mg/week for MTX (tapering by 2.5mg/month), 2 g/day for SSZ and 10 mg every other day for LFN. If the DAS increased to >2.4 after tapering to maintenance dose, the last effective dose of the last tapered drug was resumed. If DAS remained >2.4, the patient proceeded to the next treatment steps. Next steps after failure of MTX for step-up combination therapy group: Step 1: MTX (25mg/week) + SSZ (2-3g/day); if failed then Step 2: MTX (25mg/week) + SSZ (2-3 g/day) + HCQ (400mg/day) Assessments were performed by a research nurse every 3 months.. Duration up to 2 years. Concurrent medication/care: Concomitant treatment with non-glucocorticoid anti-inflammatory drugs and intra-articular injections with glucocorticoids were permitted. Other parenteral glucocorticoids were not allowed. The use of DMARDs or oral glucocorticoids was only permitted as dictated by the treatment protocol. All patients received 1 mg/day folic acid during the treatment with MTX.. Indirectness: No indirectness

	Further details: 1. Dose: Higher dose (sulfasalazine: 2 gm, methotrexate: >15 mg, leflunomide: 20mg, hydroxychloroquine: 400mg) (Step 1: MTX (25mg/week) + SSZ (2-3g/day); if failed then Step 2: MTX (25mg/week) + SSZ (2-3 g/day) + HCQ (400mg/day)). 2. Use of glucocorticoids: Short term glucocorticoids not used (Concomitant treatment with non-glucocorticoid anti-inflammatory drugs and intra-articular injections with glucocorticoid were permitted. Other parenteral glucocorticoids were not allowed. The use of DMARDs or oral glucocorticoids was only permitted as dictated by the treatment protocol.).
Funding	Study funded by industry

RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: SEQUENTIAL MONOTHERAPY - SSZ THEN LFN versus STEP UP THERAPY - MTX+SSZ THEN MTX+SSZ+HCQ

Protocol outcome 1: Low disease activity at 12 months
- Actual outcome for MTX failed: LDA = DAS ≤2.4 after Step 1 (SSZ mono- or combination therapy) at during 2 years; Group 1: 15/69, Group 2: 15/69
Risk of bias: All domain - High, Selection - Low, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low, Subgroups - High; Indirectness of outcome: No indirectness ; Group 1 Number missing: 0; Group 2 Number missing: 0
- Actual outcome for MTX failed: LDA = DAS ≤2.4 after Step 2 (SSZ failure, followed by LFN mono Group 1 or MTX+SSZ+HCQ Group 2) at during 2 years; Group 1: 7/54, Group 2: 16/44
Risk of bias: All domain - High, Selection - Low, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low, Subgroups - High; Indirectness of outcome: No indirectness ; Group 1 Number missing: 0; Group 2 Number missing: 0
- Actual outcome for MTX failed: LDA = DAS ≤2.4 total ('successes' from Step 1 and Step 2 combined) at during 2 years; Group 1: 22/69, Group 2: 31/69
Risk of bias: All domain - Very high, Selection - Low, Blinding - Low, Incomplete outcome data - High, Outcome reporting - Low, Measurement - Low, Crossover - Low, Subgroups - High, Comments - 54 patients in each group failed Step 1. All failures from group 1 but only 44 of group 2 failures moved onto Step 2 of treatment. The authors do not explain the reason for the 10 missing patients.
This is a subgroup analyses involving 2 out of a 4 treatment arm RCT (BeSt trial). ; Indirectness of outcome: No indirectness ; Group 1 Number missing: 0; Group 2 Number missing: 10, Reason: not mentioned

Protocol outcome 2: Withdrawal/discontinuation: adverse events at Longest time period reported
- Actual outcome for MTX failed: Adverse event during Step 1 (SSZ mono- or combination therapy) at during 2 years; Group 1: 7/69, Group 2: 13/69
Risk of bias: All domain - High, Selection - Low, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low, Subgroups - High; Indirectness of outcome: No indirectness ; Group 1 Number missing: 0; Group 2 Number missing: 0
- Actual outcome for MTX failed: Adverse event during Step 2 (SSZ failure, followed by LFN mono Group 1 or MTX+SSZ+HCQ Group 2) at during 2 years; Group 1: 6/54, Group 2: 5/44
Risk of bias: All domain - High, Selection - Low, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low, Subgroups - High; Indirectness of outcome: No indirectness ; Group 1 Number missing: 0; Group 2 Number missing: 0
- Actual outcome for MTX failed: Adverse event total (from Step 1 and Step 2 combined) at during 2 years; Group 1: 13/69, Group 2: 18/69
Risk of bias: All domain - Very high, Selection - Low, Blinding - Low, Incomplete outcome data - High, Outcome reporting - Low, Measurement - Low, Crossover - Low, Subgroups - High, Comments - 54 patients in each group failed Step 1. All failures from group 1 but only 44 of group 2 failures moved

onto Step 2 of treatment. The authors do not explain the reason for the 10 missing patients. This is a subgroup analyses involving 2 out of a 4 treatment arm RCT (BeSt trial). ; Indirectness of outcome: No indirectness ; Group 1 Number missing: 0; Group 2 Number missing: 10, Reason: not mentioned Protocol outcome 3: Withdrawal/discontinuation: inefficacy at Longest time period reported - Actual outcome for MTX failed: 'failure' = DAS >2.4 after Step 1 (SSZ mono- or combination therapy) at during 2 years; Group 1: 47/69, Group 2: 41/69 Risk of bias: All domain - High, Selection - Low, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low, Subgroups - High; Indirectness of outcome: No indirectness ; Group 1 Number missing: 0; Group 2 Number missing: 0 - Actual outcome for MTX failed: 'failure' = DAS >2.4 after Step 2 (SSZ failure, followed by LFN mono Group 1 or MTX+SSZ+HCQ Group 2) at during 2 years; Group 1: 41/54, Group 2: 21/44 Risk of bias: All domain - Very high, Selection - Low, Blinding - Low, Incomplete outcome data - High, Outcome reporting - Low, Measurement - Low, Crossover - Low, Subgroups - High, Comments - 54 patients in each group failed Step 1. All failures from group 1 but only 44 of group 2 failures moved onto Step 2 of treatment. The authors do not explain the reason for the 10 missing patients. This is a subgroup analyses involving 2 out of a 4 treatment arm RCT (BeSt trial). ; Indirectness of outcome: No indirectness ; Group 1 Number missing: 0; Group 2 Number missing: 10, Reason: not mentioned	
Protocol outcomes not reported by the study	Disease Activity Score at 12 months; Disease Activity Score at 6 months; Quality of life at 12 months; Quality of life at 6 months; Function at 6 months; Function at 12 months; Pain at 6 months; Pain at 12 months; Remission at 6 months; Remission at 12 months; Low disease activity at 6 months; ACR50 response at 6 months; ACR50 response at 12 months; Radiological progression at 12+ months; Adverse events - mortality at 12+ months

Study	Methotrexate following failed sulphasalazine therapy trial: Haagsma 1994[56]
Study type	RCT (Patient randomised; Parallel)
Number of studies (number of participants)	1 (n=40)
Countries and setting	Conducted in Netherlands; Setting: Patients having RA who had an insufficient response to sulphasalazine (SSZ) according to their treating physician were considered for selection. In all patients SSZ treatment was stopped for 2 weeks. Patients were then randomised.
Line of therapy	Mixed line
Duration of study	Intervention time: 24 weeks
Method of assessment of guideline condition	Adequate method of assessment/diagnosis
Stratum	SSZ failed
Subgroup analysis within study	Not applicable
Inclusion criteria	1. age 18 years and older 2. RA according to the revised ACR criteria (1987) 3. current SSZ treatment given for at least 6 months, but with insufficient effect 4. active arthritis defined by: a DAS of minimally 3.0 (corresponding with a Ritchie score of 5 plus six swollen joints and an ESR of 30)
Exclusion criteria	1. preceding treatment with MTX 2. contraindications for the use of MTX- insufficient kidney function defined as the estimated creatinine clearance (according to Cockroft) of less than 75 ml/min, liver disease, i.e. clinically significant hepatic impairment, liver enzymes more than twice the upper limit of the normal values or dormant serious liver disease (e.g. cirrhosis), uncontrolled diabetes mellitus (insulin dependent), severe congestive heart failure, interstitial lung disease, active peptic ulcers, inflammatory bowel disease, malignancies, leucopenia i.e. WBC count <3.5x109/l, thrombocytopenia i.e. platelet count <120 x109/l, pregnancy, intended pregnancy, breastfeeding or inability of adequate contraception, known or suspected alcoholism; 3. the use of glucocorticoids 4. no informed consent.
Recruitment/selection of patients	Patients having RA who had an insufficient response to sulphasalazine (SSZ) according to their treating physician were considered for selection.
Age, gender and ethnicity	Age - Mean (SD): MTX group: 51.8 (13.9); MTX+SSZ group: 59.3 (12.3) . Gender (M:F): 1/3. Ethnicity: not mentioned
Further population details	1. Disease duration: established RA (> 2 years) (not mentioned specifically but induced from mean (SD) disease duration: MTX 5.3 (4.2); MTX+SSZ 4.7 (4.2)).

Extra comments	Before starting on SSZ in the first phase of the study patients in both groups had used 1 median (range 0-4) DMARD previously.
Indirectness of population	No indirectness
Interventions	(n=22) Intervention 1: Parallel combination therapy - Parallel combination therapy - specify. Methotrexate (MTX; 7.5 mg/week given in a single dose)combined with Sulphasalazine (SSZ; 2g/day in two divided doses). If there was insufficient improvement after 16 weeks of study and the medication was tolerated, the MTX dose was increased to 15mg/week in two divided doses with an interval of 24 hours. If unacceptable toxicity occurred, i.e. abnormal laboratory values as defined under the heading evaluation, measured on two occasions (the liver enzymes had to be greater than twice the normal value),severe skin rash, pulmonary abnormalities attributable to the study drugs or intolerable subjective side-effects, the MTX dose was reduced to 5mg/week and the SSZ dose to 1g or the medication was stopped, followed by a re-challenge depending on the severity of adverse drug reaction. If a dose reduction had insufficient effect, folic acid in a dose of 1mg daily was added in the case of minor toxicity. Patients were evaluated 2 weeks before entry, and on weeks0, 4, 8, 12, 16, 20 and 24.. Duration 24 weeks. Concurrent medication/care: NSAIDs were given in a stable dose. No systemic glucocorticoids were allowed, one local injection of glucocorticoids was permitted but discouraged.. Indirectness: No indirectness Further details: 1. Dose: Lower dose (sulfasalazine: 1 gm, methotrexate: <=15mg, leflunomide: 10mg, hydroxychloroquine: 200mg) (MTX 7.5mg/week given in a single dose (increased to 15mg/week in two divided doses after 16 weeks if effect insufficient and MTX was tolerated) plus SSZ enteric coated 2g/day in two divided doses). 2. Use of glucocorticoids: Short term glucocorticoids not used (glucocorticoid use was part of exclusion criteria). (n=18) Intervention 2: Monotherapy - Monotherapy - specify. Methotrexate (MTX; 7.5 mg/week given in a single dose). If there was insufficient improvement after 16 weeks of study and the medication was tolerated, the MTX dose was increased to 15mg/week in two divided doses with an interval of 24 hours. If unacceptable toxicity occurred, i.e. abnormal laboratory values as defined under the heading evaluation, measured on two occasions (the liver enzymes had to be greater than twice the normal value),severe skin rash, pulmonary abnormalities attributable to the study drugs or intolerable subjective side-effects, the MTX dose was reduced to 5mg/week or the medication was stopped, followed by a re-challenge depending on the severity of adverse drug reaction. If a dose reduction had insufficient effect,folic acid in a dose of 1mg daily was added in the case of minor toxicity. Patients were evaluated 2 weeks before entry, and on weeks 0, 4, 8, 12, 16, 20 and 24.. Duration 24 weeks. Concurrent medication/care: NSAIDs were given in a stable dose. No systemic glucocorticoids were allowed, one local injection of glucocorticoids was permitted but discouraged.. Indirectness: No indirectness Further details: 1. Dose: Lower dose (sulfasalazine: 1 gm, methotrexate: <=15mg, leflunomide: 10mg, hydroxychloroquine: 200mg) (MTX 7.5mg/week given in a single dose (increased to 15mg/week in two divided doses after 16 weeks if effect insufficient and MTX was tolerated)). 2. Use of glucocorticoids: Short

	term glucocorticoids not used (glucocorticoid use was part of exclusion criteria).
Funding	Funding not stated

RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: PARALLEL COMBINATION THERAPY - MTX+SSZ versus MONOTHERAPY - MTX

Protocol outcome 1: Disease Activity Score at 6 months
- Actual outcome for SSZ failed: DAS (change from baseline- at time of randomisation) at 24 weeks; Group 1: mean -2.6 (SD 0.9); n=22, Group 2: mean -1 (SD 0.9); n=18; DAS 0-10 Top=High is poor outcome
Risk of bias: All domain - High, Selection - High, Blinding - High, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Baseline details: used 'balanced allocation method'
MTX+SSZ group older; Group 1 Number missing: 0; Group 2 Number missing: 0

Protocol outcome 2: Pain at 6 months
- Actual outcome for SSZ failed: VAS Pain (change from baseline- at time of randomisation) at 24 weeks; Group 1: mean -30 (SD 26); n=22, Group 2: mean -14 (SD 20); n=18; VAS (mm) 0-100 Top=High is poor outcome
Risk of bias: All domain - Very high, Selection - High, Blinding - High, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Baseline details: used 'balanced allocation method'
MTX+SSZ group older; Group 1 Number missing: 0; Group 2 Number missing: 0

Protocol outcome 3: Withdrawal/discontinuation: adverse events at Longest time period reported
- Actual outcome for SSZ failed: Withdrawal due to adverse events at 24 weeks; Group 1: 0/22, Group 2: 0/18
Risk of bias: All domain - High, Selection - High, Blinding - High, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Baseline details: used 'balanced allocation method'
MTX+SSZ group older; Group 1 Number missing: 0; Group 2 Number missing: 0

Protocol outcome 4: Withdrawal/discontinuation: inefficacy at Longest time period reported
- Actual outcome for SSZ failed: Withdrawal due to inefficacy at 24 weeks; Group 1: 0/22, Group 2: 0/18
Risk of bias: All domain - High, Selection - High, Blinding - High, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Baseline details: used 'balanced allocation method'
MTX+SSZ group older; Group 1 Number missing: 0; Group 2 Number missing: 0

Protocol outcomes not reported by the study	Disease Activity Score at 12 months; Quality of life at 12 months; Quality of life at 6 months; Function at 6 months; Function at 12 months; Pain at 12 months; Remission at 6 months; Remission at 12 months; Low disease activity at 6 months; Low disease activity at 12 months; ACR50 response at 6 months; ACR50 response at 12 months; Radiological progression at 12+ months; Adverse events - mortality at 12+ months

Study	Sulfasalazine failed: followed by MTX+SSZ versus MTX trial: Capell 2007[19]
Study type	RCT (Patient randomised; Parallel)
Number of studies (number of participants)	1 (n=110)
Countries and setting	Conducted in United Kingdom; Setting: A randomised controlled study in eight Scottish NHS sites - four in Glasgow, three in Lanarkshire, and one in Inverness.
Line of therapy	Mixed line
Duration of study	Intervention time: 12 months
Method of assessment of guideline condition	Adequate method of assessment/diagnosis
Stratum	SSZ failed
Subgroup analysis within study	Not applicable
Inclusion criteria	Inclusion criteria were: aged 18-80 years and disease duration <10 years, with active disease defined by DAS of >2.4.
Exclusion criteria	Patients were excluded if they had: prior exposure to either MTX or SSZ, known sulphonamide allergy, significant renal (creatinine >150 mmol/dl) or liver (alanine aminotransferase aspartate aminotransferase >80 IU/l, alkaline phosphatase >700 IU/l, Y-glulamyl transferase x3) disease, abnormal white cell count (<4x 109/l), pre-existing pulmonary fibrosis, known or planned pregnancy or use of oral glucocorticoids >7.5mg/day.
Recruitment/selection of patients	Between May 1999 and June 2003, 687 patients with rheumatoid arthritis were recruited.
Age, gender and ethnicity	Age - Mean (range): MTX+SSZ: 56 (30-78); SSZ: 55 (18-77); MTX: 53 (34-79). Gender (M:F): 1/3. Ethnicity: not mentioned specifically, but study conducted in Scotland
Further population details	1. Disease duration: Not stated / Unclear (disease duration <10 years).
Extra comments	Patients screened who did not meet the entry criteria or were not willing to participate in the study were documented. The authors do not specifically mention previous DMARD use other than one of the exclusion criteria being patients who had been on MTX or SSZ.
Indirectness of population	No indirectness
Interventions	(n=56) Intervention 1: Parallel combination therapy - Parallel combination therapy - specify. Continue SSZ at the dose achieved by 6 months with the addition of MTX initially 7.5mg/week (3x 2.5mg), increasing by 2.5mg/month (1x 2.5mg) until the maximal permitted dose of 25mg or toxicity occurred. Assessments were performed at 6, 9, 12, 15 and 18 months. Those patients whose DAS was considered 'too good' (DAS<2.4) to receive combination therapy and who continued with SSZ or an alternative drug were also assessed at 18 months.. Duration 12 months. Concurrent medication/care: Folic acid 5 mg/week

	given 3 days after MTX/MTX placebo. Concomitant non-glucocorticoid anti-inflammatory drugs and other drugs were continued. Intra-articular or intramuscular glucocorticoid was permitted, but not within 1 month of the 6, 12 or 18 month assessments.. Indirectness: No indirectness Further details: 1. Dose: Higher dose (sulfasalazine: 2 gm, methotrexate: >15 mg, leflunomide: 20mg, hydroxychloroquine: 400mg) (Continue SSZ at the dose achieved by 6 months (max dose of 4g/day) with the addition of MTX initially 7.5mg/week (3x 2.5mg), increasing by 2.5mg/month (1x 2.5mg) until the maximal permitted dose of 25mg or toxicity occurred.). 2. Use of glucocorticoids: Short term glucocorticoids used (Intra-articular or intramuscular glucocorticoid was permitted, but not within 1 month of the 6, 12 or 18 month assessments. Patients who used oral glucocorticoids >7.5mg/day were excluded.). (n=54) Intervention 2: Monotherapy - Monotherapy - specify. Placebo SSZ at the previously achieved number of tablets by6 months, with the addition of MTX, initially 7.5mg/week, increasing by 2.5mg/month until the maximal dose of 25 mg/week or toxicity occurred. Assessments were performed at 6, 9, 12, 15 and 18 months. Those patients whose DAS was considered 'too good' (DAS<2.4) to receive combination therapy and who continued with SSZ or an alternative drug were also assessed at 18 months.. Duration 12 months. Concurrent medication/care: Folic acid 5 mg/week given 3 days after MTX/MTX placebo. Concomitant non-glucocorticoid anti-inflammatory drugs and other drugs were continued. Intra-articular or intramuscular glucocorticoid was permitted, but not within 1 month of the 6, 12 or 18 month assessments.. Indirectness: No indirectness Further details: 1. Dose: Higher dose (sulfasalazine: 2 gm, methotrexate: >15 mg, leflunomide: 20mg, hydroxychloroquine: 400mg) (Placebo SSZ at the previously achieved number of tablets by 6 months, with the addition of MTX, initially 7.5mg/week, increasing by 2.5 mg/month until the maximal dose of 25 mg/week or toxicity occurred.). 2. Use of glucocorticoids: Short term glucocorticoids used (Intra-articular or intramuscular glucocorticoid was permitted, but not within 1 month of the 6, 12 or 18 month assessments. Patients who used oral glucocorticoids >7.5mg/day were excluded.).
Funding	Academic or government funding (but drugs provided by industry)

RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: PARALLEL COMBINATION THERAPY - MTX+SSZ versus MONOTHERAPY - MTX+PLACEBO

Protocol outcome 1: Disease Activity Score at 12 months
- Actual outcome for SSZ failed: DAS (median and IQR; change from baseline/6 months to 18 months) at 12 months; MTX+SSZ: -0.67 (-1.38 to -0.21) MTX+placebo: -0.26 (-0.99 to 0);
Risk of bias: All domain - High, Selection - Low, Blinding - Low, Incomplete outcome data - High, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: 17, Reason: intercurrent illness, side effects, lack of effect, non-

compliance/lost to follow-up; Group 2 Number missing: 16, Reason: intercurrent illness, side effects, lack of effect, non-compliance/lost to follow-up

Protocol outcome 2: Function at 12 months
- Actual outcome for SSZ failed: HAQ (median and IQR; change from baseline/6 months to 18 months) at 12 months; HAQ 0-100 Top=High is poor outcome; MTX+SSZ: -0.5 (-10.25 to 0.06)
MTX+placebo: -0.19 (-10.25 to 0.13);
Risk of bias: All domain - High, Selection - Low, Blinding - Low, Incomplete outcome data - High, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: 17, Reason: intercurrent illness, side effects, lack of effect, non-compliance/lost to follow-up; Group 2 Number missing: 16, Reason: intercurrent illness, side effects, lack of effect, non-compliance/lost to follow-up

Protocol outcome 3: Pain at 12 months
- Actual outcome for SSZ failed: Pain score (median and IQR; change from baseline/6 months to 18 months) at 12 months; MTX+SSZ: -8 (-27.5 to 2)
MTX+placebo: 0 (-23 to 11);
Risk of bias: All domain - High, Selection - Low, Blinding - Low, Incomplete outcome data - High, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: 17, Reason: intercurrent illness, side effects, lack of effect, non-compliance/lost to follow-up; Group 2 Number missing: 16, Reason: intercurrent illness, side effects, lack of effect, non-compliance/lost to follow-up

Protocol outcome 4: ACR50 response at 12 months
- Actual outcome for SSZ failed: ACR50 response (at 18 months) at 12 months; Group 1: 6/56, Group 2: 4/54
Risk of bias: All domain - High, Selection - Low, Blinding - Low, Incomplete outcome data - High, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: 17, Reason: intercurrent illness, side effects, lack of effect, non-compliance/lost to follow-up; Group 2 Number missing: 16, Reason: intercurrent illness, side effects, lack of effect, non-compliance/lost to follow-up

Protocol outcome 5: Withdrawal/discontinuation: adverse events at Longest time period reported
- Actual outcome for SSZ failed: withdrawal due to side effects (6 to 18 months) at 12 months; Group 1: 12/56, Group 2: 14/54
Risk of bias: All domain - Low, Selection - Low, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: 5, Reason: intercurrent illness, lack of effect, non-compliance/lost to follow-up; Group 2 Number missing: 2, Reason: intercurrent illness, lack of effect, non-compliance/lost to follow-up
- Actual outcome for SSZ failed: withdrawal due to lack of effects (6 to 18 months) at 12 months; Group 1: 2/56, Group 2: 2/54
Risk of bias: All domain - High, Selection - Low, Blinding - Low, Incomplete outcome data - High, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: 15, Reason: intercurrent illness, side effects, non-compliance/lost to follow-up; Group 2 Number missing: 14, Reason: intercurrent illness, side effects, non-compliance/lost to follow-up

Protocol outcomes not reported by the study	Disease Activity Score at 6 months; Quality of life at 12 months; Quality of life at 6 months; Function at 6 months; Pain at 6 months; Remission at 6 months; Remission at 12 months; Low disease activity at 6 months; Low disease activity at 12 months; ACR50 response at 6 months; Radiological progression at 12+ months; Adverse events - mortality at 12+ months; Withdrawal/discontinuation: inefficacy at Longest time period reported

1 2

Appendix E: Forest plots

E.1 First line DMARDs

Monotherapy versus placebo

E.1.1 Monotherapy: sulfasalazine (SSZ) versus placebo

Figure 3: Pain (VAS) at 6 months

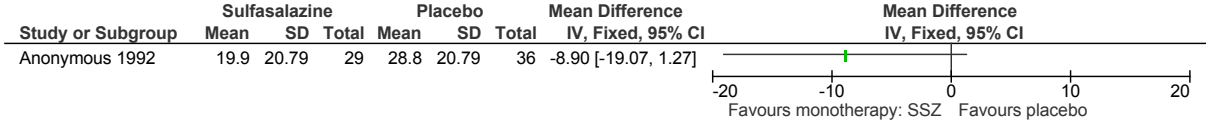


Figure 4: Radiological progression (modified Sharp score) at 12+ months

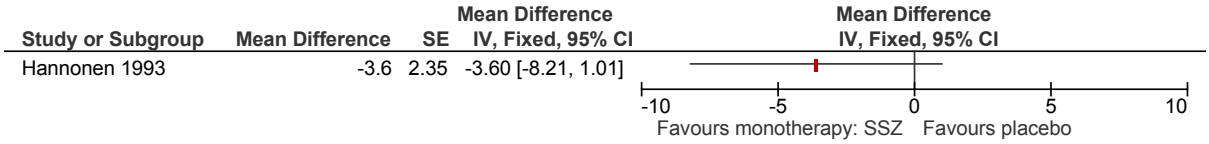


Figure 5: Adverse events - mortality

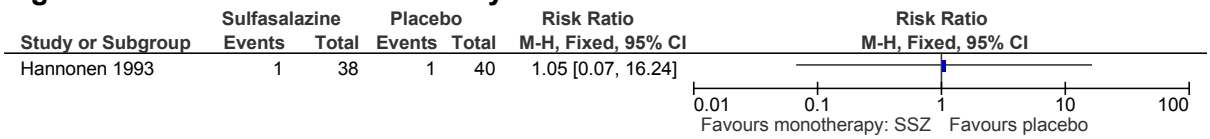


Figure 6: Withdrawal: inefficacy

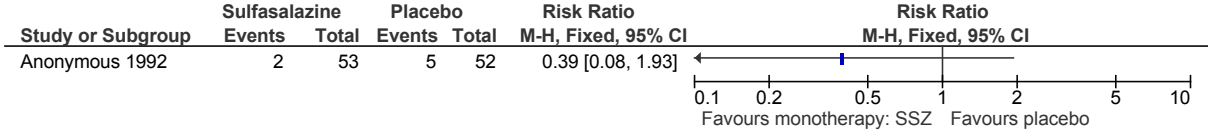
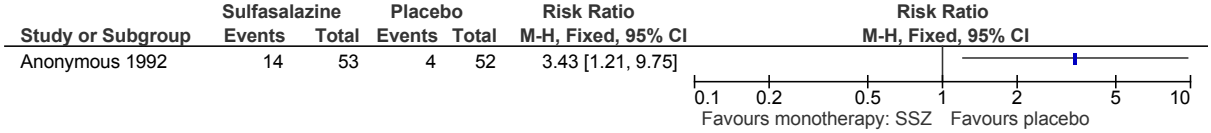


Figure 7: Withdrawal: adverse events



E.1.2 Monotherapy: hydroxychloroquine (HCQ) versus placebo

Figure 8: Change in quality of life (global wellbeing) at 12 months

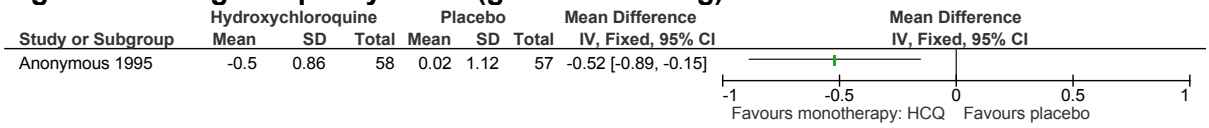


Figure 9: Change in function (psychological disability via AIMS) at 12 months

Study or Subgroup	Hydroxychloroquine Mean	SD	Total	Placebo Mean	SD	Total	Mean Difference IV, Fixed, 95% CI
Anonymous 1995	-0.44	0.95	58	-0.41	1.04	57	-0.03 [-0.39, 0.33]

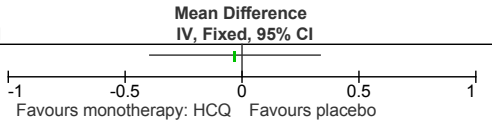


Figure 10: Change in pain (VAS) at 6 months

Study or Subgroup	Hydroxychloroquine Mean	SD	Total	Placebo Mean	SD	Total	Mean Difference IV, Fixed, 95% CI
Clark 1993	-25.8	28.75	63	-6.5	32.25	58	-19.30 [-30.22, -8.38]

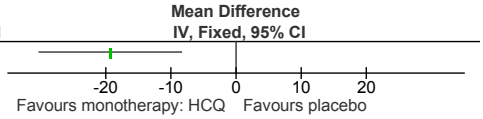


Figure 11: Withdrawal: adverse events at 12 months

Study or Subgroup	Hydroxychloroquine Events	Total	Placebo Events	Total	Risk Ratio M-H, Fixed, 95% CI
Anonymous 1995	1	54	2	46	0.43 [0.04, 4.55]

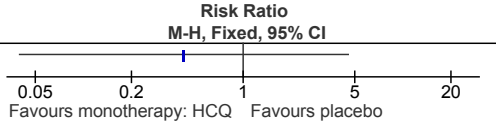
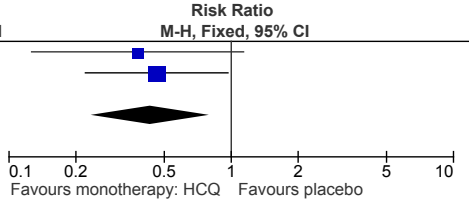


Figure 12: Withdrawal: inefficacy

Study or Subgroup	Hydroxychloroquine Events	Total	Placebo Events	Total	Weight	Risk Ratio M-H, Fixed, 95% CI
Anonymous 1995	4	57	10	54	36.8%	0.38 [0.13, 1.14]
Davis 1991	8	51	18	53	63.2%	0.46 [0.22, 0.97]
Total (95% CI)		**108**		**107**	**100.0%**	**0.43 [0.23, 0.80]**
Total events	12		28			

Heterogeneity: Chi² = 0.09, df = 1 (P = 0.77); I² = 0%
Test for overall effect: Z = 2.68 (P = 0.007)



1 Monotherapy versus monotherapy

E.1.32 Monotherapy: sulfasalazine (SSZ) versus monotherapy methotrexate (MTX)

Figure 13: Change in Disease Activity (DAS) Score at 12 months

Study or Subgroup	Monotherapy: sulfasalazine Mean	SD	Total	Monotherapy methotrexate Mean	SD	Total	Mean Difference IV, Fixed, 95% CI
Haagsma 1997	-1.8	1.2	22	-2	1.03	33	0.20 [-0.41, 0.81]

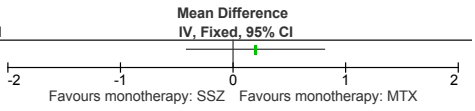


Figure 14: Change in Disease Activity Score (DAS) at 6 months

Study or Subgroup	Monotherapy: sulfasalazine Mean	SD	Total	Monotherapy methotrexate Mean	SD	Total	Mean Difference IV, Fixed, 95% CI
Haagsma 1997	-1.1	0.48	22	-1	0.59	33	-0.10 [-0.38, 0.18]

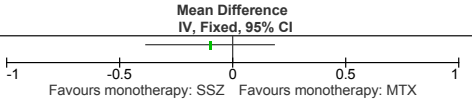


Figure 15: Change in function (HAQ) at 12 months

Study or Subgroup	Monotherapy: sulfasalazine Mean	SD	Total	Monotherapy methotrexate Mean	SD	Total	Mean Difference IV, Fixed, 95% CI
Haagsma 1997	-0.32	0.51	22	-0.46	0.63	33	0.14 [-0.16, 0.44]

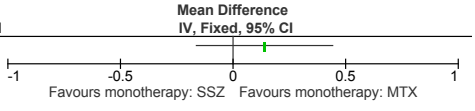


Figure 16: ACR50 response at 6 months

Study or Subgroup	Monotherapy: sulfasalazine Events	Total	Monotherapy methotrexate Events	Total	Risk Ratio M-H, Fixed, 95% CI
Ferraccioli 2002	14	37	24	42	0.66 [0.41, 1.08]

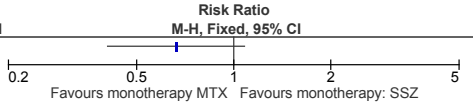


Figure 17: Change in pain (VAS) at 12 months

Study or Subgroup	Monotherapy: sulfasalazine Mean	SD	Total	Monotherapy methotrexate Mean	SD	Total	Mean Difference IV, Fixed, 95% CI
Haagsma 1997	-25.2	26.8	22	-25.1	22.72	33	-0.10 [-13.72, 13.52]

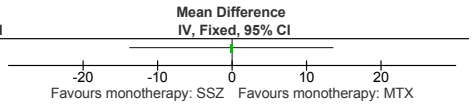


Figure 18: Change in pain (VAS) at 6 months

Study or Subgroup	Monotherapy: sulfasalazine Mean	SD	Total	Monotherapy methotrexate Mean	SD	Total	Mean Difference IV, Fixed, 95% CI
Haagsma 1997	-18.1	16.87	22	-12.3	19.64	33	-5.80 [-15.53, 3.93]

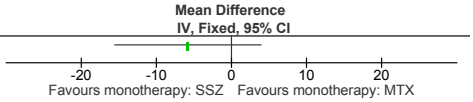


Figure 19: Withdrawal: adverse events

Study or Subgroup	Monotherapy: sulfasalazine Events	Total	Monotherapy methotrexate Events	Total	Weight	Risk Ratio M-H, Fixed, 95% CI
Dougados 1999	10	57	7	61	78.3%	1.53 [0.62, 3.74]
Haagsma 1997	9	31	2	35	21.7%	5.08 [1.19, 21.74]
Total (95% CI)		**88**		**96**	**100.0%**	**2.30 [1.10, 4.82]**
Total events	19		9			

Heterogeneity: Chi² = 1.94, df = 1 (P = 0.16); I² = 48%
Test for overall effect: Z = 2.21 (P = 0.03)

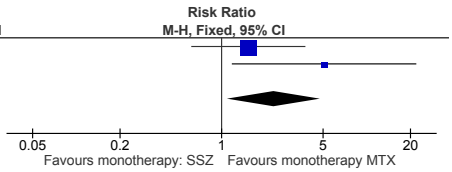
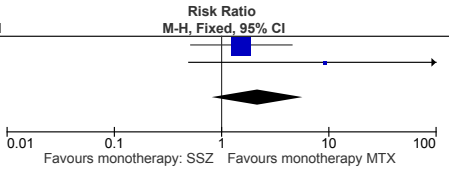


Figure 20: Withdrawal: inefficacy

Study or Subgroup	Monotherapy: sulfasalazine Events	Total	Monotherapy methotrexate Events	Total	Weight	Risk Ratio M-H, Fixed, 95% CI
Dougados 1999	7	54	5	59	91.7%	1.53 [0.52, 4.53]
Haagsma 1997	3	25	0	33	8.3%	9.15 [0.49, 169.53]
Total (95% CI)		**79**		**92**	**100.0%**	**2.16 [0.82, 5.74]**
Total events	10		5			

Heterogeneity: Chi² = 1.33, df = 1 (P = 0.25); I² = 25%
Test for overall effect: Z = 1.55 (P = 0.12)



E.1.41 Monotherapy: leflunomide (LFN) versus monotherapy: methotrexate (MTX)

Figure 21: Change in Disease Activity Score (DAS28) at 12 months

Study or Subgroup	Mean Difference	SE	Mean Difference IV, Fixed, 95% CI
Jaimes-Hernandez 2012	0.45	0.63	0.45 [-0.78, 1.68]

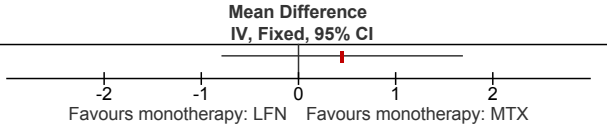


Figure 22: Change in Disease Activity Score (DAS28) at 6 months

Study or Subgroup	Monotherapy: LFN Mean	SD	Total	Monotherapy: MTX Mean	SD	Total	Mean Difference IV, Fixed, 95% CI
Lisbona 2012	-0.87	1.22	29	-1.46	1.6	33	0.59 [-0.11, 1.29]

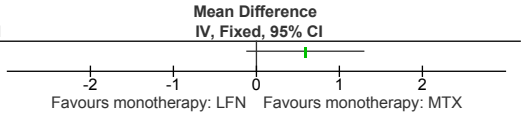


Figure 23: Change in function (HAQ-Di) at 12 months

Study or Subgroup	Mean Difference	SE	Mean Difference IV, Fixed, 95% CI
Jaimes-Hernandez 2012	-0.29	0.145	-0.29 [-0.57, -0.01]

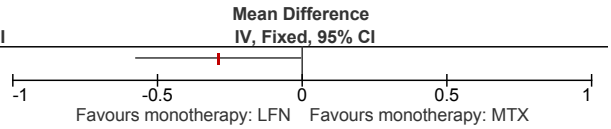


Figure 24: Change in function (HAQ) at 6 months

Study or Subgroup	Monotherapy: LFN Mean	SD	Total	Monotherapy: MTX Mean	SD	Total	Mean Difference IV, Fixed, 95% CI
Lisbona 2012	-0.235	0.374	29	-0.242	0.543	33	0.01 [-0.22, 0.24]

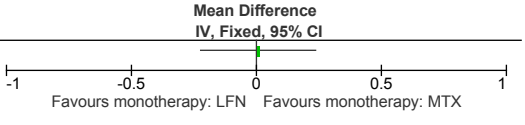


Figure 25: DAS remission at 12 months

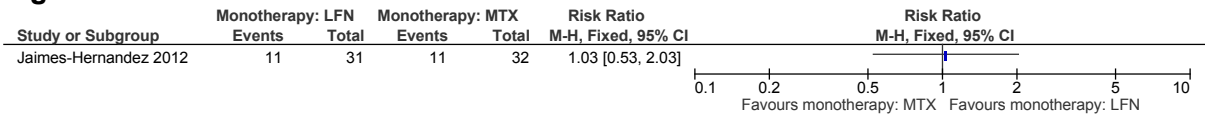


Figure 26: Change in pain (VAS) at 6 months

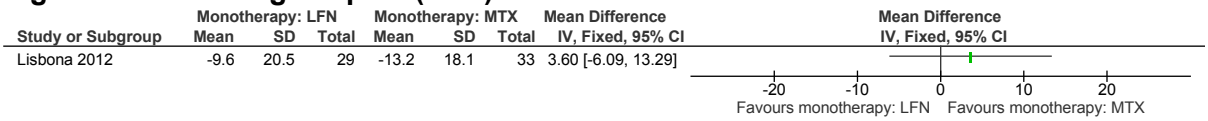


Figure 27: Withdrawal: adverse events

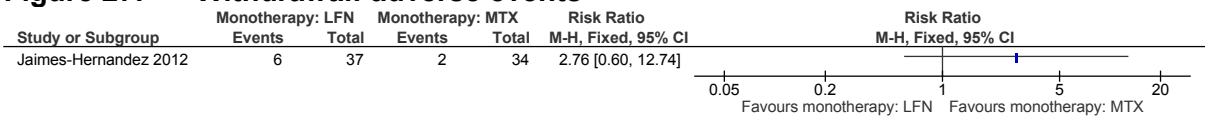
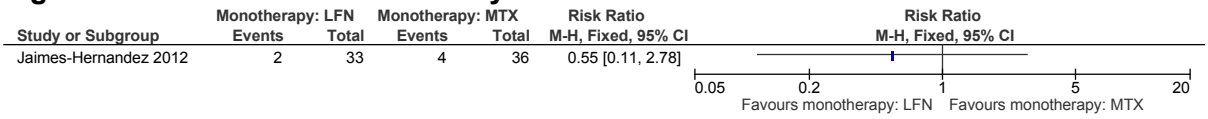


Figure 28: Withdrawal: inefficacy



E.1.51 Monotherapy: hydroxychloroquine (HCQ) versus monotherapy: sulfasalazine 2 (SSZ)

Figure 29: Pain (VAS) at 12 months

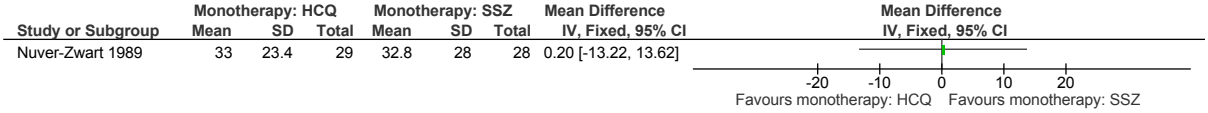


Figure 30: Pain (VAS) at 6 months

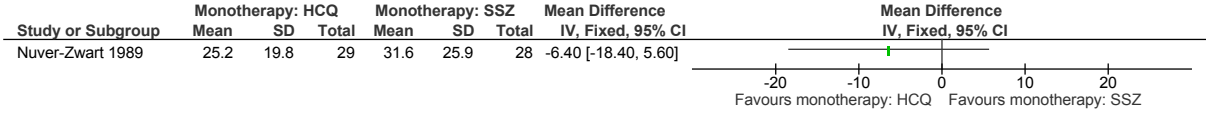


Figure 31: Change in radiological progression (SvdH score) at 12+ months

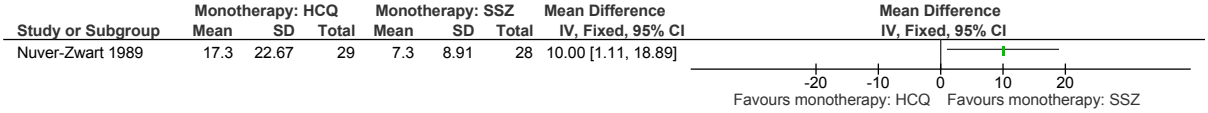


Figure 32: Withdrawal: adverse events

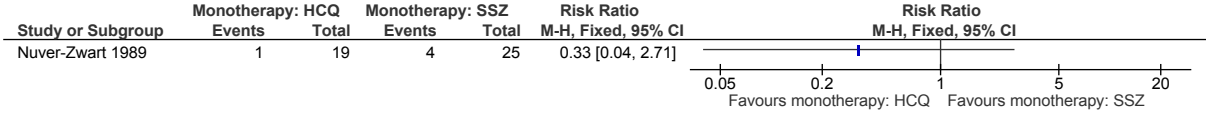
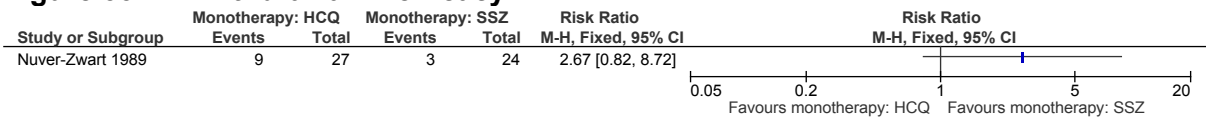


Figure 33: Withdrawal: inefficacy



E.1.6 Monotherapy: hydroxychloroquine (HCQ) versus monotherapy: methotrexate (MTX)

Figure 34: Change in function (HAQ) at 12 months

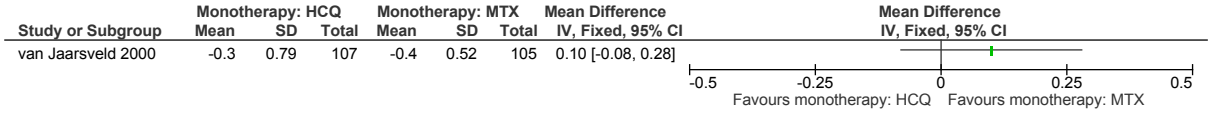


Figure 35: ACR remission at 12 months

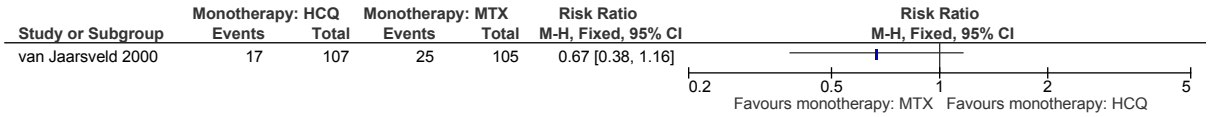


Figure 36: Change in pain (VAS) at 12 months

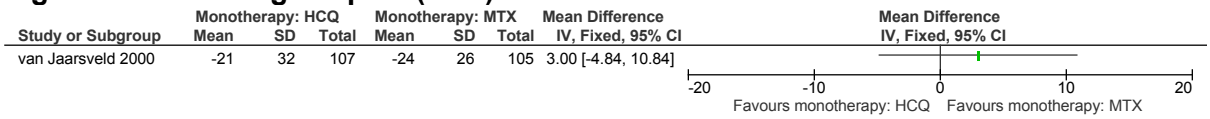


Figure 37: Discontinuation of strategy: adverse events at 12 months

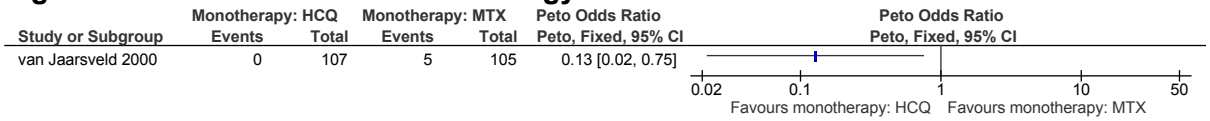
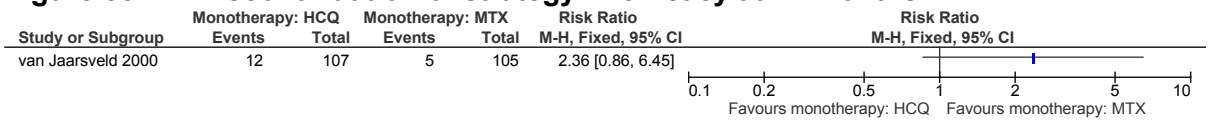


Figure 38: Discontinuation of strategy: inefficacy at 12 months



Monotherapy versus other treatment class

E.1.7 Step-down therapy: sulfasalazine (SSZ), methotrexate (MTX) versus monotherapy: sulfasalazine (SSZ)

Figure 39: Change in Disease Activity Score (DAS) at 12 months

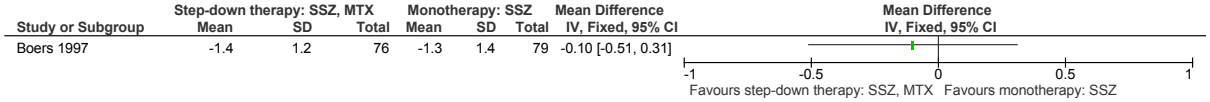


Figure 40: Change in Disease Activity Score (DAS) at 6 months

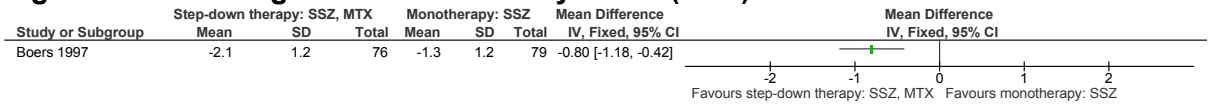


Figure 41: Change in function (HAQ) at 12 months

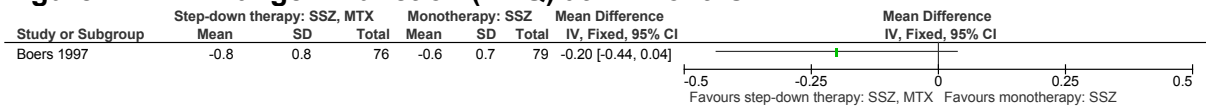


Figure 42: Change in function (HAQ) at 6 months

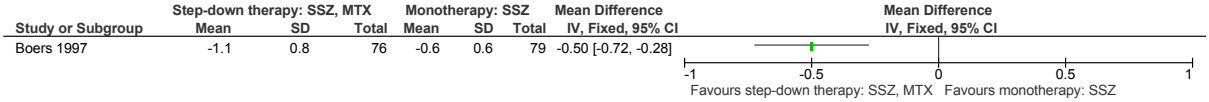


Figure 43: Change in function (MACTAR) at 12 months

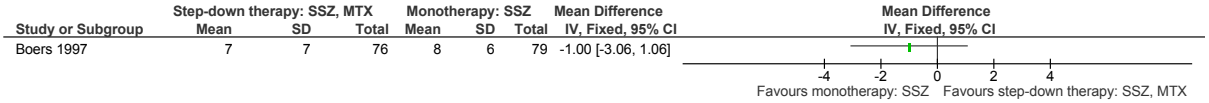


Figure 44: Change in function (MACTAR) at 6 months

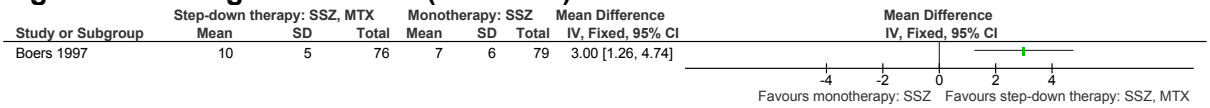


Figure 45: ACR remission at 12 months

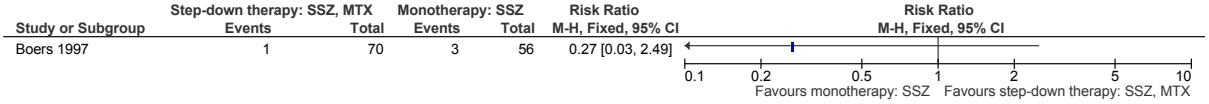


Figure 46: ACR50 response at 6 months

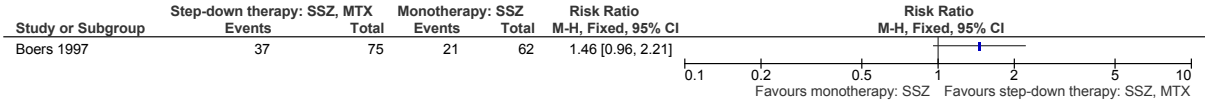


Figure 47: Change in pain (VAS) at 12 months

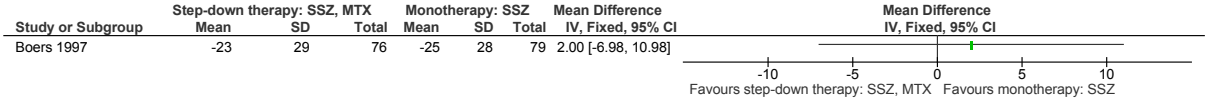


Figure 48: Change in pain (VAS) at 6 months

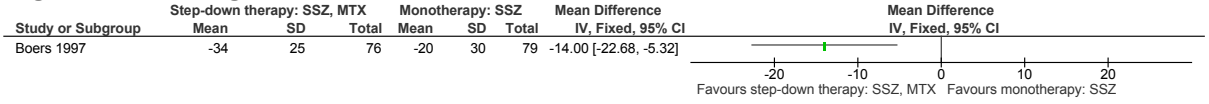


Figure 49: Withdrawal: adverse events

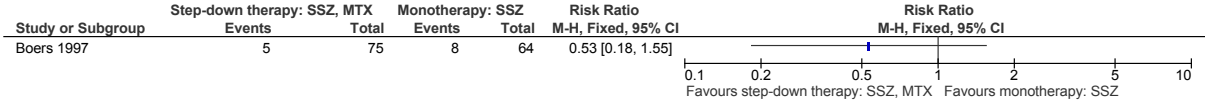
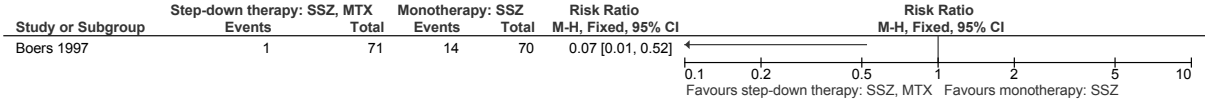


Figure 50: Withdrawal: inefficacy



E.1.81 Parallel combination therapy: methotrexate (MTX), sulfasalazine (SSZ) versus 2 monotherapy: sulfasalazine (SSZ)

Figure 51: Change in Disease Activity Score (DAS) at 12 months

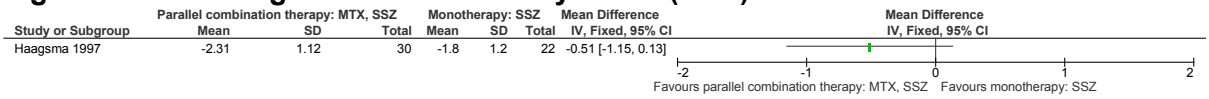


Figure 52: Change in Disease Activity Score (DAS) at 6 months

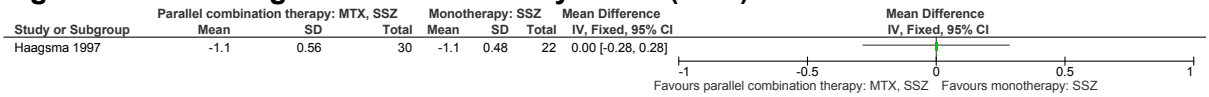


Figure 53: Change in function (HAQ) at 12 months

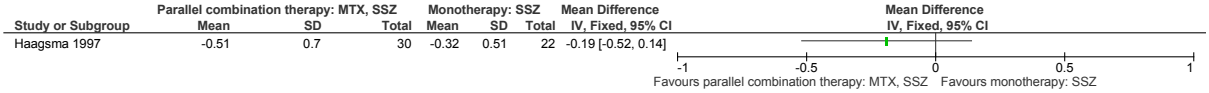


Figure 54: Change in pain (VAS) at 12 months

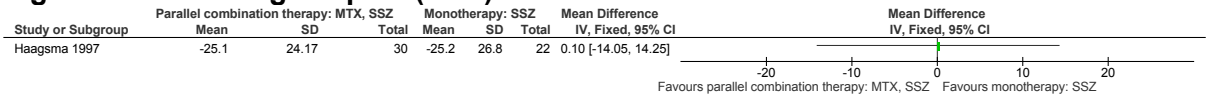


Figure 55: Change in pain (VAS) at 6 months

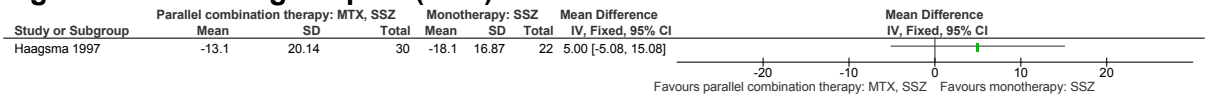


Figure 56: Withdrawal: adverse events

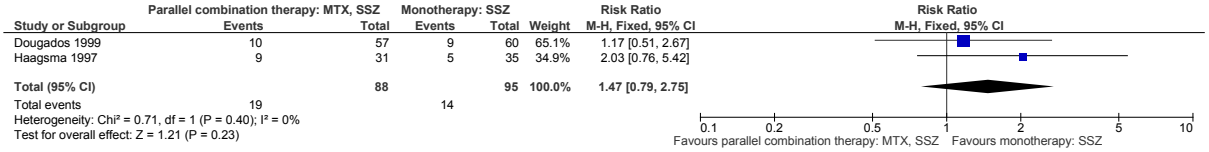
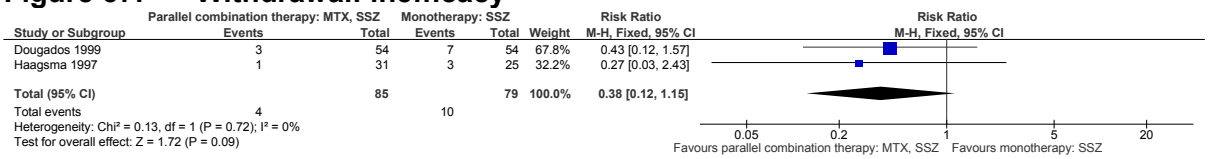


Figure 57: Withdrawal: inefficacy



E.1.93 Parallel combination therapy: methotrexate (MTX), sulfasalazine (SSZ) versus 4 monotherapy: methotrexate (MTX)

Figure 58: Change in Disease Activity Score (DAS) at 12 months

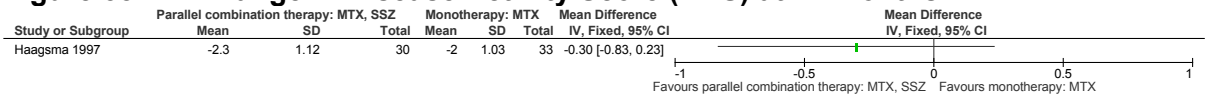


Figure 59: Change in Disease Activity Score (DAS) at 6 months

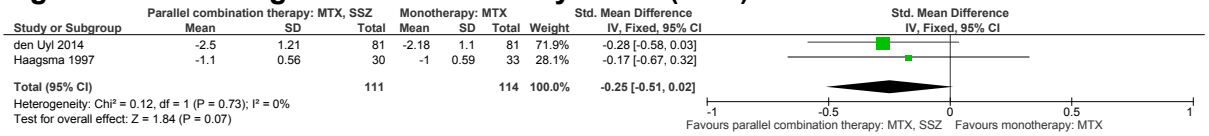


Figure 60: Change/final function (HAQ) at 12 months

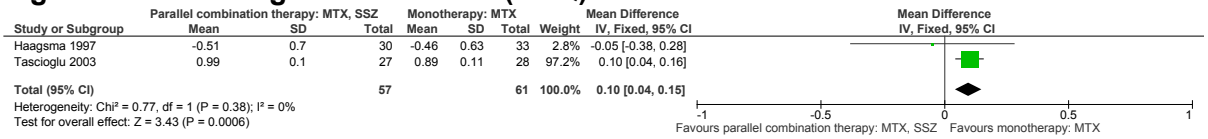


Figure 61: Change/final function (HAQ) at 6 months

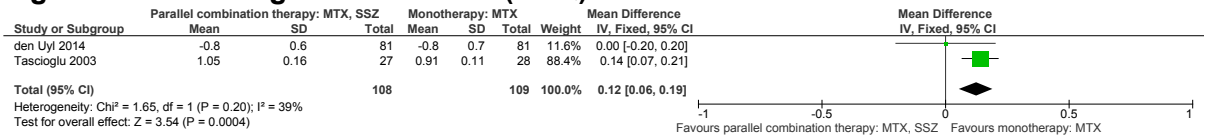


Figure 62: ACR/EULAR Boolean remission at 6 months

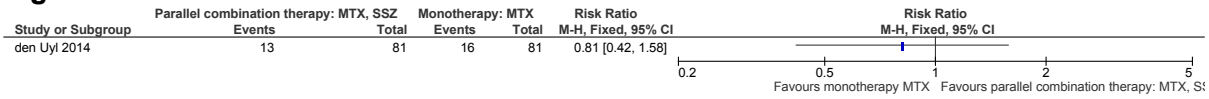


Figure 63: ACR50 response at 6 months

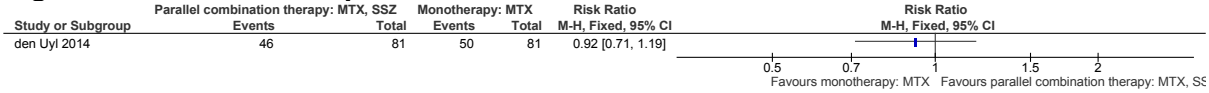


Figure 64: Change/final pain (VAS) at 12 months

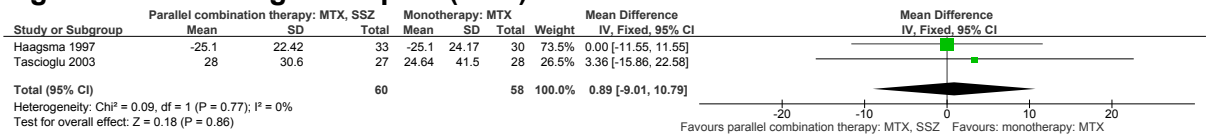


Figure 65: Change/final pain (VAS) at 6 months

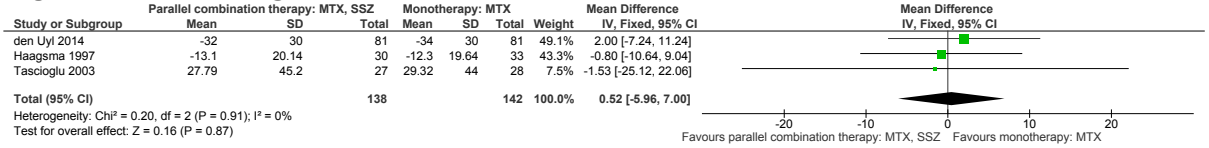


Figure 66: Withdrawal: adverse events

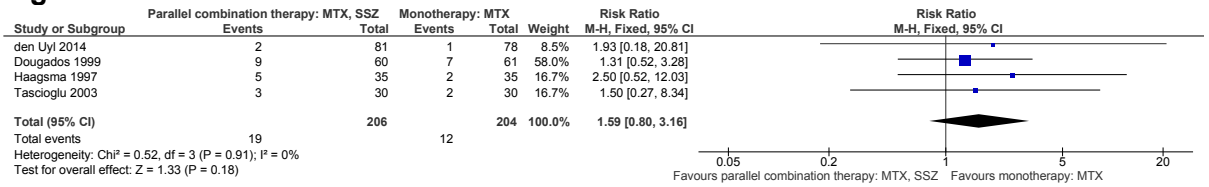
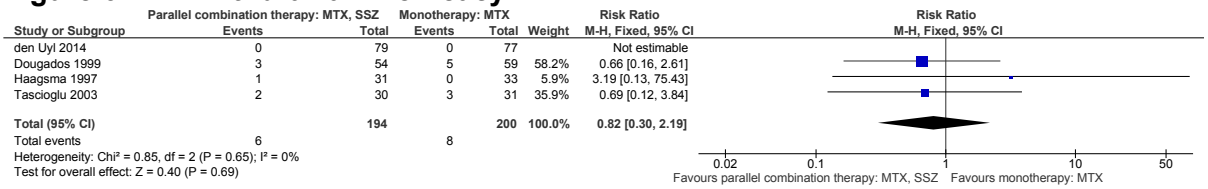


Figure 67: Withdrawal: inefficacy



E.1.101 Parallel combination therapy: methotrexate (MTX), sulfasalazine (SSZ), hydroxychloroquine (HCQ) versus monotherapy: methotrexate (MTX)

Figure 68: Change in Disease Activity Score (DAS) at 6 months

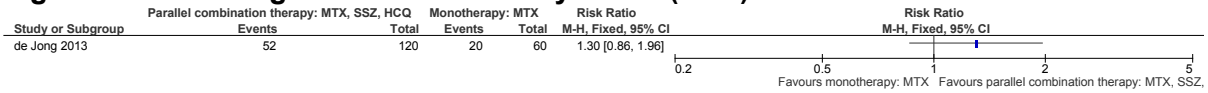


Figure 69: Change in function (HAQ) at 6 months

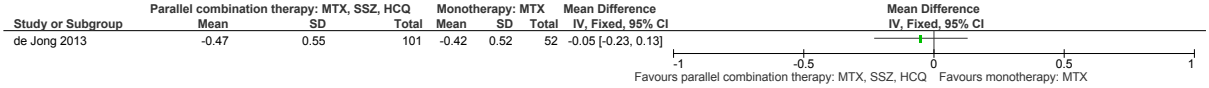
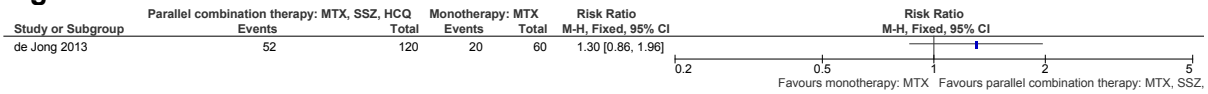


Figure 70: DAS remission at 6 months



E.1.113 Parallel combination therapy: methotrexate (MTX), sulfasalazine (SSZ), hydroxychloroquine (HCQ) versus monotherapy: sulfasalazine (SSZ)

Figure 71: DAS remission at 6 months

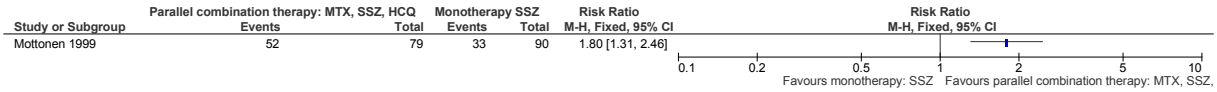


Figure 72: Withdrawal: adverse events

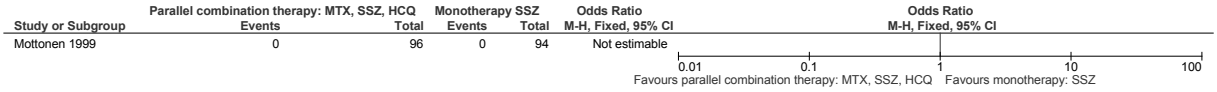
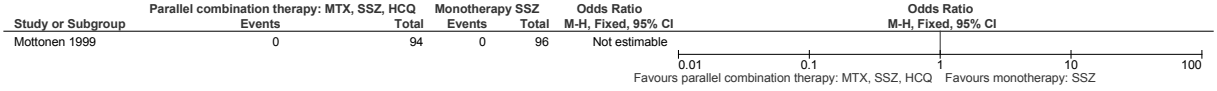


Figure 73: Withdrawal: inefficacy



Comparison of non-monotherapy treatment classes

E.1.121 Step up therapy: methotrexate (MTX), sulfasalazine (SSZ), hydroxychloroquine 2 (HCQ) versus sequential monotherapy: methotrexate (MTX), sulfasalazine 3 (SSZ), leflunomide (LFN)

Figure 74: Change in function (HAQ) score at 12 months

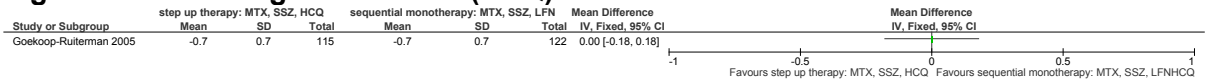
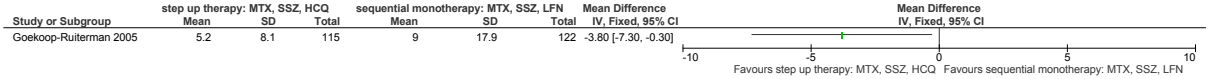


Figure 75: Change in radiographic score (SvdH) at 12 months



E.1.134 Parallel combination therapy: sulfasalazine (SSZ), hydroxychloroquine (HCQ) 5 versus parallel combination therapy: methotrexate (MTX), hydroxychloroquine 6 (HCQ)

Figure 76: Disease Activity Score (DAS28) at 6 months

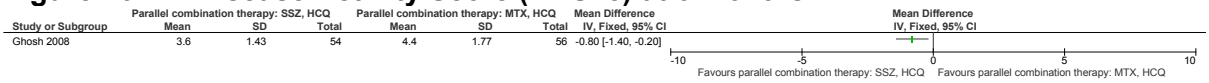
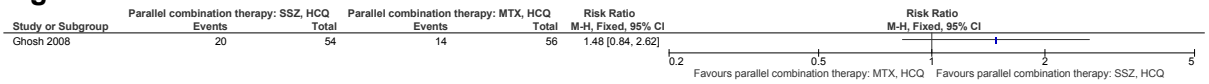


Figure 77: DAS remission at 6 months



E.1.147 Step up therapy: sulfasalazine (SSZ), methotrexate (MTX), hydroxychloroquine 8 (HCQ) versus parallel combination therapy: methotrexate (MTX), sulfasalazine 9 (SSZ), hydroxychloroquine (HCQ)

Figure 78: Change in Disease Activity Score (DAS28) at 12 months

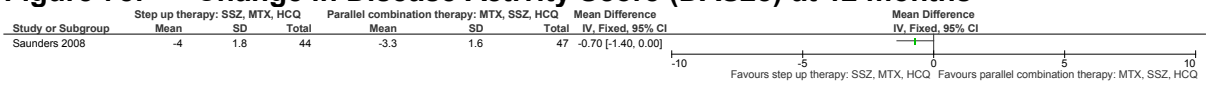


Figure 79: Change in health related quality of life (SF-36) at 12 months

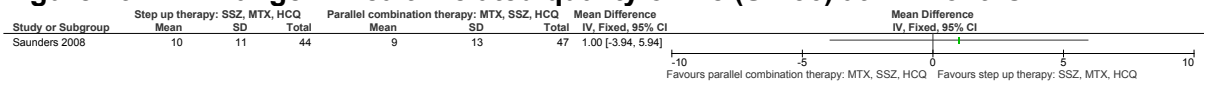


Figure 80: Change in function (HAQ) at 12 months

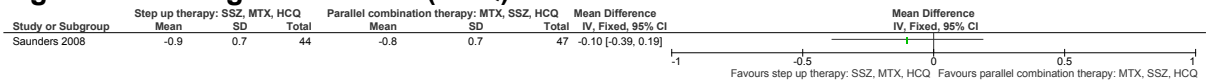


Figure 81: Low disease activity at 12 months

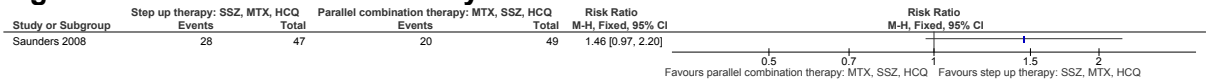


Figure 82: DAS remission at 12 months

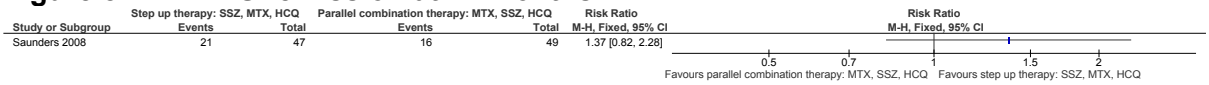


Figure 83: ACR50 response at 12 months

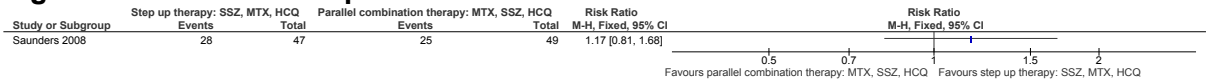


Figure 84: Change in pain score (VAS) at 12 months

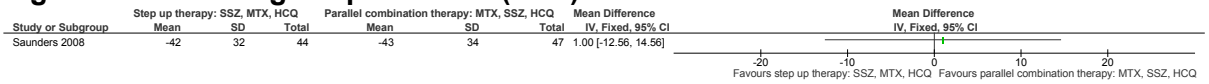
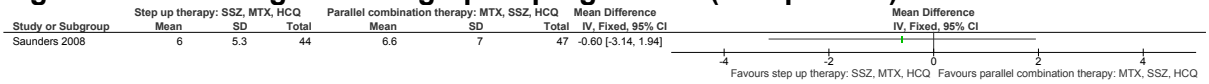


Figure 85: Change in radiographic progression (Sharp score) at 12 months



Poor prognosis subgroup

E.1.15 Parallel combination therapy: methotrexate (MTX), leflunomide (LFN) versus parallel combination therapy: methotrexate (MTX), sulfasalazine (SSZ)

Figure 86: Change in Disease Activity Score (DAS28) at 12 months

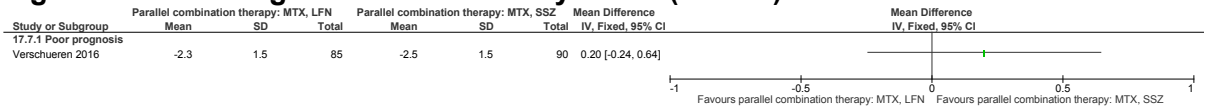


Figure 87: Change in Disease Activity Score (DAS28) at 6 months

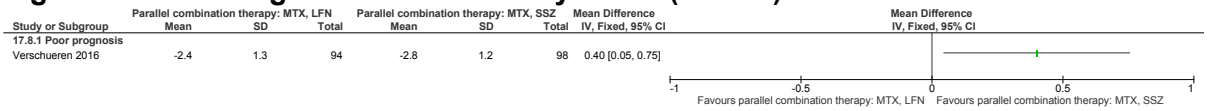


Figure 88: Change in function (HAQ) at 12 months

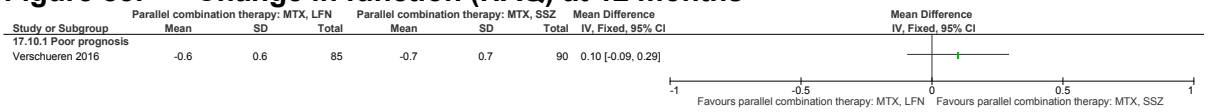


Figure 89: Change in function (HAQ) at 6 months

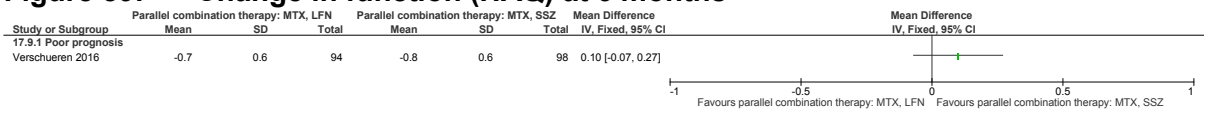


Figure 90: Low disease activity at 12 months

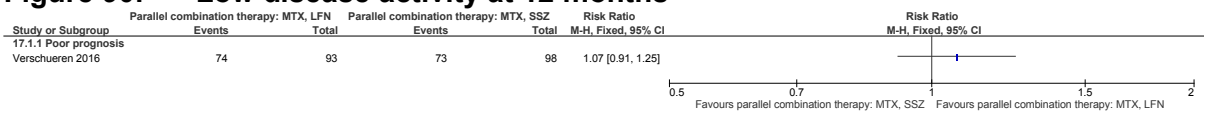


Figure 91: Low disease activity at 6 months

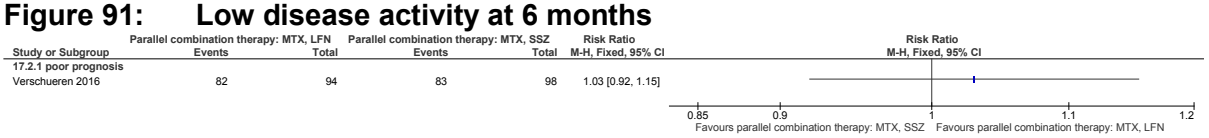


Figure 92: DAS remission at 12 months

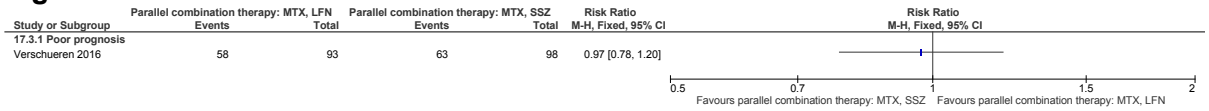


Figure 93: DAS remission at 6 months

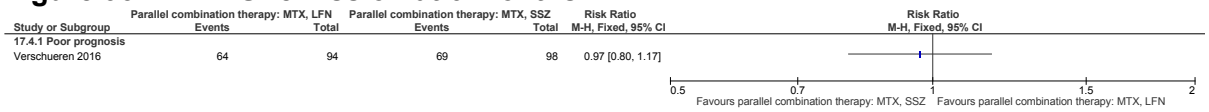


Figure 94: Change in radiological progression (SvdH) at 12 months

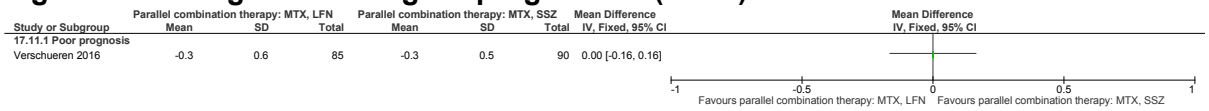


Figure 95: Withdrawal: adverse events

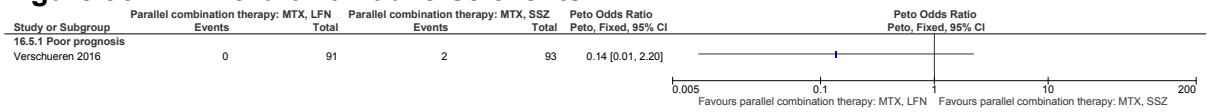
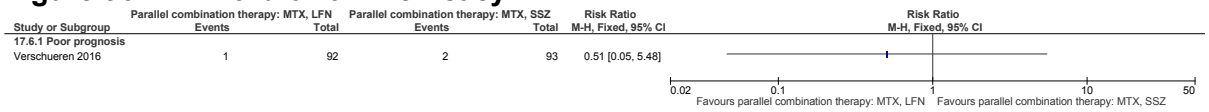


Figure 96: Withdrawal: inefficacy



E.1.161 Step up therapy: methotrexate (MTX), leflunomide (LFN) versus parallel 2 combination therapy: methotrexate (MTX), sulfasalazine (SSZ)

Figure 97: Change in Disease Activity Score (DAS28) at 12 months

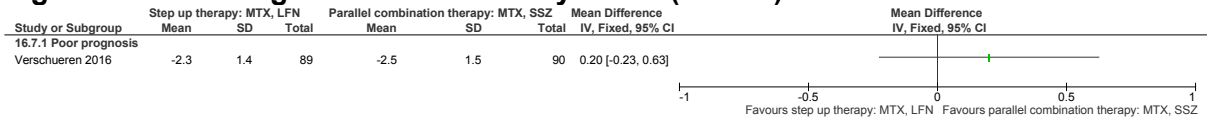


Figure 98: Change in Disease Activity Score (DAS28) at 6 months

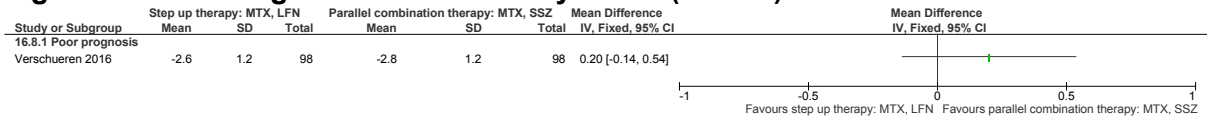


Figure 99: Change in function (HAQ) at 12 months

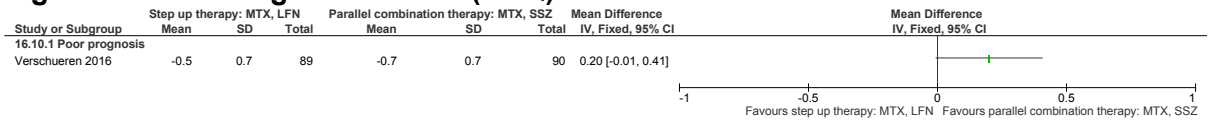


Figure 100: Change in function (HAQ) at 6 months

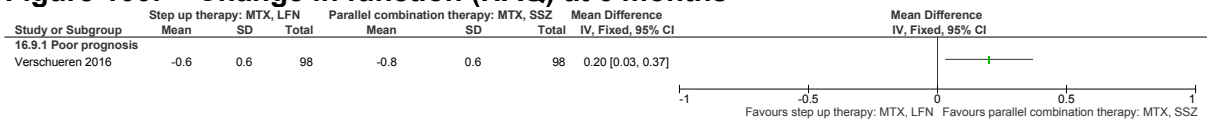


Figure 101: Low disease activity at 12 months

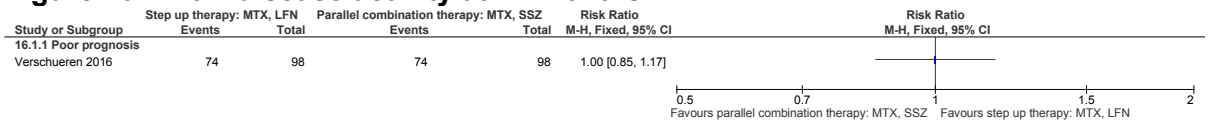


Figure 102: Low disease activity at 6 months

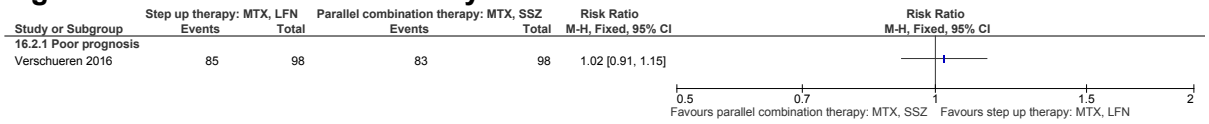


Figure 103: DAS remission at 12 months

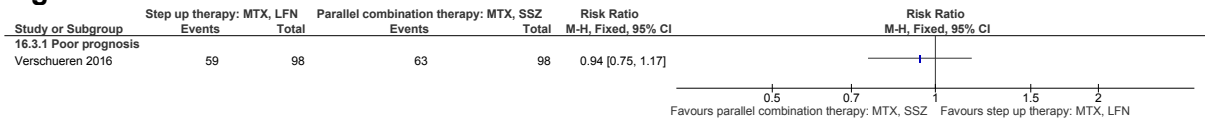


Figure 104: DAS remission at 6 months

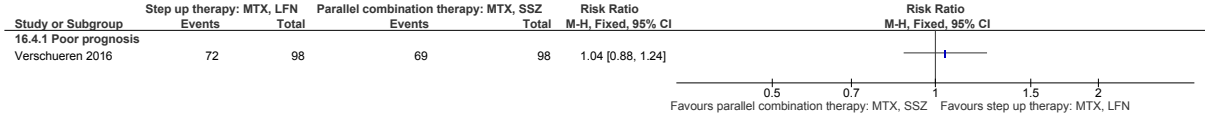


Figure 105: Change in radiological progression (SvdH) at 12 months

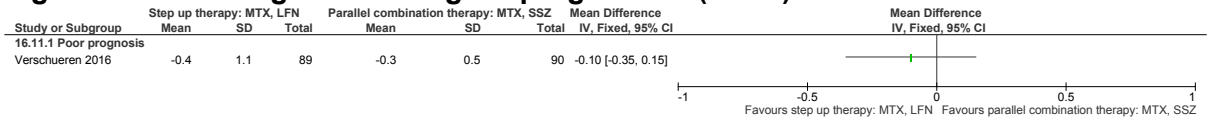


Figure 106: Withdrawal: adverse events

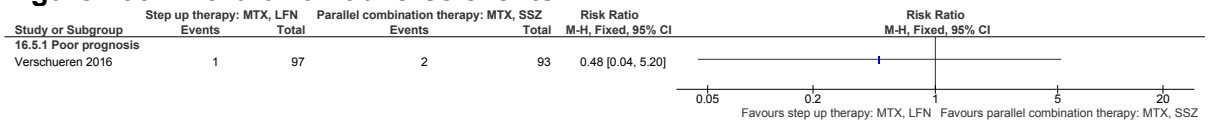
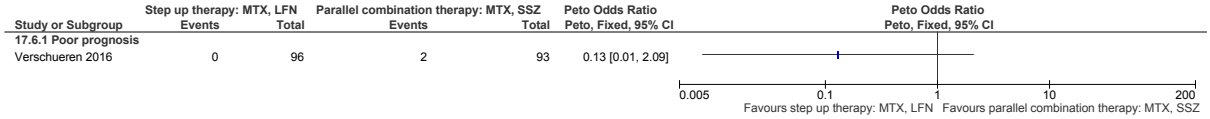


Figure 107: Withdrawal: inefficacy



E.1.171 Step up therapy: methotrexate (MTX), leflunomide (LFN) versus parallel 2 combination therapy: methotrexate (MTX), leflunomide (LFN)

Figure 108: Change in Disease Activity Score (DAS28) at 12 months

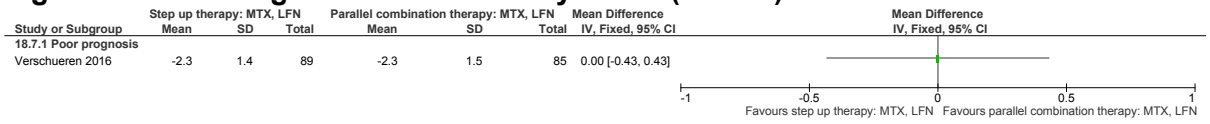


Figure 109: Change in Disease Activity Score (DAS28) at 6 months

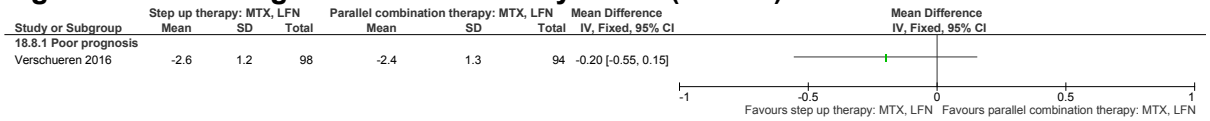


Figure 110: Change in function (HAQ) at 12 months

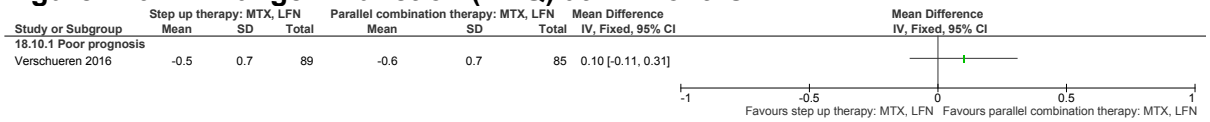


Figure 111: Change in function (HAQ) at 6 months

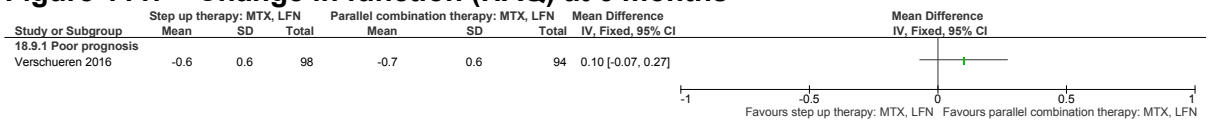


Figure 112: Low disease activity at 12 months

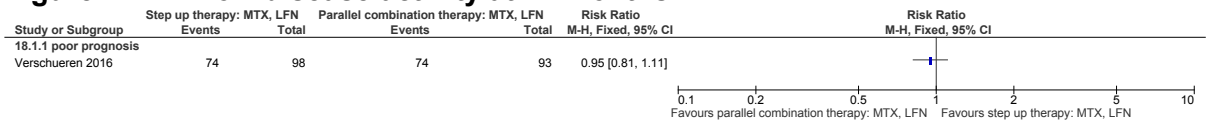


Figure 113: Low disease activity at 6 months

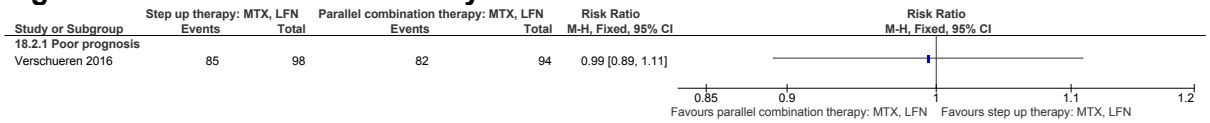


Figure 114: DAS remission at 12 months

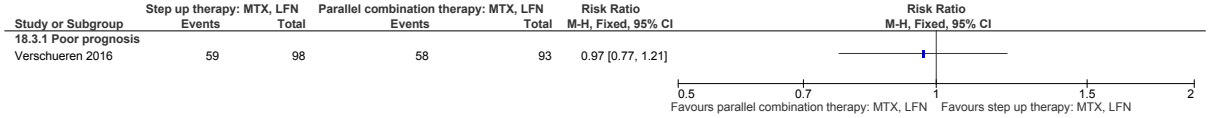


Figure 115: DAS remission at 6 months

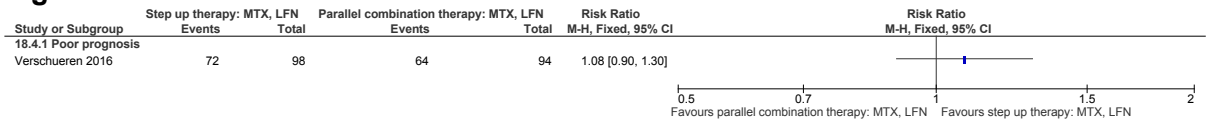


Figure 116: Change in radiological progression (SvdH) at 12 months

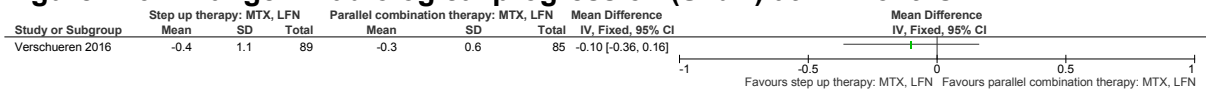


Figure 117: Withdrawal: adverse events

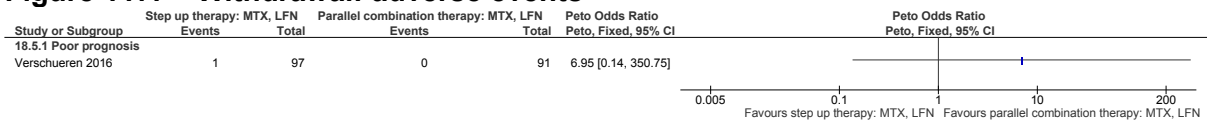
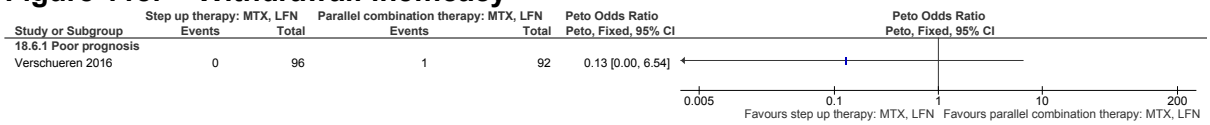


Figure 118: Withdrawal: inefficacy



E.21 Failed DMARDs

E.2.12 Step-up therapy (sulfasalazine plus leflunomide (SSZ plus LEF)) versus sequential monotherapy (sulfasalazine (SSZ) plus placebo) in people who failed leflunomide monotherapy

Figure 119: Health Assessment Questionnaire at 6 months

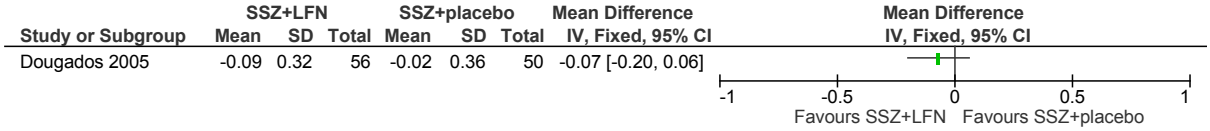
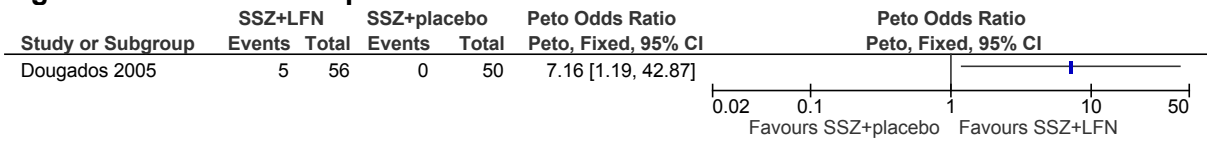


Figure 120: ACR50 response at 6 months



5

Figure 121: Pain at 6 months

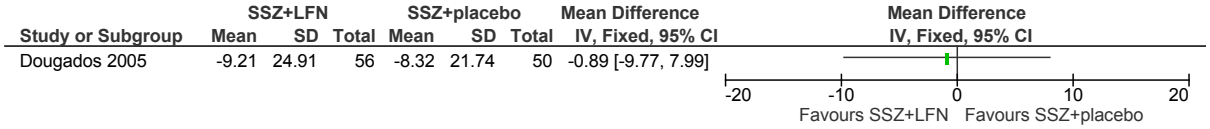


Figure 122: Withdrawal due to adverse events

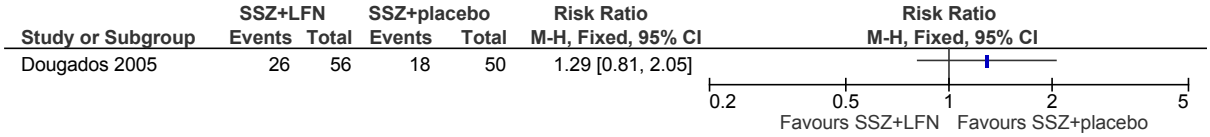
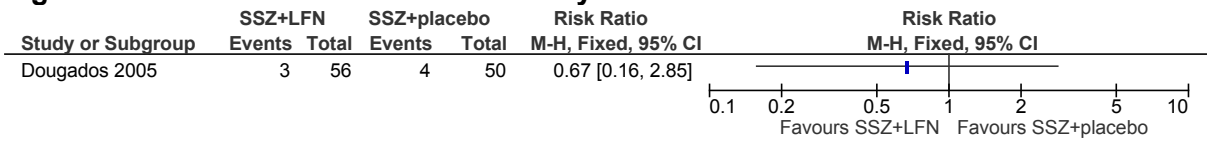


Figure 123: Withdrawal due to inefficacy



E.2.26 Step-up therapy (methotrexate plus sulfasalazine (MTX plus SSZ)) versus sequential monotherapy (methotrexate (MTX)) in people who failed sulfasalazine monotherapy

Figure 124: DAS change at 6 months

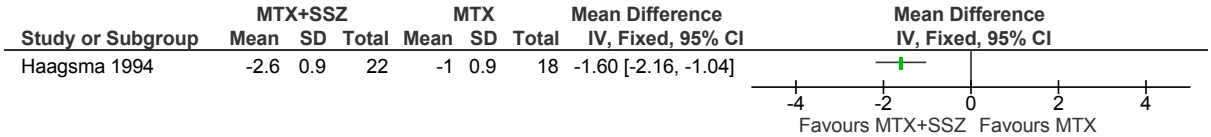


Figure 125: ACR50 response at 1 year

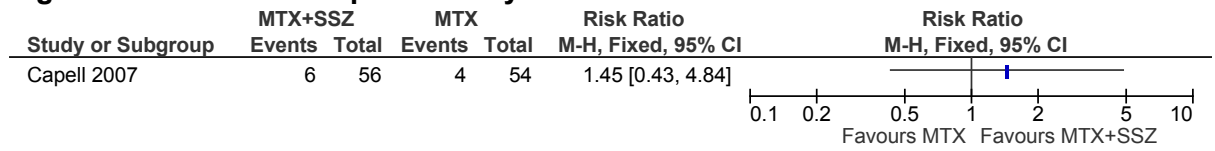


Figure 126: Pain at 6 months

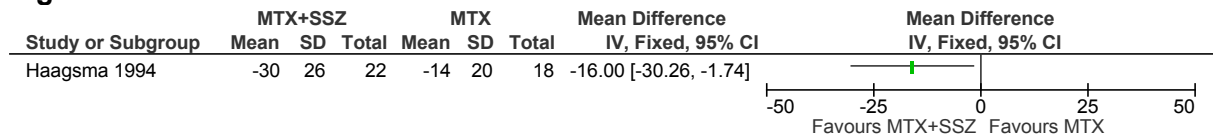


Figure 127: Withdrawal due to adverse events

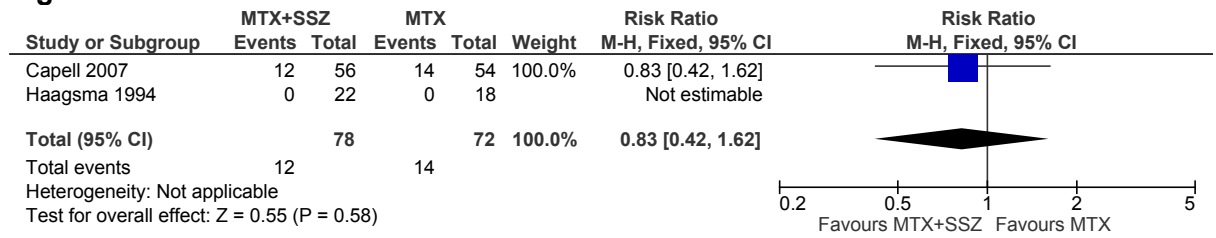
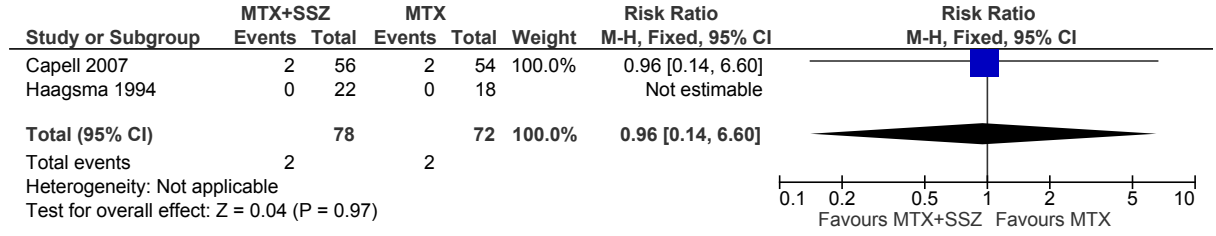


Figure 128: Withdrawal due to inefficacy



E.2.3 Step-up therapy (methotrexate plus sulfasalazine then methotrexate plus sulfasalazine plus hydroxychloroquine) versus sequential monotherapy (sulfasalazine then leflunomide) in people who failed methotrexate monotherapy

Figure 129: Low disease activity at 12 months (after step 1 and step 2)

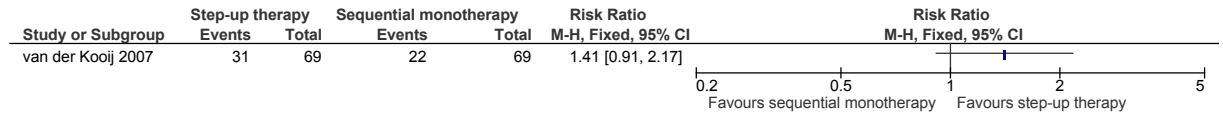


Figure 130: Low disease activity at 6 months (after step 1)

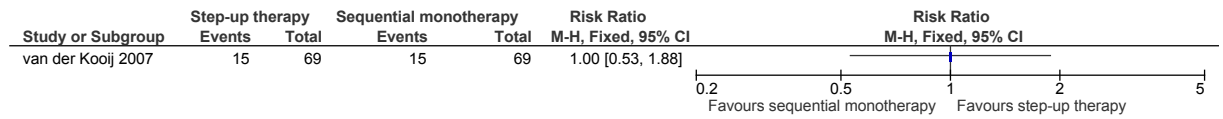


Figure 131: Low disease activity at 6 months (after step 2)

Study or Subgroup	Step-up therapy Events	Total	Sequential monotherapy Events	Total	Risk Ratio M-H, Fixed, 95% CI
van der Kooij 2007	16	44	7	54	2.81 [1.27, 6.21]

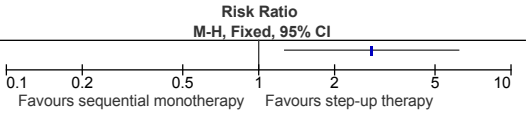


Figure 132: Withdrawal due to adverse events (after step 1 and step 2)

Study or Subgroup	Step-up therapy Events	Total	Sequential monotherapy Events	Total	Risk Ratio M-H, Fixed, 95% CI
van der Kooij 2007	18	69	13	69	1.38 [0.74, 2.60]

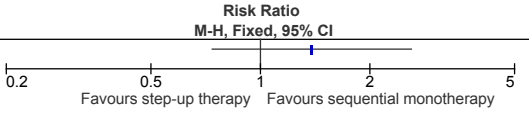


Figure 133: Withdrawal due to adverse events (after step 1)

Study or Subgroup	Step-up therapy Events	Total	Sequential monotherapy Events	Total	Risk Ratio M-H, Fixed, 95% CI
van der Kooij 2007	13	69	7	69	1.86 [0.79, 4.37]

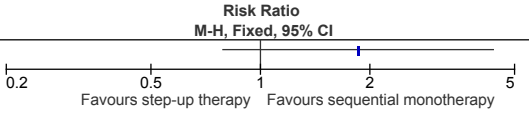


Figure 134: Withdrawal due to adverse events (after step 2)

Study or Subgroup	Step-up therapy Events	Total	Sequential monotherapy Events	Total	Risk Ratio M-H, Fixed, 95% CI
van der Kooij 2007	5	44	6	54	1.02 [0.33, 3.13]

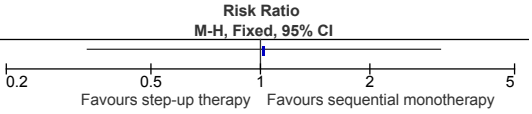


Figure 135: Withdrawal due to inefficacy (after step 1)

Study or Subgroup	Step-up therapy Events	Total	Sequential monotherapy Events	Total	Risk Ratio M-H, Fixed, 95% CI
van der Kooij 2007	41	69	47	69	0.87 [0.68, 1.12]

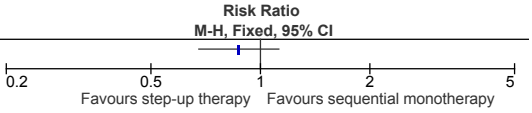
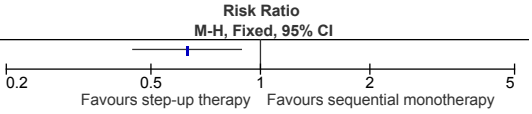


Figure 136: Withdrawal due to inefficacy (after step 2)

Study or Subgroup	Step-up therapy Events	Total	Sequential monotherapy Events	Total	Risk Ratio M-H, Fixed, 95% CI
van der Kooij 2007	21	44	41	54	0.63 [0.45, 0.89]



Appendix F: GRADE tables

F.1 First line DMARDs

Table 35: Clinical evidence profile: Monotherapy: sulfasalazine (SSZ) versus placebo

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Monotherapy: SSZ	Placebo	Relative (95% CI)	Absolute		
Pain (VAS) at 6 months (range of scores: 0-100; Better indicated by lower values)												
1	randomised trials	very serious[1]	no serious inconsistency	no serious indirectness	serious[2]	none	29	36	-	MD 8.9 lower (19.07 lower to 1.27 higher)	⊕OOO VERY LOW	IMPORTANT
Radiological progression (modified Sharp score) at 12+ months (Better indicated by lower values)												
1	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	serious[2]	none	36	37	-	MD 3.6 lower (8.21 lower to 1.01 higher)	⊕⊕OO LOW	IMPORTANT
Adverse events - mortality (follow-up 48 weeks)												
1	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	very serious[2]	none	1/38 (2.6%)	1/40 (2.5%)	RR 1.05 (0.07 to 16.24)	1 more per 1000 (from 23 fewer to 381 more)	⊕OOO VERY LOW	IMPORTANT
Withdrawal: adverse events (follow-up 6 months)												
1	randomised trials	very serious[1]	no serious inconsistency	no serious indirectness	no serious imprecision	none	14/53 (26.4%)	4/52 (7.7%)	RR 3.43 (1.21 to 9.75)	187 more per 1000 (from 16 more to 673 more)	⊕⊕OO LOW	IMPORTANT
Withdrawal: inefficacy (follow-up 6 months)												

1	randomised trials	very serious[1]	no serious inconsistency	no serious indirectness	serious[2]	none	2/53 (3.8%)	5/52 (9.6%)	RR 0.39 (0.08 to 1.93)	59 fewer per 1000 (from 88 fewer to 89 more)	⊕OOO VERY LOW	IMPORTANT

[1] Downgraded by 1 increment if the majority of the evidence was at high risk of bias, and downgraded by 2 increments if the majority of the evidence was at very high risk of bias
[2] Downgraded by 1 increment if the confidence interval crossed one MID or by 2 increments if the confidence interval crossed both MIDs

Table 36: Clinical evidence profile: Monotherapy: hydroxychloroquine versus placebo

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	**Design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**Monotherapy: HCQ**	**Placebo**	**Relative (95% CI)**	**Absolute**		
Change in quality of life (global well being) at 12 months (Better indicated by lower values)												
1	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	serious[1]	none	58	57	-	MD 0.52 lower (0.89 to 0.15 lower)	⊕⊕⊕O MODERATE	
Change in function (psychological disability via AIMS) at 12 months (Better indicated by lower values)												
1	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	no serious imprecision[1]	none	58	57	-	MD 0.03 lower (0.39 lower to 0.33 higher)	⊕⊕⊕⊕ HIGH	CRITICAL
Change in pain (VAS) at 6 months (range of scores: 0-100; Better indicated by lower values)												
1	randomised trials	very serious[2]	no serious inconsistency	no serious indirectness	serious[3]	none	63	58	-	MD 19.3 lower (30.22 to 8.38 lower)	⊕OOO VERY LOW	CRITICAL
Withdrawal: adverse events (follow-up 9 months)												
1	randomised trials	serious[2]	no serious inconsistency	no serious indirectness	very serious[1]	none	1/54 (1.9%)	2/46 (4.3%)	RR 0.43 (0.04 to 4.55)	25 fewer per 1000 (from 42 fewer to 154 more)	⊕OOO VERY LOW	IMPORTANT
Withdrawal: inefficacy (follow-up 10 months)												
2	randomised trials	serious[2]	no serious inconsistency	no serious indirectness	serious[2]	none	12/108 (11.1%)	28/107 (26.2%)	RR 0.43 (0.23 to 0.8)	149 fewer per 1000 (from 52 fewer to 201 fewer)	⊕⊕OO LOW	

[1] Downgraded by 1 increment if the confidence interval crossed one MID or by 2 increments if the confidence interval crossed both MIDs
[2] Downgraded by 1 increment if the majority of the evidence was at high risk of bias, and downgraded by 2 increments if the majority of the evidence was at very high risk of bias
[3] Downgraded by 1 increment if the confidence interval crossed 1 MID or by 2 increments if the confidence interval crossed both MIDs.

Table 37: Clinical evidence profile: Monotherapy: sulfasalazine (SSZ) versus monotherapy methotrexate (MTX)

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Monotherapy: SSZ	Monotherapy MTX	Relative (95% CI)	Absolute		
Change in Disease Activity Score at 12 months (range of scores: 2-10; Better indicated by lower values)												
1	randomised trials	very serious[1]	no serious inconsistency	no serious indirectness	serious[2]	none	22	33	-	MD 0.2 higher (0.41 lower to 0.81 higher)	⊕OOO VERY LOW	CRITICAL
Change in Disease Activity Score at 6 months (range of scores: 2-10; Better indicated by lower values)												
1	randomised trials	very serious[1]	no serious inconsistency	no serious indirectness	serious[2]	none	22	33	-	MD 0.1 lower (0.38 lower to 0.18 higher)	⊕OOO VERY LOW	CRITICAL
Change in function (HAQ) at 12 months (range of scores: 0-3; Better indicated by lower values)												
1	randomised trials	very serious[1]	no serious inconsistency	no serious indirectness	serious[2]	none	22	33	-	MD 0.14 higher (0.16 lower to 0.44 higher)	⊕OOO VERY LOW	CRITICAL
ACR50 response at 6 months												
1	randomised trials	very serious[1]	no serious inconsistency	serious[3]	serious[2]	none	14/37 (37.8%)	24/42 (57.1%)	RR 0.66 (0.41 to 1.08)	194 fewer per 1000 (from 337 fewer to 46 more)	⊕OOO VERY LOW	IMPORTANT
Change in pain (VAS) at 12 months (range of scores: 0-100; Better indicated by lower values)												
1	randomised trials	very serious[1]	no serious inconsistency	no serious indirectness	very serious[2]	none	22	33	-	MD 0.1 lower (13.72 lower to 13.52 higher)	⊕OOO VERY LOW	IMPORTANT

Change in pain (VAS) at 6 months (range of scores: 0-100; Better indicated by lower values)												
1	randomised trials	very serious[1]	no serious inconsistency	no serious indirectness	serious[2]	none	22	33	-	MD 5.8 lower (15.53 lower to 3.93 higher)	⊕OOO VERY LOW	IMPORTANT
Withdrawal: adverse events (follow-up 12 months)												
2	randomised trials	very serious[1]	no serious inconsistency	no serious indirectness	serious[2]	none	19/88 (21.6%)	9/96 (9.4%)	RR 2.3 (1.1 to 4.82)	122 more per 1000 (from 9 more to 358 more)	⊕OOO VERY LOW	IMPORTANT
Withdrawal: inefficacy (follow-up mean 12 months)												
2	randomised trials	very serious[1]	no serious inconsistency	no serious indirectness	serious[2]	none	10/79 (12.7%)	5/92 (5.4%)	RR 2.16 (0.82 to 5.74)	63 more per 1000 (from 10 fewer to 258 more)	⊕OOO VERY LOW	IMPORTANT

[1] Downgraded by 1 increment if the majority of the evidence was at high risk of bias, and downgraded by 2 increments if the majority of the evidence was at very high risk of bias
[2] Downgraded by 1 increment if the confidence interval crossed one MID or by 2 increments if the confidence interval crossed both MIDs
[3] Downgraded for indirectness: all patients had previously received at least a 4 month course of antimalarials

Table 38: Clinical evidence profile: Monotherapy: leflunomide (LFN) versus monotherapy: methotrexate (MTX)

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	**Design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**Monotherapy: LFN**	**Monotherapy: MTX**	**Relative (95% CI)**	**Absolute**		
Disease Activity Score at 12 months (follow-up 12 months; measured with: DAS28. Change score.; range of scores: 0-9.4; Better indicated by lower values)												
1	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	serious[2]	none	31	32	-	MD 0.45 higher (0.78 lower to 1.68 higher)	⊕⊕OO LOW	CRITICAL
Disease Activity Score at 6 months (follow-up 4 months; measured with: DAS28. Change score; range of scores: 0-9.4; Better indicated by lower values)												
1	randomised trials	very serious[1]	no serious inconsistency	no serious indirectness	serious[2]	none	29	33	-	MD 0.59 higher (0.11 lower to 1.29 higher)	⊕OOO VERY LOW	IMPORTANT

Function at 12 months (follow-up 12 months; measured with: HAQ-Di. Change score; range of scores: 0-3; Better indicated by lower values)												
1	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	serious[2]	none	31	32	-	MD 0.29 lower (0.57 to 0.01 lower)	⊕⊕OO LOW	CRITICAL
Function at 6 months (follow-up 4 months; measured with: HAQ. Change score; range of scores: 0-3; Better indicated by lower values)												
1	randomised trials	very serious[1]	no serious inconsistency	no serious indirectness	serious[2]	none	29	33	-	MD 0.01 higher (0.22 lower to 0.24 higher)	⊕OOO VERY LOW	CRITICAL
DAS remission at 12 months (follow-up 12 months; assessed with: DAS28)												
1	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	very serious[2]	none	11/31 (35.5%)	11/32 (34.4%)	RR 1.03 (0.53 to 2.03)	10 more per 1000 (from 162 fewer to 354 more)	⊕OOO VERY LOW	IMPORTANT
Pain at 6 months (follow-up 4 months; measured with: VAS. Change score; range of scores: 0-100; Better indicated by lower values)												
1	randomised trials	very serious[1]	no serious inconsistency	no serious indirectness	serious[2]	none	29	33	-	MD 3.6 higher (6.09 lower to 13.29 higher)	⊕OOO VERY LOW	IMPORTANT
Withdrawal: adverse events (follow-up 12 months)												
1	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	very serious[2]	none	6/37 (16.2%)	2/34 (5.9%)	RR 2.76 (0.6 to 12.74)	104 more per 1000 (from 24 fewer to 691 more)	⊕OOO VERY LOW	IMPORTANT
Withdrawal: inefficacy (follow-up 12 months)												
1	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	very serious[2]	none	2/33 (6.1%)	4/36 (11.1%)	RR 0.55 (0.11 to 2.78)	50 fewer per 1000 (from 99 fewer to 198 more)	⊕OOO VERY LOW	IMPORTANT

[1] Downgraded by 1 increment if the majority of the evidence was at high risk of bias, and downgraded by 2 increments if the majority of the evidence was at very high risk of bias
[2] Downgraded by 1 increment if the confidence interval crossed one MID or by 2 increments if the confidence interval crossed both MIDs

Table 39: Clinical evidence profile: Monotherapy: hydroxychloroquine (HCQ) versus monotherapy: sulfasalazine (SSZ)

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Monotherapy: HCQ	Monotherapy: SSZ	Relative (95% CI)	Absolute		
Change in radiological progression (SvdH score) at 12+ months (Better indicated by lower values)												
1	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	serious[2]	none	29	28	-	MD 10 higher (1.11 to 18.89 higher)	⊕⊕OO LOW	IMPORTANT
Pain (VAS) at 12 months (range of scores: 0-100; Better indicated by lower values)												
1	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	very serious[2]	none	29	28	-	MD 0.2 higher (13.22 lower to 13.62 higher)	⊕OOO VERY LOW	IMPORTANT
Pain (VAS) at 6 months (range of scores: 0-100; Better indicated by lower values)												
1	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	serious[2]	none	29	28	-	MD 6.4 lower (18.4 lower to 5.6 higher)	⊕⊕OO LOW	IMPORTANT
Withdrawal: adverse events (follow-up 48 weeks)												
1	randomised trials	very serious[1]	no serious inconsistency	no serious indirectness	very serious[2]	none	1/19 (5.3%)	4/25 (16%)	RR 0.33 (0.04 to 2.71)	107 fewer per 1000 (from 154 fewer to 274 more)	⊕OOO VERY LOW	IMPORTANT
Withdrawal: inefficacy (follow-up 48 weeks)												
1	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	serious[2]	none	9/27 (33.3%)	3/24 (12.5%)	RR 2.67 (0.82 to 8.72)	209 more per 1000 (from 23 fewer to 965 more)	⊕⊕OO LOW	IMPORTANT

[1] Downgraded by 1 increment if the majority of the evidence was at high risk of bias, and downgraded by 2 increments if the majority of the evidence was at very high risk of bias
[2] Downgraded by 1 increment if the confidence interval crossed 1 MID or by 2 increments if the confidence interval crossed both MIDs.

Table 40: Clinical evidence profile: hydroxychloroquine (HCQ) versus monotherapy: methotrexate (MTX)

Quality assessment	No of patients	Effect	Quality	Importance

No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Monotherapy: HCQ	Monotherapy: MTX	Relative (95% CI)	Absolute		
Change in quality of life (wellbeing score) at 12 months (range of scores: 0-100; Better indicated by lower values)												
1	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	no serious imprecision	none	107	105	-	MD 1 higher (7.49 lower to 9.49 higher)	⊕⊕⊕O MODERATE	CRITICAL
Change in function (HAQ) at 12 months (range of scores: 0-3; Better indicated by lower values)												
2	randomised trials	serious[1]	no serious inconsistency	serious[2]	no serious imprecision	none	107	105	-	MD 0.1 higher (0.08 lower to 0.28 higher)	⊕⊕OO LOW	CRITICAL
Remission at 12 months												
1	randomised trials	very serious[1]	no serious inconsistency	very serious[3]	serious[4]	none	17/107 (15.9%)	25/105 (23.8%)	RR 0.67 (0.38 to 1.16)	79 fewer per 1000 (from 148 fewer to 38 more)	⊕OOO VERY LOW	IMPORTANT
Change in pain (VAS) at 12 months (range of scores: 0-100; Better indicated by lower values)												
1	randomised trials	very serious[1]	no serious inconsistency	serious[2]	no serious imprecision	none	107	105	-	MD 3 higher (4.84 lower to 10.84 higher)	⊕OOO VERY LOW	IMPORTANT
Discontinuation of strategy: adverse events (follow-up 12 months)												
1	randomised trials	very serious[1]	no serious inconsistency	serious[2]	very serious[4]	none	0/107 (0%)	5/105 (4.8%)	RR 0.09 (0 to 1.59)	43 fewer per 1000 (from 48 fewer to 28 more)	⊕OOO VERY LOW	IMPORTANT
Discontinuation of strategy: inefficacy (follow-up 12 months)												
1	randomised trials	very serious[1]	no serious inconsistency	serious[2]	serious[4]	none	12/107 (11.2%)	5/105 (4.8%)	RR 2.36 (0.86 to 6.45)	65 more per 1000 (from 7 fewer to 260 more)	⊕OOO VERY LOW	IMPORTANT

[1] Downgraded by 1 increment if the majority of the evidence was at high risk of bias, and downgraded by 2 increments if the majority of the evidence was at very high risk of bias
[2] Indirect evidence: out of scope drug utilised in the case of adverse reaction

[3] Indirect evidence: out of scope drug utilised in the case of adverse reaction and outcome does not use DAS or similar score
[4] Downgraded by 1 increment if the confidence interval crossed one MID or by 2 increments if the confidence interval crossed both MIDs

Table 41: Clinical evidence profile: Step-down therapy: sulfasalazine (SSZ), methotrexate (MTX) versus monotherapy: sulfasalazine (SSZ)

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Step-down therapy: SSZ, MTX	Monotherapy: SSZ	Relative (95% CI)	Absolute		
Change in Disease activity score at 12 months (range of scores: 0-10; Better indicated by lower values)												
1	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	no serious imprecision	none	76	79	-	MD 0.1 lower (0.51 lower to 0.31 higher)	⊕⊕⊕O MODERATE	CRITICAL
Change in Disease activity score at 6 months (range of scores: 0-10; Better indicated by lower values)												
1	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	serious[2]	none	76	79	-	MD 0.8 lower (1.18 to 0.42 lower)	⊕⊕OO LOW	CRITICAL
Change in function (HAQ) at 12 months (range of scores: 0-3; Better indicated by lower values)												
1	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	serious[2]	none	76	79	-	MD 0.2 lower (0.44 lower to 0.04 higher)	⊕⊕OO LOW	CRITICAL
Change in function (HAQ) at 6 months (range of scores: 0-3; Better indicated by lower values)												
1	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	serious[2]	none	76	79	-	MD 0.5 lower (0.72 to 0.28 lower)	⊕⊕OO LOW	CRITICAL
Change in function (MACTAR) at 12 months (Better indicated by lower values)												
1	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	no serious imprecision	none	76	79	-	MD 1 lower (3.06 lower to 1.06 higher)	⊕⊕⊕O MODERATE	CRITICAL
Change in function (MACTAR) at 6 months (Better indicated by lower values)												

1	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	serious[2]	none	76	79	-	MD 3 higher (1.26 to 4.74 higher)	⊕⊕OO LOW	CRITICAL
ACR remission at 12 months												
1	randomised trials	serious[1]	no serious inconsistency	Serious indirectness[3]	very serious[2]	none	1/70 (1.4%)	3/56 (5.4%)	RR 0.27 (0.03 to 2.49)	39 fewer per 1000 (from 52 fewer to 80 more)	⊕OOO VERY LOW	IMPORTANT
ACR50 response at 6 months												
1	randomised trials	very serious[1]	no serious inconsistency	no serious indirectness	serious[2]	none	37/75 (49.3%)	21/62 (33.9%)	RR 1.46 (0.96 to 2.21)	156 more per 1000 (from 14 fewer to 410 more)	⊕OOO VERY LOW	IMPORTANT
Change in pain (VAS) at 12 months (range of scores: 0-100; Better indicated by lower values)												
1	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	no serious imprecision	none	76	79	-	MD 2 higher (6.98 lower to 10.98 higher)	⊕⊕⊕O MODERATE	IMPORTANT
Change in pain (VAS) at 6 months (range of scores: 0-100; Better indicated by lower values)												
1	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	serious[2]	none	76	79	-	MD 14 lower (22.68 to 5.32 lower)	⊕⊕OO LOW	IMPORTANT
Withdrawal: adverse events (follow-up 56 weeks)												
1	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	very serious[2]	none	5/75 (6.7%)	8/64 (12.5%)	RR 0.53 (0.18 to 1.55)	59 fewer per 1000 (from 102 fewer to 69 more)	⊕OOO VERY LOW	IMPORTANT
Withdrawal: inefficacy (follow-up 56 weeks)												
1	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	no serious imprecision	none	1/71 (1.4%)	14/70 (20%)	RR 0.07 (0.01 to 0.52)	186 fewer per 1000 (from 96 fewer to 198 fewer)	⊕⊕⊕O MODERATE	IMPORTANT

[1] Downgraded by 1 increment if the majority of the evidence was at high risk of bias, and downgraded by 2 increments if the majority of the evidence was at very high risk of bias
[2] Downgraded by 1 increment if the confidence interval crossed 1 MID or by 2 increments if the confidence interval crossed both MIDs.
[3] Indirect evidence: outcome does not use DAS

Table 42: Clinical evidence profile: Parallel combination therapy: methotrexate (MTX), sulfasalazine (SSZ) versus monotherapy: sulfasalazine (SSZ)

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Parallel combination therapy: MTX, SSZ	Monotherapy: SSZ	Relative (95% CI)	Absolute		
Change in Disease Activity Score (DAS) at 12 months (follow-up 12 months; range of scores: 2-10; Better indicated by lower values)												
1	randomised trials	very serious[1]	no serious inconsistency	no serious indirectness	serious[2]	none	30	22	-	MD 0.51 lower (1.15 lower to 0.13 higher)	⊕OOO VERY LOW	CRITICAL
Change in Disease Activity Score (DAS) at 6 months (follow-up 3 months; range of scores: 2-10; Better indicated by lower values)												
1	randomised trials	very serious[1]	no serious inconsistency	no serious indirectness	very serious[2]	none	30	22	-	MD 0 higher (0.28 lower to 0.28 higher)	⊕OOO VERY LOW	CRITICAL
Quality of life at 6 or 12 months (no data) - not reported												
0	-	-	-	-	-	none	-	-	-	-		
								0%		-		
Change in function (HAQ) at 12 months (follow-up 12 months; range of scores: 0-3; Better indicated by lower values)												
1	randomised trials	very serious[1]	no serious inconsistency	no serious indirectness	serious[2]	none	30	22	-	MD 0.19 lower (0.52 lower to 0.14 higher)	⊕OOO VERY LOW	CRITICAL
Function at 6 months (no data) - not reported												
0	-	-	-	-	-	none	-	-	-	-		
								0%		-		
Change in pain (VAS) at 12 months (follow-up 12 months; range of scores: 0-100; Better indicated by lower values)												

1	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	very serious[2]	none	30	22	-	MD 0.1 higher (14.05 lower to 14.25 higher)	⊕OOO VERY LOW	IMPORTANT
Change in pain (VAS) at 6 months (follow-up 3 months; range of scores: 0-100; Better indicated by lower values)												
1	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	serious[2]	none	30	22	-	MD 5 higher (5.08 lower to 15.08 higher)	⊕⊕OO LOW	IMPORTANT
Withdrawal: adverse events (follow-up 10 months)												
2	randomised trials	very serious[1]	no serious inconsistency	no serious indirectness	serious[2]	none	19/88 (21.6%)	14/95 (14.7%)	RR 1.47 (0.79 to 2.75)	69 more per 1000 (from 31 fewer to 258 more)	⊕OOO VERY LOW	IMPORTANT
Withdrawal: inefficacy (follow-up 10 months)												
2	randomised trials	very serious[1]	no serious inconsistency	no serious indirectness	serious[2]	none	4/85 (4.7%)	10/79 (12.7%)	RR 0.38 (0.12 to 1.15)	78 fewer per 1000 (from 111 fewer to 19 more)	⊕OOO VERY LOW	IMPORTANT

[1] Downgraded by 1 increment if the majority of the evidence was at high risk of bias, and downgraded by 2 increments if the majority of the evidence was at very high risk of bias
[2] Downgraded by 1 increment if the confidence interval crossed 1 MID or by 2 increments if the confidence interval crossed both MIDs.

Table 43: Clinical evidence profile: Parallel combination therapy: methotrexate (MTX), sulfasalazine (SSZ) versus monotherapy: methotrexate (MTX)

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	**Design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**Parallel combination therapy: MTX, SSZ**	**Monotherapy: MTX**	**Relative (95% CI)**	**Absolute**		
Change in Disease Activity Score at 12 months (range of scores: 2-10; Better indicated by lower values)												
1	randomised	very	no serious	no serious	serious[2]	none	30	33	-	MD 0.3 lower (0.83	⊕OOO	CRITICAL

	trials	serious[1]	inconsistency	indirectness						lower to 0.23 higher)	VERY LOW	
Change in Disease Activity Score at 6 months (range of scores: 2-10; Better indicated by lower values)												
2	randomised trials	very serious[1]	no serious inconsistency	no serious indirectness	no serious imprecision	none	111	114	-	MD 0.19 lower (0.41 lower to 0.04 higher)	⊕⊕OO LOW	CRITICAL
Change/final function (HAQ) at 12 months (range of scores: 0-3; Better indicated by lower values)												
2	randomised trials	very serious[1]	no serious inconsistency	no serious indirectness	no serious imprecision	none	57	61	-	MD 0.1 higher (0.09 to 0.11 higher)	⊕⊕OO LOW	CRITICAL
Change/final function (HAQ) at 6 months (range of scores: 0-3; Better indicated by lower values)												
2	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	no serious imprecision	none	108	109	-	MD 0.14 higher (0.13 to 0.15 higher)	⊕⊕⊕O MODERATE	CRITICAL
ACR remission at 6 months												
1	randomised trials	serious[1]	no serious inconsistency	Serious indirectness[3]	very serious[2]	none	13/81 (16%)	16/81 (19.8%)	RR 0.81 (0.42 to 1.58)	38 fewer per 1000 (from 115 fewer to 115 more)	⊕OOO VERY LOW	IMPORTANT
ACR50 response at 6 months												
1	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	serious[2]	none	46/81 (56.8%)	50/81 (61.7%)	RR 0.92 (0.71 to 1.19)	49 fewer per 1000 (from 179 fewer to 117 more)	⊕⊕OO LOW	IMPORTANT
Change/final pain (VAS) at 12 months (range of scores: 0-100; Better indicated by lower values)												
2	randomised trials	very serious[1]	no serious inconsistency	no serious indirectness	serious[2]	none	60	58	-	MD 3.05 higher (0.43 lower to 6.54 higher)	⊕OOO VERY LOW	IMPORTANT
Change/final pain (VAS) at 6 months (range of scores: 0-100; Better indicated by lower values)												
3	randomised trials	very serious[1]	no serious inconsistency	no serious indirectness	serious[2]	none	138	142	-	MD 0.85 lower (4.59 lower to 2.9 higher)	⊕OOO VERY LOW	IMPORTANT
Withdrawal: adverse events (follow-up mean 9 months)												
4	randomised trials	very serious[1]	no serious inconsistency	no serious indirectness	serious[2]	none	19/206 (9.2%)	12/204 (5.9%)	RR 1.59 (0.8 to 3.16)	35 more per 1000 (from 12 fewer to 127 more)	⊕OOO VERY LOW	IMPORTANT

Withdrawal: inefficacy (follow-up 9 months)												
4	randomised trials	very serious[1]	no serious inconsistency	no serious indirectness	very serious[2]	none	6/194 (3.1%)	8/200 (4%)	RR 0.82 (0.3 to 2.19)	7 fewer per 1000 (from 28 fewer to 48 more)	⊕OOO VERY LOW	IMPORTANT
1	randomised trials	Serious[1]	no serious inconsistency	no serious indirectness	Unable to assess imprecision due to nonparametric measure of efficacy	none	69	63		Pain (VAS) (median (IQR)) in the intervention group was 21 (14-52) (median difference: 14 lower in the intervention group.))	⊕⊕⊕O MODERATE	IMPORTANT
1	randomised trials	Serious[1]	no serious inconsistency	no serious indirectness	Unable to assess imprecision due to nonparametric measure of efficacy	none	57	63		Pain (VAS) (median (IQR)) was 22 (13-34) in the intervention group (median difference: 13 lower in the intervention group)	⊕⊕⊕O MODERATE	IMPORTANT

[1] Downgraded by 1 increment if the majority of the evidence was at high risk of bias, and downgraded by 2 increments if the majority of the evidence was at very high risk of bias
[2] Downgraded by 1 increment if the confidence interval crossed one MID or by 2 increments if the confidence interval crossed both MIDs
[3] Indirect evidence: outcome does not use DAS

Table 44: Clinical evidence profile: Parallel combination therapy: methotrexate (MTX), sulfasalazine (SSZ), hydroxychloroquine (HCQ) versus monotherapy: methotrexate (MTX)

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Parallel combination therapy: MTX, SSZ, HCQ	Monotherapy: MTX	Relative (95% CI)	Absolute		
Change in DAS at 6 months (range of scores: 0-10; Better indicated by lower values)												
1	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	serious[2]	none	55	30	-	MD 0.36 lower (0.81 lower to 0.09 higher)	⊕⊕OO LOW	CRITICAL
Change in DAS at 6 months (range of scores: 0-10; Better indicated by lower values)												
1	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	serious[2]	none	65	30	-	MD 0.14 lower (0.56 lower to 0.28 higher)	⊕⊕OO LOW	CRITICAL
Change in function (HAQ) at 6 months (range of scores: 0-3; Better indicated by lower values)												
1	randomised trials	very serious[1]	no serious inconsistency	no serious indirectness	serious[2]	none	47	26	-	MD 0.05 lower (0.3 lower to 0.2 higher)	⊕OOO VERY LOW	CRITICAL
Change in function (HAQ) at 6 months (range of scores: 0-3; Better indicated by lower values)												
1	randomised trials	very serious[1]	no serious inconsistency	no serious indirectness	serious[2]	none	54	26	-	MD 0.05 lower (0.3 lower to 0.2 higher)	⊕OOO VERY LOW	CRITICAL
Remission at 6 months												
1	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	very serious[2]	none	24/55 (43.6%)	10/30 (33.3%)	RR 1.31 (0.73 to 2.36)	103 more per 1000 (from 90 fewer to 453 more)	⊕OOO VERY LOW	IMPORTANT

Remission at 6 months												
1	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	very serious[2]	none	28/65 (43.1%)	10/30 (33.3%)	RR 1.29 (0.72 to 2.3)	97 more per 1000 (from 93 fewer to 433 more)	⊕OOO VERY LOW	IMPORTANT
Median pain (VAS) at 6 months (Better indicated by lower values)												
1	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	[3]	none	65	59	-	not pooled		
Median pain (VAS) at 6 months (Better indicated by lower values)												
1	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	[3]	none	0	-	-	not pooled		IMPORTANT

[1] Downgraded by 1 increment if the majority of the evidence was at high risk of bias, and downgraded by 2 increments if the majority of the evidence was at very high risk of bias
[2] Downgraded by 1 increment if the confidence interval crossed 1 MID or by 2 increments if the confidence interval crossed both MIDs.
[3] Unable to assess imprecision due to nonparametric measure of efficacy

Table 45: Clinical evidence profile: Parallel combination therapy: methotrexate (MTX), sulfasalazine (SSZ) versus monotherapy: sulfasalazine (SSZ)

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	**Design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**Parallel combination therapy: MTX, SSZ, HCQ**	**Monotherapy SSZ**	**Relative (95% CI)**	**Absolute**		
DAS remission at 6 months (follow-up 6 months)												
1	randomised trials	very serious[1]	no serious inconsistency	no serious indirectness	serious[2]	none	52/79 (65.8%)	33/90 (36.7%)	RR 1.8 (1.31 to 2.46)	293 more per 1000 (from 114 more to 535 more)	⊕OOO VERY LOW	IMPORTANT
Withdrawal: adverse events (follow-up 6 months)												
1	randomised trials	very serious[1]	no serious inconsistency	no serious indirectness	very serious[3]	none	0/96 (0%)	0/94 (0%)	Not estimable	0 fewer per 1000 (from 20 fewer to 20 more)[4]	⊕OOO VERY LOW	IMPORTANT

Withdrawal: inefficacy (follow-up 6 months)												
1	randomised trials	very serious[1]	no serious inconsistency	no serious indirectness	very serious[3]	none	0/94 (0%)	0/96 (0%)	Not estimable	0 fewer per 1000 (from 20 fewer to 20 more)[4]	⊕OOO VERY LOW	IMPORTANT

[1] Downgraded by 1 increment if the majority of the evidence was at high risk of bias, and downgraded by 2 increments if the majority of the evidence was at very high risk of bias
[2] Downgraded by 1 increment if the confidence interval crossed one MID or by 2 increments if the confidence interval crossed both MIDs
[3] Downgraded by 1 increment if the confidence interval crossed one MID or by 2 increments if the confidence interval crossed both MIDs
[4] Risk difference utilised to calculate absolute effect

Table 46: Clinical evidence profile: Step up therapy: methotrexate (MTX), sulfasalazine (SSZ), hydroxychloroquine (HCQ) versus sequential monotherapy: methotrexate (MTX), sulfasalazine (SSZ), leflunomide (LFN)

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	**Design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**Step up therapy: MTX, SSZ, HCQ**	**Sequential monotherapy: MTX, SSZ, LFN**	**Relative (95% CI)**	**Absolute**		
Change in function (HAQ) score at 12 months (range of scores: 0-3; Better indicated by lower values)												
1	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	no serious imprecision	none	115	122	-	MD 0 higher (0.18 lower to 0.18 higher)	⊕⊕⊕O MODERATE	CRITICAL
Change in radiographic score (SvdH) at 12 months (range of scores: 0-448; Better indicated by lower values)												
1	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	no serious imprecision	none	115	122	-	MD 3.8 lower (7.3 to 0.3 lower)	⊕⊕⊕O MODERATE	IMPORTANT

[1] Downgraded by 1 increment if the majority of the evidence was at high risk of bias, and downgraded by 2 increments if the majority of the evidence was at very high risk of bias

Table 47: Clinical evidence profile: Parallel combination therapy: sulfasalazine (SSZ), hydroxychloroquine (HCQ) versus parallel combination therapy: methotrexate (MTX), hydroxychloroquine (HCQ)

Quality assessment	No of patients	Effect	Quality	Importance

No of studies	**Design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**Parallel combination therapy: SSZ, HCQ**	**Parallel combination therapy: MTX, HCQ**	**Relative (95% CI)**	**Absolute**		
Disease Activity Score (DAS28) at 6 months (range of scores: 2-10; Better indicated by lower values)												
1	randomised trials	very serious[1]	no serious inconsistency	no serious indirectness	serious[2]	none	54	56	-	MD 0.8 lower (1.4 to 0.2 lower)	⊕OOO VERY LOW	CRITICAL
Remission at 6 months												
1	randomised trials	very serious[1]	no serious inconsistency	no serious indirectness	serious[2]	none	20/54 (37%)	14/56 (25%)	RR 1.48 (0.84 to 2.62)	120 more per 1000 (from 40 fewer to 405 more)	⊕OOO VERY LOW	IMPORTANT

[1] Downgraded by 1 increment if the majority of the evidence was at high risk of bias, and downgraded by 2 increments if the majority of the evidence was at very high risk of bias
[2] Downgraded by 1 increment if the confidence interval crossed 1 MID or by 2 increments if the confidence interval crossed both MIDs.

Table 48: Clinical evidence profile: Step up therapy: sulfasalazine (SSZ), methotrexate (MTX), hydroxychloroquine (HCQ) versus parallel combination therapy: methotrexate (MTX), sulfasalazine (SSZ), hydroxychloroquine (HCQ)

Quality assessment							**No of patients**		**Effect**		**Quality**	**Importance**
No of studies	**Design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**Step up therapy: SSZ, MTX, HCQ**	**Parallel combination therapy: MTX, SSZ, HCQ**	**Relative (95% CI)**	**Absolute**		
Change in Disease Activity Score (DAS28) at 12 months (range of scores: 2-10; Better indicated by lower values)												
1	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	serious[2]	none	44	47	-	MD 0.7 lower (1.4 lower to 0 higher)	⊕⊕OO LOW	CRITICAL
Change in health related quality of life (SF-36) at 12 months (range of scores: 0-100; Better indicated by lower values)												

1	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	no serious imprecision	none	44	47	-	MD 1 higher (3.94 lower to 5.94 higher)	⊕⊕⊕O MODERATE	CRITICAL
Change in function (HAQ) at 12 months (range of scores: 0-3; Better indicated by lower values)												
1	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	serious[2]	none	44	47	-	MD 0.1 lower (0.39 lower to 0.19 higher)	⊕⊕OO LOW	CRITICAL
Low disease activity at 12 months												
1	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	serious[2]	none	28/47 (59.6%)	20/49 (40.8%)	RR 1.46 (0.97 to 2.2)	188 more per 1000 (from 12 fewer to 490 more)	⊕⊕OO LOW	IMPORTANT
Remission at 12 months												
1	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	serious[2]	none	21/47 (44.7%)	16/49 (32.7%)	RR 1.37 (0.82 to 2.28)	121 more per 1000 (from 59 fewer to 418 more)	⊕⊕OO LOW	IMPORTANT
ACR50 response at 12 months												
1	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	serious[2]	none	28/47 (59.6%)	25/49 (51%)	RR 1.17 (0.81 to 1.68)	87 more per 1000 (from 97 fewer to 347 more)	⊕⊕OO LOW	IMPORTANT
Change in pain score (VAS) at 12 months (range of scores: 0-100; Better indicated by lower values)												
1	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	no serious imprecision	none	44	47	-	MD 1 higher (12.56 lower to 14.56 higher)	⊕⊕⊕O MODERATE	
Change in radiographic progression (Sharp score) at 12+ months (Better indicated by lower values)												
1	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	serious[2]	none	44	47	-	MD 0.6 lower (3.14 lower to 1.94 higher)	⊕⊕⊕O MODERATE	IMPORTANT

[1] Downgraded by 1 increment if the majority of the evidence was at high risk of bias, and downgraded by 2 increments if the majority of the evidence was at very high risk of bias
[2] Downgraded by 1 increment if the confidence interval crossed 1 MID or by 2 increments if the confidence interval crossed both MIDs.

Table 49: Clinical evidence profile: Step up therapy: methotrexate (MTX), leflunomide (LFN) versus parallel combination therapy: methotrexate (MTX), sulfasalazine (SSZ)

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Step up therapy: MTX, LFN	Parallel combination therapy: MTX, SSZ	Relative (95% CI)	Absolute		
Disease Activity Score at 12 months (follow-up 12 months; measured with: DAS28. Change score; range of scores: 0-9.4; Better indicated by lower values)												
1	randomised trials	very serious[1]	no serious inconsistency	no serious indirectness	no serious imprecision	none	89	90	-	MD 0.2 higher (0.23 lower to 0.63 higher)	⊕⊕OO LOW	CRITICAL
Disease Activity Score at 6 months (follow-up 3 months; measured with: DAS28. Change score; range of scores: 0-9.4; Better indicated by lower values)												
1	randomised trials	very serious[1]	no serious inconsistency	no serious indirectness	no serious imprecision	none	98	98	-	MD 0.2 higher (0.14 lower to 0.54 higher)	⊕⊕OO LOW	CRITICAL
Function at 12 months (follow-up 12 months; measured with: HAQ. Change score; range of scores: 0-3; Better indicated by lower values)												
1	randomised trials	very serious[1]	no serious inconsistency	no serious indirectness	serious[2]	none	89	90	-	MD 0.2 higher (0.01 lower to 0.41 higher)	⊕OOO VERY LOW	IMPORTANT
Function at 6 months (follow-up 3 months; measured with: HAQ. Change score; range of scores: 0-3; Better indicated by lower values)												
1	randomised trials	very serious[1]	no serious inconsistency	no serious indirectness	serious[2]	none	98	98	-	MD 0.2 higher (0.03 to 0.37 higher)	⊕OOO VERY LOW	IMPORTANT
Low disease activity at 12 months (follow-up 12 months)												
1	randomised trials	very serious[1]	no serious inconsistency	no serious indirectness	no serious imprecision	none	74/98 (75.5%)	74/98 (75.5%)	RR 1 (0.85 to 1.17)	0 fewer per 1000 (from 113 fewer to 128 more)	⊕⊕OO LOW	

Low disease activity at 6 months (follow-up 3 months)												
1	randomised trials	very serious[1]	no serious inconsistency	no serious indirectness	no serious imprecision	none	85/98 (86.7%)	83/98 (84.7%)	RR 1.02 (0.91 to 1.15)	17 more per 1000 (from 76 fewer to 127 more)	⊕⊕OO LOW	IMPORTANT
DAS remission at 12 months (follow-up 12 months; assessed with: DAS28)												
1	randomised trials	very serious[1]	no serious inconsistency	no serious indirectness	serious[2]	none	59/98 (60.2%)	63/98 (64.3%)	RR 0.94 (0.75 to 1.17)	39 fewer per 1000 (from 161 fewer to 109 more)	⊕OOO VERY LOW	IMPORTANT
DAS remission at 6 months (follow-up 3 months; assessed with: DAS28)												
1	randomised trials	very serious[1]	no serious inconsistency	no serious indirectness	no serious imprecision	none	72/98 (73.5%)	69/98 (70.4%)	RR 1.04 (0.88 to 1.24)	28 more per 1000 (from 84 fewer to 169 more)	⊕⊕OO LOW	IMPORTANT
Radiological progression at 12+ months (follow-up 12 months; measured with: SvdH score. Change score; range of scores: 0-448; Better indicated by lower values)												
1	randomised trials	very serious[1]	no serious inconsistency	no serious indirectness	no serious imprecision	none	89	90	-	MD 0.1 lower (0.35 lower to 0.15 higher)	⊕⊕OO LOW	IMPORTANT
Withdrawal: adverse events (follow-up 3 months)												
1	randomised trials	very serious[1]	no serious inconsistency	no serious indirectness	very serious[2]	none	1/97 (1%)	2/93 (2.2%)	RR 0.48 (0.04 to 5.2)	11 fewer per 1000 (from 21 fewer to 90 more)	⊕OOO VERY LOW	IMPORTANT
Withdrawal: inefficacy (follow-up 3 months)												
1	randomised trials	very serious[1]	no serious inconsistency	no serious indirectness	very serious[2]	none	0/96 (0%)	2/93 (2.2%)	Peto OR 0.13 (0.01 to 2.09)	20 fewer per 1000 (from 60 fewer to 10 more)[3]	⊕OOO VERY LOW	IMPORTANT

[1] Downgraded by 1 increment if the majority of the evidence was at high risk of bias, and downgraded by 2 increments if the majority of the evidence was at very high risk of bias
[2] Downgraded by 1 increment if the confidence interval crossed one MID or by 2 increments if the confidence interval crossed both MIDs
[3] Risk difference utilised to calculate absolute effect

Table 50: Clinical evidence profile: Parallel combination therapy: methotrexate (MTX), sulfasalazine (SSZ) versus parallel combination therapy: methotrexate (MTX), leflunomide (LFN)

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Parallel combination therapy: MTX, LFN	Parallel combination therapy: MTX, SSZ	Relative (95% CI)	Absolute		
Disease Activity Score at 12 months (follow-up 12 months; measured with: DAS28. Change score; range of scores: 0-9.4; Better indicated by lower values)												
1	randomised trials	very serious[1]	no serious inconsistency	no serious indirectness	no serious imprecision	none	85	90	-	MD 0.2 higher (0.24 lower to 0.64 higher)	⊕⊕OO LOW	CRITICAL
Disease Activity Score at 6 months (follow-up 3 months; measured with: DAS28. Change score; range of scores: 0-9.4; Better indicated by lower values)												
1	randomised trials	very serious[1]	no serious inconsistency	no serious indirectness	serious[2]	none	94	98	-	MD 0.4 higher (0.05 to 0.75 higher)	⊕OOO VERY LOW	CRITICAL
Function at 12 months (follow-up 12 months; measured with: HAQ. Change score; range of scores: 0-3; Better indicated by lower values)												
1	randomised trials	very serious[1]	no serious inconsistency	no serious indirectness	no serious imprecision	none	85	90	-	MD 0.1 higher (0.09 lower to 0.29 higher)	⊕⊕OO LOW	CRITICAL
Function at 6 months (follow-up 3 months; measured with: HAQ. Change score; range of scores: 0-3; Better indicated by lower values)												
1	randomised trials	very serious[1]	no serious inconsistency	no serious indirectness	no serious imprecision	none	94	98	-	MD 0.1 higher (0.07 lower to 0.27 higher)	⊕⊕OO LOW	CRITICAL
Low disease activity at 12 months (follow-up 12 months)												
1	randomised trials	very serious[1]	no serious inconsistency	no serious indirectness	no serious imprecision	none	74/93 (79.6%)	73/98 (74.5%)	RR 1.07 (0.91 to 1.25)	52 more per 1000 (from 67 fewer to 186 more)	⊕⊕OO LOW	IMPORTANT
Low disease activity at 6 months (follow-up 3 months)												

1	randomised trials	very serious[1]	no serious inconsistency	no serious indirectness	no serious imprecision	none	82/94 (87.2%)	83/98 (84.7%)	RR 1.03 (0.92 to 1.15)	25 more per 1000 (from 68 fewer to 127 more)	⊕⊕OO LOW	IMPORTANT
DAS remission at 12 months (follow-up 12 months; assessed with: DAS28)												
1	randomised trials	very serious[1]	no serious inconsistency	no serious indirectness	serious[2]	none	58/93 (62.4%)	63/98 (64.3%)	RR 0.97 (0.78 to 1.2)	19 fewer per 1000 (from 141 fewer to 129 more)	⊕OOO VERY LOW	IMPORTANT
DAS remission at 6 months (follow-up 3 months; assessed with: DAS28)												
1	randomised trials	very serious[1]	no serious inconsistency	no serious indirectness	no serious imprecision	none	64/94 (68.1%)	69/98 (70.4%)	RR 0.97 (0.8 to 1.17)	21 fewer per 1000 (from 141 fewer to 120 more)	⊕⊕OO LOW	IMPORTANT
Radiological progression at 12+ months (follow-up 12 months; measured with: SvdH score. Change score; range of scores: 0-448; Better indicated by lower values)												
1	randomised trials	very serious[1]	no serious inconsistency	no serious indirectness	no serious imprecision	none	85	90	-	MD 0 higher (0.16 lower to 0.16 higher)	⊕⊕OO LOW	IMPORTANT
Withdrawal: adverse events (follow-up 3 months)												
1	randomised trials	very serious[1]	no serious inconsistency	no serious indirectness	very serious[2]	none	0/91 (0%)	2/93 (2.2%)	Peto OR 0.14 (0.01 to 2.2)	20 fewer per 1000 (from 60 fewer to 10 more)[3]	⊕OOO VERY LOW	IMPORTANT
Withdrawal: inefficacy (follow-up 3 months)												
1	randomised trials	very serious[1]	no serious inconsistency	no serious indirectness	very serious[2]	none	1/92 (1.1%)	2/93 (2.2%)	RR 0.51 (0.05 to 5.48)	11 fewer per 1000 (from 20 fewer to 96 more)	⊕OOO VERY LOW	IMPORTANT

[1] Downgraded by 1 increment if the majority of the evidence was at high risk of bias, and downgraded by 2 increments if the majority of the evidence was at very high risk of bias
[2] Downgraded by 1 increment if the confidence interval crossed one MID or by 2 increments if the confidence interval crossed both MIDs
[3] Risk difference utilised to calculate absolute effect

Table 51: Clinical evidence profile: Step up therapy: methotrexate (MTX), leflunomide (LFN) versus parallel combination therapy: methotrexate (MTX), leflunomide (LFN)

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Step up therapy: MTX, LFN		Relative (95% CI)	Absolute		
Disease Activity Score at 12 months (follow-up 12 months; measured with: DAS28. Change score.; range of scores: 0-9.4; Better indicated by lower values)												
1	randomised trials	very serious[1]	no serious inconsistency	no serious indirectness	no serious imprecision	none	89	85	-	MD 0 higher (0.43 lower to 0.43 higher)	⊕⊕OO LOW	CRITICAL
Disease Activity Score at 6 months (follow-up 3 months; measured with: DAS28. Change score; range of scores: 0-9.4; Better indicated by lower values)												
1	randomised trials	very serious[1]	no serious inconsistency	no serious indirectness	no serious imprecision	none	98	94	-	MD 0.2 lower (0.55 lower to 0.15 higher)	⊕⊕OO LOW	CRITICAL
Function at 12 months (follow-up 12 months; measured with: HAQ. Change score; range of scores: 0-3; Better indicated by lower values)												
1	randomised trials	very serious[1]	no serious inconsistency	no serious indirectness	no serious imprecision	none	89	85	-	MD 0.1 higher (0.11 lower to 0.31 higher)	⊕⊕OO LOW	CRITICAL
Function at 6 months (follow-up 3 months; measured with: HAQ. Change score; range of scores: 0-3; Better indicated by lower values)												
1	randomised trials	very serious[1]	no serious inconsistency	no serious indirectness	no serious imprecision	none	98	94	-	MD 0.1 higher (0.07 lower to 0.27 higher)	⊕⊕OO LOW	IMPORTANT
Low disease activity at 12 months (follow-up 12 months)												
1	randomised trials	very serious[1]	no serious inconsistency	no serious indirectness	no serious imprecision	none	74/98 (75.5%)	74/93 (79.6%)	RR 0.95 (0.81 to 1.11)	40 fewer per 1000 (from 151 fewer to 88 more)	⊕⊕OO LOW	IMPORTANT
Low disease activity at 6 months (follow-up 3 months)												
1	randomised trials	very serious[1]	no serious inconsistency	no serious indirectness	no serious imprecision	none	85/98 (86.7%)	82/94 (87.2%)	RR 0.99 (0.89 to 1.11)	9 fewer per 1000 (from 96 fewer to 96 more)	⊕⊕OO LOW	IMPORTANT
DAS remission at 12 months (follow-up 12 months; assessed with: DAS28)												

1	randomised trials	very serious[1]	no serious inconsistency	no serious indirectness	no serious imprecision	none	59/98 (60.2%)	58/93 (62.4%)	RR 0.97 (0.77 to 1.21)	19 fewer per 1000 (from 143 fewer to 131 more)	⊕⊕OO LOW	IMPORTANT
DAS remission at 6 months (follow-up 3 months; assessed with: DAS28)												
1	randomised trials	very serious[1]	no serious inconsistency	no serious indirectness	serious[2]	none	72/98 (73.5%)	64/94 (68.1%)	RR 1.08 (0.9 to 1.3)	54 more per 1000 (from 68 fewer to 204 more)	⊕OOO VERY LOW	IMPORTANT
Radiological progression at 12+ months (follow-up 12 months; measured with: SvdH score. Change score. Unclear range. ; range of scores: 0-448; Better indicated by lower values)												
1	randomised trials	very serious[1]	no serious inconsistency	no serious indirectness	no serious imprecision	none	89	85	-	MD 0.1 lower (0.36 lower to 0.16 higher)	⊕⊕OO LOW	IMPORTANT
Withdrawal: adverse events (follow-up 3 months)												
1	randomised trials	very serious[1]	no serious inconsistency	no serious indirectness	very serious[2]	none	1/97 (1%)	0/91 (0%)	Peto OR 6.95 (0.14 to 350.75)	10 more per 1000 (from 20 fewer to 40 more)[3]	⊕OOO VERY LOW	IMPORTANT
Withdrawal: inefficacy (follow-up 3 months)												
1	randomised trials	very serious[1]	no serious inconsistency	no serious indirectness	very serious[2]	none	0/96 (0%)	1/92 (1.1%)	Peto OR 0.13 (0 to 6.54)	10 fewer per 1000 (from 40 fewer to 20 more)[3]	⊕OOO VERY LOW	IMPORTANT

[1] Downgraded by 1 increment if the majority of the evidence was at high risk of bias, and downgraded by 2 increments if the majority of the evidence was at very high risk of bias
[2] Downgraded by 1 increment if the confidence interval crossed one MID or by 2 increments if the confidence interval crossed both MIDs
[3] Risk difference utilised to calculate absolute effect

F.2 Failed DMARDs

Table 52: Clinical evidence profile: Step-up therapy (sulfasalazine plus leflunomide) versus sequential monotherapy (sulfasalazine plus placebo) in people who failed leflunomide monotherapy

Quality assessment	No of patients	Effect	Quality	Importance

No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Step-up therapy (sulfasalazine plus leflunomide)	Sequential monotherapy (sulfasalazine plus placebo)	Relative (95% CI)	Absolute		
Disease Activity Score at 6 or 12 months - not reported												
0	-	-	-	-	-	none	-	-	-	-		CRITICAL
Quality of life at 6 or 12 months - not reported												
0	-	-	-	-	-	none	-	-	-	-		CRITICAL
Function at 12 months - not reported												
0	-	-	-	-	-	none	-	-	-	-		CRITICAL
Function at 6 months (follow-up 24 weeks; measured with: Change in HAQ; range of scores: 0-3; Better indicated by lower values)												
1	randomised trials	very serious[1]	no serious inconsistency	no serious indirectness	serious[2]	none	56	50	-	MD 0.07 lower (0.2 lower to 0.06 higher)	⊕OOO VERY LOW	CRITICAL
ACR50 response at 6 months (follow-up 24 weeks)												
1	randomised trials	very serious[1]	no serious inconsistency	no serious indirectness	serious[2]	none	5/56 (8.9%)	0/50 (0%)	Peto OR 7.16 (1.19 to 42.87)[3]	90 more per 1000 (from 10 more to 170 more)[4]	⊕OOO VERY LOW	IMPORTANT
Pain at 6 months (follow-up 24 weeks; measured with: Change in VAS; range of scores: 0-100; Better indicated by lower values)												
1	randomised trials	very serious[1]	no serious inconsistency	no serious indirectness	no serious imprecision	none	56	50	-	MD 0.89 lower (9.77 lower to 7.99 higher)	⊕⊕OO LOW	IMPORTANT
Withdrawal: side effects (follow-up 24 weeks)												
1	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	serious[2]	none	26/56 (46.4%)	18/50 (36%)	RR 1.29 (0.81 to 2.05)	104 more per 1000 (from 68 fewer to 378	⊕⊕OO LOW	IMPORTANT

										more)		
Withdrawal: inefficacy (follow-up 24 weeks)												
1	randomised trials	very serious[1]	no serious inconsistency	no serious indirectness	very serious[2]	none	3/56 (5.4%)	4/50 (8%)	RR 0.67 (0.16 to 2.85)	26 fewer per 1000 (from 67 fewer to 148 more)	⊕OOO VERY LOW	IMPORTANT

[1] Downgraded by 1 increment if the majority of the evidence was at high risk of bias, and downgraded by 2 increments if the majority of the evidence was at very high risk of bias
[2] Downgraded by 1 increment if the confidence interval crossed one MID or by 2 increments if the confidence interval crossed both MIDs
[3] Peto Odds ratio was used due to low numbers of events.
[4] Risk difference for the absolute effect.

Table 53: Clinical evidence profile: Step-up therapy (methotrexate plus sulfasalazine) versus sequential monotherapy (methotrexate) in people who failed sulfasalazine monotherapy

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	**Design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**Step-up therapy**	**Sequential monotherapy**	**Relative (95% CI)**	**Absolute**		
Disease Activity Score at 6 months - not reported												
0	-	-	-	-	-	none	-	-	-	-		CRITICAL
Quality of life at 6 or 12 months - not reported												
0	-	-	-	-	-	none	-	-	-	-		CRITICAL
Change in function at 6 months - not reported												
0	-	-	-	-	-	none	-	-	-	-		CRITICAL
Change in DAS at 12 months (follow-up 1 year; range of scores: 0-10; Better indicated by lower values)												
1	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	Cannot assess imprecision using median (IQR)	none	56	54	The change in DAS from baseline (median (IQR)) in the control groups was -0.26 (-0.99 to	The change in DAS from baseline (median (IQR)) in the intervention groups was -0.67 (-1.38 to -0.21)	⊕⊕⊕O MODERATE	CRITICAL

									0)	(median difference 0.41)		
Change in DAS at 6 months (follow-up 24 weeks; range of scores: 0-10; Better indicated by lower values)												
1	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	no serious imprecision	none	22	18	-	MD 1.6 lower (2.16 to 1.04 lower)	⊕⊕⊕O MODERATE	CRITICAL
Change in HAQ at 12 months (follow-up 1 year; range of scores: 0-10; Better indicated by lower values)												
1	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	Cannot assess imprecision using median (IQR)	none	56	54	The change in HAQ from baseline (median (IQR)) in the control groups was -0.19 (-10.25 to 0.13)	The change in HAQ from baseline (median (IQR)) in the intervention groups was -0.5 (-10.25 to 0.06) (median difference 0.31)	⊕⊕⊕O MODERATE	CRITICAL
ACR50 response at 12 months (follow-up 1 years)												
1	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	very serious[2]	none	6/56 (10.7%)	4/54 (7.4%)	RR 1.45 (0.43 to 4.84)	33 more per 1000 (from 42 fewer to 284 more)	⊕OOO VERY LOW	IMPORTANT
Change in pain score at 12 months (follow-up 1 year; range of scores: unclear; Better indicated by lower values)												
1	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	Cannot assess imprecision using median (IQR)	none	56	54	The change in Pain score change from baseline (median (IQR)) in the control groups was 0 (-23 to 11)	The change in Pain score from baseline (median (IQR)) in the intervention groups was -8 (-27.5 to 2) (median difference 8)	⊕⊕⊕O MODERATE	IMPORTANT
Change in pain (VAS) score at 6 months (follow-up 24 weeks; range of scores: 0-100; Better indicated by lower values)												
1	randomised trials	very serious[1]	no serious inconsistency	no serious indirectness	serious[2]	none	22	18	-	MD 16 lower (30.26 to 1.74 lower)	⊕OOO VERY LOW	IMPORTANT
Withdrawal: side effects (follow-up mean 38 weeks)												
2	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	very serious[2]	none	12/78 (15.4%)	14/72 (19.4%)	RR 0.83 (0.42 to 1.62)	33 fewer per 1000 (from 113 fewer to 121 more)	⊕⊕OO LOW	IMPORTANT
Withdrawal: inefficacy (follow-up mean 38 weeks)												

2	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	very serious[2]	none	2/78 (2.6%)	2/72 (2.8%)	RR 0.96 (0.14 to 6.6)	1 fewer per 1000 (from 24 fewer to 156 more)	⊕⊕OO LOW	IMPORTANT

[1] Downgraded by 1 increment if the majority of the evidence was at high risk of bias, and downgraded by 2 increments if the majority of the evidence was at very high risk of bias
[2] Downgraded by 1 increment if the confidence interval crossed one MID or by 2 increments if the confidence interval crossed both MIDs

Table 54: Clinical evidence profile: step-up therapy (methotrexate plus sulfasalazine then methotrexate plus sulfasalazine plus hydroxychloroquine) versus sequential monotherapy (sulfasalazine then leflunomide) in people who failed methotrexate monotherapy

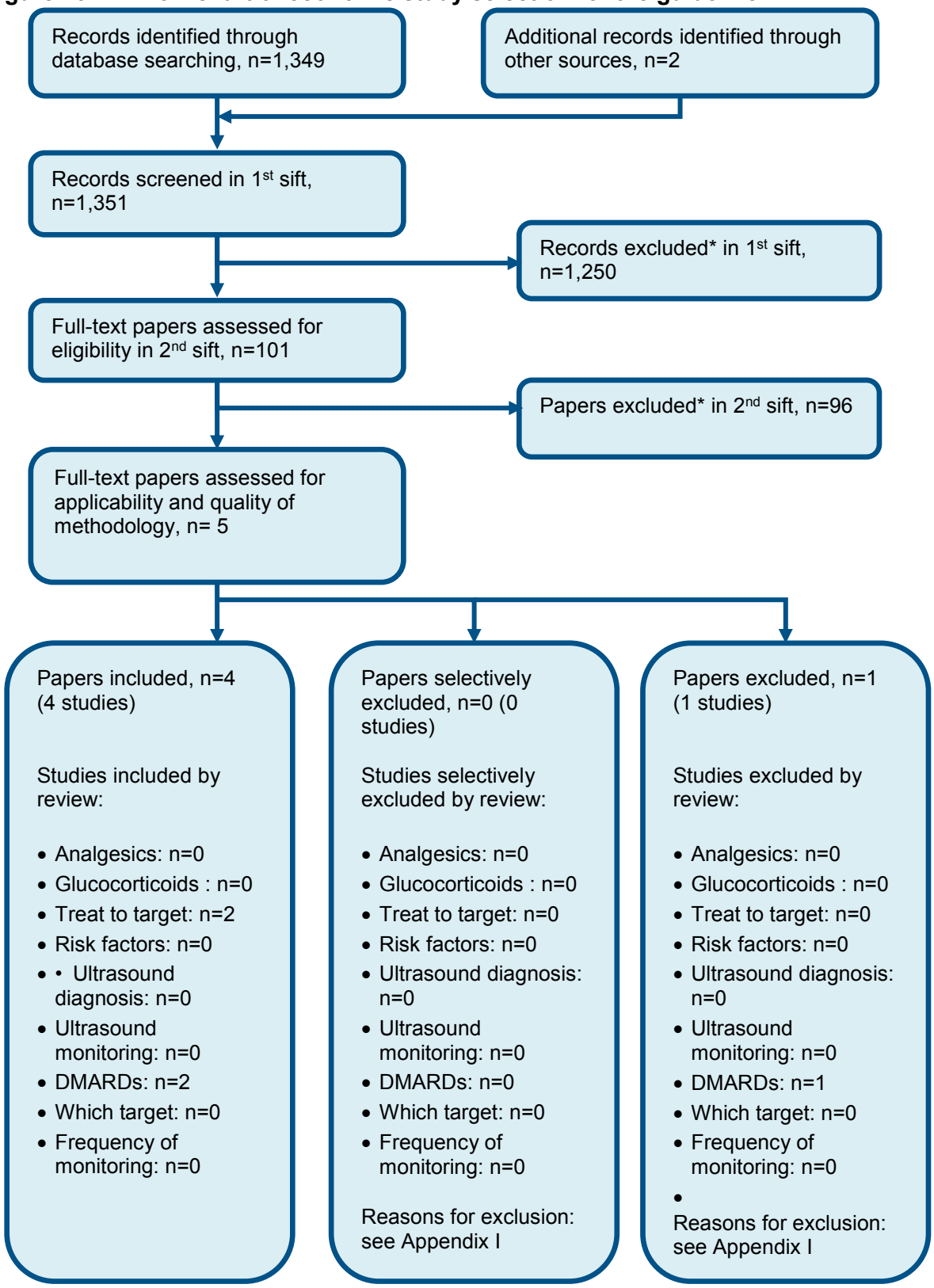
Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Step-up therapy	Sequential monotherapy	Relative (95% CI)	Absolute		
Disease Activity Score at 6 or 12 months - not reported												
0	-	-	-	-	-	none	-	-	-	-		CRITICAL
Quality of life at 6 or 12 months - not reported												
0	-	-	-	-	-	none	-	-	-	-		CRITICAL
Change in function at 6 or 12 months - not reported												
0	-	-	-	-	-	none	-	-	-	-		CRITICAL
Low disease activity (DAS<2.4) total at 12 months (follow-up 9 months)												
1	randomised trials	very serious[1]	no serious inconsistency	no serious indirectness	serious[2]	none	31/69 (44.9%)	22/69 (31.9%)	RR 1.41 (0.91 to 2.17)	131 more per 1000 (from 29 fewer to 373 more)	⊕OOO VERY LOW	IMPORTANT
Low disease activity (DAS<2.4) after step 1 at 6 months (follow-up 6 months)												
1	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	very serious[2]	none	15/69 (21.7%)	15/69 (21.7%)	RR 1 (0.53 to 1.88)	0 fewer per 1000 (from 102 fewer to 191 more)	⊕OOO VERY LOW	IMPORTANT

Low disease activity (DAS<2.4) after step 2 at 6 months (follow-up 3 months)												
1	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	serious[2]	none	16/44 (36.4%)	7/54 (13%)	RR 2.81 (1.27 to 6.21)	235 more per 1000 (from 35 more to 675 more)	⊕⊕OO LOW	IMPORTANT
Withdrawal: adverse events total (follow-up 9 months)												
1	randomised trials	very serious[1]	no serious inconsistency	no serious indirectness	very serious[2]	none	18/69 (26.1%)	13/69 (18.8%)	RR 1.38 (0.74 to 2.6)	72 more per 1000 (from 49 fewer to 301 more)	⊕OOO VERY LOW	IMPORTANT
Withdrawal: adverse events during step 1 (follow-up 6 months)												
1	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	very serious[2]	none	13/69 (18.8%)	7/69 (10.1%)	RR 1.86 (0.79 to 4.37)	87 more per 1000 (from 21 fewer to 342 more)	⊕OOO VERY LOW	IMPORTANT
Withdrawal: adverse events during step 2 (follow-up 3 months)												
1	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	very serious[2]	none	5/44 (11.4%)	6/54 (11.1%)	RR 1.02 (0.33 to 3.13)	2 more per 1000 (from 74 fewer to 237 more)	⊕OOO VERY LOW	IMPORTANT
Withdrawal: inefficacy (DAS >2.4) after step 1 (follow-up 6 months)												
1	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	serious[2]	none	41/69 (59.4%)	47/69 (68.1%)	RR 0.87 (0.68 to 1.12)	89 fewer per 1000 (from 218 fewer to 82 more)	⊕⊕OO LOW	IMPORTANT
Withdrawal: inefficacy (DAS >2.4) after step 2 (follow-up 3 months)												
1	randomised trials	very serious[2]	no serious inconsistency	no serious indirectness	serious[2]	none	21/44 (47.7%)	41/54 (75.9%)	RR 0.63 (0.45 to 0.89)	281 fewer per 1000 (from 84 fewer to 418 fewer)	⊕OOO VERY LOW	IMPORTANT

[1] Downgraded by 1 increment if the majority of the evidence was at high risk of bias, and downgraded by 2 increments if the majority of the evidence was at very high risk of bias
[2] Downgraded by 1 increment if the confidence interval crossed one MID or by 2 increments if the confidence interval crossed both MIDs.

Appendix G: Health economic evidence selection

Figure 137: Flow chart of economic study selection for the guideline



** Non-relevant population, intervention, comparison, design or setting; non-English language*

1

2

Appendix H: Health economic evidence tables

H.1 First line DMARDs

Study	Tosh 2011[157] and NICE CG79[111]			
Study details	**Population & interventions**	**Costs**	**Health outcomes**	**Cost effectiveness**
Economic analysis: CUA (health outcome: QALYs) **Study design:** Discreet event simulation **Approach to analysis:** Model tracks the course of the disease for hypothetical, individual patients, one at a time, along each of the alternative treatment pathways. This includes 6 month initial treatment response (ACR 20 and 50 response), duration of treatment strategy for responders, progression of disease (in terms of HAQ) while treatment continues, and future treatments (including biologics) likely to be provided over the remaining patient lifetime after withdrawal from initial DMARD	**Population:** Adults with recent onset rheumatoid arthritis. Mean disease duration 0.68 years (SD: 0.508) Mean baseline HAQ 1.11 (SD: 07) **Cohort settings:** Start age: 54.8 years (SD: 13.6) Male: 44.4% **Intervention 1:** Monotherapy: DMARD monotherapy (first line methotrexate 15mg/week, second line sulfasalazine 1g/day) **Intervention 2:** Parallel combination: two or more DMARDs given in combination at the same time	**Total costs (mean per patient):** Intervention 1: £55,996 Intervention 2: £55,573 Intervention 3: £50,791 Intervention 4: £48,849 Intervention 5: £61,046 Incremental analysis see cost effectiveness column (95% CI: NR; p=NR) **Currency & cost year:** 2007/8 UK pounds **Cost components incorporated:** Drug costs (including drugs, monitoring, review and administration where applicable); annual costs of managing RA stratified by HAQ score (hospital days, outpatient visits and joint replacements). Cost of adverse events not directly quantified, indirectly quantified	**QALYs (mean per patient):** Intervention 1: 13.73 Intervention 2: 13.42 Intervention 3: 11.91 Intervention 4: 15.32 Intervention 5: 15.77 Incremental analysis see cost effectiveness column (95% CI: NR; p=NR)	**Full incremental analysis** Int. | Cost | QALY | ICER 3 | £50,791 | 11.91 | Dominated by 4 2 | £55,573 | 13.42 | Dominated by 4 1 | £55,996 | 13.73 | Dominated by 4 4 | £48,849 | 15.32 | Baseline 5 | £61,046 | 15.77 | £27,392 per QALY **Analysis of uncertainty:** Probabilistic sensitivity analysis conducted comparing all 6 interventions, not the 5 relevant interventions reported here. Results demonstrated: Probability Intervention 4 cost effective (£20K): 50% Probability Intervention 5 cost effective (£20K): 43% In addition, a range of one way sensitivity analyses were conducted to test robustness of results to the assumptions

strategy. No treatment related mortality effect modelled. **Perspective:** UK NHS **Time horizon:** lifetime **Treatment effect duration:**[(a)] 6 months **Discounting:** Costs: 3.5%; Outcomes: 3.5%	**Intervention 3:** Step-up combination: Start on DMARD monotherapy, a second DMARD is added if inadequate response is observed (within first 6 months) **Intervention 4:** Step-down combination: initial parallel combination followed by downward dose titration and withdrawal **Intervention 5:** Intensive step-up combination: initial parallel combination and rapid dose increases (to above BNF recommended doses) made where an inadequate response is observed (within 6 months) A sixth intervention was reported but does not meet the protocol (glucocorticoid plus monotherapy) and so is not reported. All strategies used glucocorticoids 'as	through treatment withdrawal.		and measurement values used. Analyses included: alternative specifications of the relationship between HAQ and EQ-5D; patient baseline characteristics (HAQ and age), discount rates and frequencies of monitoring required while taking treatment. Assumption non-responders continue treatment until an adverse event or loss of efficacy is experienced. Assumption that there is no HAQ increase once achieved an ACR20 or 50 response for those receiving combination DMARDs (base-case assumed progression for all and was based on monotherapy evidence). Overall results were robust to all sensitivity analyses.

	needed'.			
Data sources				
Health outcomes: Baseline characteristics from UK Early Rheumatoid Arthritis Study (Kobelt 2002), mortality from standard UK lifetables, initial 6-month treatment response (ACR 20 and ACR 50) and 6-month treatment withdrawal rate taken from a network meta-analysis of 13 RCTs identified through a systematic literature review. Of the 13 trials used to estimate the treatment effects, 8 of them were excluded from our clinical review either because they included ciclosporin A, a DMARD excluded from the protocol, or because the treatment arms of the trial were the same and only differed in the amount of monitoring received (TICORA). Therefore, only 5 of the trials used are included in the clinical review. Percentage HAQ improvement for a ACR 20 and 50 response taken from estimate published by the US National Databank for Rheumatic Diseases, annual HAQ progression (increase) taken from meta-analysis of natural disease data. Lifetime QALYs of biologic therapy taken from biologics economic model by Brennan et al 2007. Adverse events not directly quantified, indirectly quantified through treatment withdrawal. **Quality-of-life weights:** HAQ converted to EQ-5D (UK tariff) using US National Databank for Rheumatic Diseases regression model. **Cost sources:** Resource use: Annual RA resource use stratified by HAQ taken from a UK cohort (Norfolk Arthritis Registry). Lifetime costs of biologics taken from biologics economic model (Brennan et al 2007). Unit costs: BNF 2008 and PSSRU 2007.				
Comments				
Source of funding: NICE as part of CG79. **Limitations:** Does not specify DMARDs but rather refers to treatment strategies, although authors note that a systematic review of monotherapy found no statistically significant difference between DMARDs. EQ-5D mapped from HAQ rather than directly elicited from patients in trials. Patient covariates are not included to determine differences in clinical response or treatment withdrawal as both of these inputs are based on trials not a registry. Criteria set by NICE for biologic eligibility is failing 2 DMARDs (incl. methotrexate) and having a DAS >5.1. As model is HAQ based and conversion from HAQ to DAS is not possible, this requirement not included in model. This analysis is based on 5 of the 21 studies included for this question and includes 8 studies that were not included in the clinical review and so does not reflect full body of evidence and may provide treatment effect estimates that do not reflect that identified in the clinical review. **Other:** None				
Overall applicability:[(b)] Partially applicable **Overall quality:**[(c)] Potentially serious limitations				

Abbreviations: 95% CI: 95% confidence interval; CUA: cost–utility analysis; EQ-5D: EuroQol 5 dimensions (scale: 0.0 [death] to 1.0 [full health], negative values mean worse than death); ICER: incremental cost-effectiveness ratio; NR: not reported; pa: probabilistic analysis; QALYs: quality-adjusted life years

(a) For studies where the time horizon is longer than the treatment duration, an assumption needs to be made about the continuation of the study effect. For example, does a difference in utility between groups during treatment continue beyond the end of treatment and if so for how long.

(b) Directly applicable / Partially applicable / Not applicable

(c) Minor limitations / Potentially serious limitations / Very serious limitations

Study	**Van den Hout 2009** [162]			
Study details	**Population & interventions**	**Costs**	**Health outcomes**	**Cost effectiveness**
Economic analysis: CUA (health outcome: QALYs)	**Population:** Adults with early RA (<2years) with active	**Total costs (mean per patient):** Intervention 1: £9,211	**QALYs (mean per patient):** Intervention 1: 1.29	**Intervention 2 dominates intervention 1**

Study design: Within-trial analysis (RCT: BeST trial) **Approach to analysis:** Analysis of individual level data for EQ-5D and resource use. Unit costs applied. **Perspective:** Dutch healthcare system **Follow-up:** 2 years **Treatment effect duration:**[a] n/a **Discounting:** Costs: 3%; Outcomes: 3%	disease and who have not previously received DMARDs. **Cohort settings:** Start age: 54 years (SD: 13) Intervention1: Male: 32% Intervention 2: Male: 28% **Intervention 1:** Sequential monotherapy (MTX, then Sulfasalazine, then leflunomide, then MTX + infliximab, then gold with methylprednisolone, then MTX with ciclosporin A + prednisolone then azathioprine with prednisone) **Intervention 2:** Step-up combination (MTX, then MTX + sulfasalazine, then MTX with sulfasalazine and HCQ, then MTX, sulfasalazine+ HCQ + prednisone, then MTX + infliximab, then MTX with ciclosporin A + prednisolone, then leflunomide, then azathioprine with	Intervention 2: £7,053 Incremental (2−1): saves £2,158 (95% CI: NR; p=NR) **Currency & cost year:** 2008 Euros (presented here as 2008 UK pounds[b]) **Cost components incorporated:** Medication costs, consultations, admissions and homecare.	Intervention 2: 1.31 Incremental (2−1): 0.02 (95% CI: NR; p=NR)	**Analysis of uncertainty:** Bootstrapping undertaken for all 4 interventions in study, not the 2 relevant interventions reported here. Results demonstrated: probability Intervention 2 cost effective (£20K threshold): ~50% (from a graph). Analysis was done including two additional comparators that did not meet the protocol. Results presented graphically only so values are approximate.

	prednisone) For both 1 and 2, treatment was adapted based on DAS measured every 3 months, if >2.4 next treatment step started, if <2.4, present treatment continued and after 6 months the last added drug was tapered until one DMARD in a maintenance dose remained. Two more interventions were included in the trial but not reported here as they did not meet the review protocol (one included use of biologics and the other glucocorticoid as part of their combinations)			

Data sources
Health outcomes: Within trial analysis, EQ-5D data from BeST trial (same paper). QALYs calculated as the area under the curve. Other outcomes measured include HAQ and DAS but not used for analysis. **Quality-of-life weights:** EQ-5D UK tariff measured at baseline and every three months thereafter. **Cost sources:** Resource use from within trial, using case records and patient cost diaries filled quarterly. Unit costs were standard published Dutch prices.
Comments
Source of funding: Dutch Healthcare Insurance Board. **Limitations:** Evidence from a Dutch healthcare perspective. Discounting at 3% rather than 3.5% as required by the NICE reference case. Does not include a comparison of all possible treatment combinations identified in the clinical evidence. 2-year follow-up unlikely to be sufficient to capture all downstream costs and treatment effects. Dutch unit costs, may not reflect current NHS costs. Within trial analysis based on RCT BeST. This analysis is based on 1 of the 21 studies included for this question and so does not reflect full body of evidence. **Other:** None
Overall applicability:[c] Partially applicable **Overall quality:**[d] Potentially serious limitations

Abbreviations: 95% CI: 95% confidence interval; CUA: cost–utility analysis; EQ-5D: EuroQol 5 dimensions (scale: 0.0 [death] to 1.0 [full health], negative values mean worse than death); ICER: incremental cost-effectiveness ratio; NR: not reported; pa: probabilistic analysis; QALYs: quality-adjusted life years

(a) For studies where the time horizon is longer than the treatment duration, an assumption needs to be made about the continuation of the study effect. For example, does a difference in utility between groups during treatment continue beyond the end of treatment and if so for how long.
(b) Converted using 2008 purchasing power parities[123]
(c) Directly applicable / Partially applicable / Not applicable
(d) Minor limitations / Potentially serious limitations / Very serious limitations

H.2 Failed DMARDs

None.

1 Appendix I: Excluded studies

2 **Table 55: Studies excluded from the clinical review for first line DMARDs**

Study	Exclusion reason
Ahmed 2010[1]	Not review population
Akdemir 2016[2]	ACPA negative subgroup of BeSt study
Alam 2012[3]	Not review population
Anon 1992[150]	Not in English language
Bao 2000[9]	Not originally in English language and poor translation
Bao 2003[8]	Not review population
Box 1997[15]	Systematic review: included studies checked for inclusion in this evidence review
Braun 2008[16]	Not review population
Burgers 2017[17]	Not guideline condition
Calguneri 1999[18]	Not review population
Charles-schoeman 2016[20]	Not review population
Charles-schoeman 2017[21]	Not review population
Clegg 1997[23]	Not review population
Cohen 2001[24]	Not review population
Das 2007[26]	Not review population
Dougados 1997[32]	Not in English language
Emery 2000[36]	Not review population
Faarvang 1993[37]	Not review population
Farr 1995[38]	Not review population
Fedorenko 2012[39]	Not review population
Ferraz 1994[41]	Not review population
Fiehn 2007[42]	Not review population
Fleischmann 2017[43]	Incorrect interventions
Furst 1989[44]	Not review population
Gaujoux-viala 2010[45]	Systematic review: included studies checked for inclusion in this evidence review
Goekoop-ruiterman 2007[47]	RCT participant survey
Golicki 2012[49]	Systematic review: included studies checked for inclusion in this evidence review
Graudal 2014[50]	Systematic review: included studies checked for inclusion in this evidence review
Gubar 2008[52]	Not in English language
Gunasekera 2016[53]	Full text paper could not be acquired
Haschka 2016[58]	Not review population
Hazlewood 2016[59]	Systematic review: included papers checked for inclusion in this evidence review
Hazlewood 2016[60]	Systematic review: included papers checked for inclusion in this evidence review
Heimans 2016[61]	Inappropriate comparison
Hissink muller 2017[62]	Not guideline condition
Horslev-petersen 2016[63]	Incorrect interventions

Study	Exclusion reason
Hu 2001[64]	Not review population
Ishaq 2011[65]	Not review population
Islam 2000[66]	Not review population
Jaji 1988[69]	Not in English language
Jiang 2000[70]	Full text paper not in English language
Jiang 2000[71]	Not in English language
Jiang 2001[72]	Not in English language
Kalden 2001[73]	Not review population
Klarenbeek 2011[75]	Remission subgroup from the BeSt study
Konijn 2017[76]	Incorrect interventions
Kraan 2000[78]	Not review population
Kraan 2000[79]	Not review population
Kraan 2004[80]	Investigation of a subset of participants in an RCT not included in the evidence review
Kremer 2002[82]	Inappropriate comparison
Kremer 2004[81]	Inappropriate comparison. Not review population
Kuriachan 2012[84]	Incorrect study design
Kuusalo 2016[85]	Incorrect interventions
Lao 2001[89]	Not in English language
Lao 2002[90]	Not review population
Larsen 2001[91]	Not review population
Lau 2002[92]	Not review population
Li 2016[94]	Systematic review: included studies checked for inclusion in this evidence review
Li 2016[95]	Not review population
Maillefert 2003[97]	Inappropriate comparison
Markusse 2014[99]	Incorrect interventions
Mathur 2017[100]	Not review population
Mcinnes 1996[101]	Inappropriate comparison
Mehrotra a 2006[102]	Not review population
Mladenovic 1995[103]	Not review population
Modi 2017[104]	Dose comparison of hydroxychloroquine
Moreland 2012[105]	Not review population
Mottaghi 2005[106]	Not review population
Mottonen 2002[107]	Not review population
Musikic 1992[109]	Not in English language
Navarro-millan 2013[113]	Not review population
Neumann 1985[114]	Not review population
Nisar 1994[117]	Incorrect study design
O'dell 1996[121]	Not review population
O'dell 1996[120]	Not review population
O'dell 2002[122]	Not review population
O'dell 2013[119]	Not review population
Pavelka 1989[124]	Not in English language
Pinals 1986[125]	Not review population
Proudman 2000[126]	Inappropriate comparison

Study	Exclusion reason
Pullar 1983[127]	Not review population
Reece 2002[133]	Not review population
Riel 1994[134]	Not in English language
Rodríguez 1997[135]	Not in English language
Salaffi 1995[136]	Not review population
Schipper 2009[138]	Incorrect study design
Scott 2001[140]	Not review population
Shashikumar 2010[141]	Not review population
Shevchuk 2003[142]	Not in English language
Shuai 2002[143]	Not originally in English language and poor translation
Singh 2012[144]	Not review population
Smolen 1999[145]	Not review population
Smolen 1999[146]	Not review population
Strand 1999[149]	Not review population
Strand 1999[147]	Not review population
Strand 2005[148]	Not review population
Svensson 2003[151]	Inappropriate comparison
Tascioglu 2003[153]	No relevant outcomes reported
Taylor 2017[154]	Incorrect interventions
Tchetverikov 2008[155]	Not review population
Ter wee 2015[156]	Incorrect interventions
Trnavsky 1993[158]	Not review population
Tugwell 2000[160]	Not review population
Van aken 2004[161]	Incorrect study design
Van der heide 1996[163]	Inappropriate comparison
Van riel 2003[173]	Not review population
Verschueren 2008[179]	Incorrect study design
Verstappen 2003[180]	Inappropriate comparison
Walker-bone 2007[182]	Systematic review: included studies checked for inclusion in this evidence review
Weinblatt 1985[183]	Not review population
Williams 1985[185]	Not review population
Williams 1988[184]	Narrative review
Zeb 2016[186]	Not review population
Zhang 2004[187]	Not originally in English language and poor translation
Zhao 2017[188]	Incorrect interventions

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2 **Table 56: Studies excluded from the clinical review for failed DMARDs**

Study	Exclusion reason
Ahmed 2010[1]	Not review population
Akdemir 2016[2]	ACPA negative subgroup of BeSt study
Alam 2012[3]	Not review population
Anon 1992[150]	Not in English language
Bao 2000[9]	Not originally in English language and poor translation
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Study	Exclusion reason
Box 1997[15]	Systematic review: included studies checked for inclusion in this evidence review
Braun 2008[16]	Not review population
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Calguneri 1999[18]	Not review population
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Cohen 2001[24]	Not review population
Das 2007[26]	Not review population
Dougados 1997[32]	Not in English language
Emery 2000[36]	Not review population
Faarvang 1993[37]	Not review population
Farr 1995[38]	Not review population
Fedorenko 2012[39]	Not review population
Ferraz 1994[41]	Not review population
Fiehn 2007[42]	Not review population
Fleischmann 2017[43]	Incorrect interventions
Furst 1989[44]	Not review population
Gaujoux-viala 2010[45]	Systematic review: included studies checked for inclusion in this evidence review
Goekoop-ruiterman 2007[47]	RCT participant survey
Golicki 2012[49]	Systematic review: included studies checked for inclusion in this evidence review
Graudal 2014[50]	Systematic review: included studies checked for inclusion in this evidence review
Gubar 2008[52]	Not in English language
Gubar 2008[51]	Not in English language
Gunasekera 2016[53]	Full text paper could not be acquired
Haschka 2016[58]	Not review population
Hazlewood 2016[59]	Systematic review: included papers checked for inclusion in this evidence review
Hazlewood 2016[60]	Systematic review: included papers checked for inclusion in this evidence review
Heimans 2016[61]	Inappropriate comparison
Hissink muller 2017[62]	Not guideline condition
Horslev-petersen 2016[63]	Incorrect interventions
Hu 2001[64]	Not review population
Ishaq 2011[65]	Not review population
Islam 2000[66]	Not review population
Jaji 1988[69]	Not in English language
Jiang 2000[70]	Full text paper not in English language
Jiang 2000[71]	Not in English language
Jiang 2001[72]	Not in English language
Kalden 2001[73]	Not review population
Klarenbeek 2011[75]	Remission subgroup from the BeSt study
Konijn 2017[76]	Incorrect interventions

Study	Exclusion reason
Kraan 2000[78]	Not review population
Kraan 2000[79]	Not review population
Kraan 2004[80]	Investigation of a subset of participants in an RCT not included in the evidence review
Kremer 2002[82]	Inappropriate comparison
Kremer 2004[81]	Inappropriate comparison. Not review population
Kuriachan 2012[84]	Incorrect study design
Kuusalo 2016[85]	Incorrect interventions
Lao 2001[89]	Not in English language
Lao 2002[90]	Not review population
Larsen 2001[91]	Not review population
Lau 2002[92]	Not review population
Li 2016[94]	Systematic review: included studies checked for inclusion in this evidence review
Li 2016[95]	Not review population
Maillefert 2003[97]	Inappropriate comparison
Markusse 2014[99]	Incorrect interventions
Mathur 2017[100]	Not review population
Mcinnes 1996[101]	Inappropriate comparison
Mehrotra a 2006[102]	Not review population
Mladenovic 1995[103]	Not review population
Modi 2017[104]	Dose comparison of hydroxychloroquine
Moreland 2012[105]	Not review population
Mottaghi 2005[106]	Not review population
Mottonen 2002[107]	Not review population
Musikic 1992[109]	Not in English language
Navarro-millan 2013[113]	Not review population
Neumann 1985[114]	Not review population
Nisar 1994[117]	Incorrect study design
O'dell 1996[121]	Not review population
O'dell 1996[120]	Not review population
O'dell 2002[122]	Not review population
O'dell 2013[119]	Not review population
Pavelka 1989[124]	Not in English language
Pinals 1986[125]	Not review population
Proudman 2000[126]	Inappropriate comparison
Pullar 1983[127]	Not review population
Reece 2002[133]	Not review population
Riel 1994[134]	Not in English language
Rodríguez 1997[135]	Not in English language
Salaffi 1995[136]	Not review population
Schipper 2009[138]	Incorrect study design
Scott 2001[140]	Not review population
Shashikumar 2010[141]	Not review population
Shevchuk 2003[142]	Not in English language
Shuai 2002[143]	Not originally in English language and poor translation

Study	Exclusion reason
Singh 2012[144]	Not review population
Smolen 1999[145]	Not review population
Smolen 1999[146]	Not review population
Strand 1999[149]	Not review population
Strand 1999[147]	Not review population
Strand 2005[148]	Not review population
Svensson 2003[151]	Inappropriate comparison
Tascioglu 2003[153]	No relevant outcomes reported
Taylor 2017[154]	Incorrect interventions
Tchetverikov 2008[155]	Not review population
Ter wee 2015[156]	Incorrect interventions
Trnavsky 1993[158]	Not review population
Tugwell 2000[160]	Not review population
Van aken 2004[161]	Incorrect study design
Van der heide 1996[163]	Inappropriate comparison
Van riel 2003[173]	Not review population
Verschueren 2008[179]	Incorrect study design
Verstappen 2003[180]	Inappropriate comparison
Walker-bone 2007[182]	Systematic review: included studies checked for inclusion in this evidence review
Weinblatt 1985[183]	Not review population
Williams 1985[185]	Not review population
Williams 1988[184]	Narrative review
Zeb 2016[186]	Not review population
Zhang 2004[187]	Not originally in English language and poor translation
Zhao 2017[188]	Incorrect interventions

I.12 Excluded health economic studies

Table 57: Studies excluded from the health economic review for first line DMARDs

Reference	Reason for exclusion
Schipper 2011[139]	This study was assessed as partially applicable with very serious limitations and therefore was excluded. This economic analysis was based on cohort data that was not included in the clinical review.

Table 58: Studies excluded from the health economic review for failed DMARDs

Reference	Reason for exclusion
None	

Appendix J: Research recommendations

J.1 Subcutaneous methotrexate

Research question: What is the clinical and cost effectiveness of subcutaneous methotrexate compared with oral methotrexate for adults with early onset rheumatoid arthritis starting a new DMARD?

Why this is important:

Methotrexate is an important drug in the treatment of rheumatoid arthritis. Subcutaneous administration can be an alternative option for people who have side effects to oral therapy. It has been proposed that subcutaneous methotrexate may be more effective than oral therapy but evidence to support this is lacking. The committee were unable to find sufficient evidence to recommend subcutaneous methotrexate, but agreed that the effects may be superior due to increased bioavailability and side effects fewer than with oral cDMARDs. However, because subcutaneous methotrexate is significantly more expensive than other cDMARD options, the committee was not able to recommend this without evidence of clinical benefit over oral cDMARDs.

Criteria for selecting high-priority research recommendations:

PICO question	Population: Adults with active RA commencing a new DMARD Intervention(s):Oral methotrexate Comparator: Subcutaneous methotrexate titrated rapidly to 20mg weekly Outcome(s):DAS 28, HAQ, Pain VAS, Quality of life
Importance to patients or the population	If evidence were available demonstrating that subcutaneous methotrexate was a clinically and cost effective option, this could lead to improved efficacy for people with RA due to better tolerability of subcutaneous therapy.
Relevance to NICE guidance	There was no evidence identified in the current evidence review included in this guideline to inform a recommendation for subcutaneous methotrexate. Therefore research in this area would inform future updates of this guidance.
Relevance to the NHS	Subcutaneous methotrexate is currently prescribed by some rheumatologists. Whilst it is important maximise the benefit of treatment, subcutaneous preparations of methotrexate are considerably more expensive than oral therapy and evidence of its clinical and cost effectiveness is important so that its use within the NHS can be evidence based. As it is proposed to be better tolerated than oral preparations, it is possible that the increased costs of the drug are balanced by the improved management of the condition and hence a reduction in resource use.
National priorities	N/A
Current evidence base	There was no evidence identified in the review undertaken in this guideline for subcutaneous methotrexate compared to oral cDMARDS. See literature review in chapter F.
Equality	Yes. Some patients who are have worse RA may not be offered this treatment currently, but it could be more beneficial to them.
Study design	This should be a randomised controlled trial. Adults with active

	RA(DAS>5.0) who are DMARD naïve, randomised to oral or subcutaneous methotrexate in a double blind design. The suggested dose would be commenced at 15mg weekly and increased after 4 weeks to 20mg weekly. Standard assessments of disease activity (including HAQ, VAS pain and quality of life) and drug toxicity monitoring every 4 weeks for 6 months.
Feasibility	Yes. There are no anticipated feasibility issues if it is made clear to patients they can withdraw for side effects or inefficacy.
Other comments	Nil
Importance	• High: the research is essential to inform future updates of key recommendations in the guideline. This treatment could be cost effective for the NHS if it leads to better patient outcomes.

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