Appendix: Evidence Reports

Question 1

In patients with early RA with moderate or high disease activity, who are DMARD-naive, what is the impact of combination double DMARD therapy vs. mono-DMARD therapy on symptoms and AEs?

Summary: This PICO was addressed directly by two double-blind RCTs*^ and indirectly by one double-blind RCT#. All three trials compared combination therapy with methotrexate and sulfasalazine with methotrexate alone. In the two trials that directly matched the PICO population, no statistically significant between-group differences were found for disease activity (assessed by DAS), physical function (HAQ), or radiographic disease progression (Sharp score). In one RCT in which patients had previously failed to achieve a DAS score ≧ 2.3 despite six months of sulfasalazine monotherapy, ACR20, 50, and 70 responses were assessed#. This trial found a statistically non-significant trend in favor of double-therapy for ACR20, 50, and 70 scores. Because of this population's prior incomplete response to sulfasalazine monotherapy, this evidence only indirectly addresses this PICO question. None of the three trials reported significant between-group differences in withdrawals due to adverse events#*^.

Quality of evidence across all critical outcomes: Moderate ⊕⊕⊕⊖

Traditional DMARD double-therapy compared to Traditional DMARD monotherapy for patients with early RA with moderate/high disease activity who are DMARD-naive

Bibliography: Traditional DMARD double-therapy vs. traditional DMARD monotherapy for patients with early RA with moderate/high disease activity who are DMARD-naive

Outcomes	No of Participants (studies) Follow up	Quality of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects	
				Number of people who benefit with a single DMARD	Additional number of people who benefit with 2 DMARDs (95% CI)
Disease Activity Score (DAS) (RA disease activity) (higher score indicates more severe disease activity)	105 (1 study) 12 months	⊕⊕⊕⊖ **MODERATE**[1] due to imprecision			The mean disease activity score (DAS) (RA disease activity) in the intervention groups was **0.05 lower** (0.38 lower to 0.28 higher)
ACR 20 response (RA disease activity)	110 (1 study) 18 months	⊕⊕⊖⊖ **LOW**[2,3] due to indirectness, imprecision	**RR 1.93** (0.9 to 4.13)	**148 per 1000**	**138 more per 1000** (from 15 fewer to 464 more)
ACR 50 response (RA disease activity)	110 (1 study) 18 months	⊕⊕⊖⊖ **LOW**[2,3] due to indirectness, imprecision	**RR 1.45** (0.43 to 4.84)	**74 per 1000**	**33 more per 1000** (from 42 fewer to 284 more)
ACR 70 response (RA disease activity)	110 (1 study) 18 months	⊕⊕⊖⊖ **LOW**[2,3] due to indirectness,	**RR 1.93** (0.18 to 20.65)	**19 per 1000**	**17 more per 1000** (from 15 fewer to 364 more)

		imprecision			
Health Assessment Questionnaire (HAQ) (higher score indicates more severe physical disability)	105 (1 study) 12 months	⊕⊕⊕⊖ **MODERATE**[1] due to imprecision			The mean Health Assessment Questionnaire (HAQ) in the intervention groups was **0.14 higher** (0.2 lower to 0.47 higher)
Percent of patients with detectable radiographic progression (assessed using total Sharp score)	137 (1 study) 12 months	⊕⊕⊕⊖ **MODERATE**[4] due to imprecision	**RR 0.55** (0.22 to 1.41)	**159 per 1000**	**72 fewer per 1000** (from 124 fewer to 65 more)
Withdrawal due to adverse events	208 (2 studies) 12 months	⊕⊕⊕⊖ **MODERATE**[5] due to imprecision	**RR 1.53** (0.69 to 3.41)	**87 per 1000**	**46 more per 1000** (from 27 fewer to 209 more)

CI: Confidence interval; **RR:** Risk ratio; **RA:** rheumatoid arthritis; **DMARD**: disease-modifying anti-rheumatic drug (Abbreviation explanations included in all tables).

[1] Wide confidence intervals around effect estimate due to small sample size (Haagsma et al., 1997).

[2] Indirect evidence: this PICO addresses those with early RA and no prior DMARD failure, however, patients in this trial had all previously been administered sulfasalazine monotherapy and had failed to achieve a DAS score lower than 2.4 (Capell et al., 2007).

[3] Wide confidence intervals around effect estimate due to small sample size (Capell et al., 2007).

[4] Wide confidence intervals around effect estimate due to small sample size (Dougados et al., 1999).

[5] Wide confidence intervals around effect estimate due to small sample size (Dougados et al., 1999; Haagsma et al., 1997).

Question 1 includes three RCTs:	Capell et al., 2007[#]; Dougados et al., 1999*; Haagsma et al., 1997^

[#]Capell HA, Madhok R, Porter DR, Munro RA, McInnes IB, Hunter JA, et al. Combination therapy with sulfasalazine and methotrexate is more effective than either drug alone in patients with rheumatoid arthritis with a suboptimal response to sulfasalazine: results from the double-blind placebo-controlled MASCOT study. Ann Rheum Dis. 2007;66(2):235-41.

*Dougados M, Combe B, Cantagrel A, Goupille P, Olive P, Schattenkirchner M, et al. Combination therapy in early rheumatoid arthritis: a randomised, controlled, double blind 52 week clinical trial of sulfasalazine and methotrexate compared with the single components. Ann Rheum Dis. 1999;58(4):220-5.

^Haagsma CJ, van Riel PL, de Jong AJ, van de Putte LB. Combination of sulfasalazine and methotrexate versus the single components in early rheumatoid arthritis: a randomized, controlled, double-blind, 52 week clinical trial. Br J Rheumatol. 1997;36(10):1082-8.

Question 2

In patients with early RA with moderate or high disease activity, who are DMARD-naive, what is the impact of combination triple traditional DMARD therapy vs. mono-DMARD therapy on symptoms and AEs?

Summary: This PICO was directly addressed by four RCTs, two of which were double-blind*^, and two single-blind#§. Results from three studies found lower RA disease activity (as measured by DAS-28 and ACR 50 response) in those receiving triple-DMARD therapy than in those receiving DMARD monotherapy#*§. No significant between-group differences were found for HAQ scores, serious adverse events (SAEs), infections, or gastrointestinal adverse events. Hepatotoxicity was observed somewhat more frequently in those receiving DMARD monotherapy than in those receiving DMARD triple-therapy#§^.

Quality of evidence across all critical outcomes: High ⊕⊕⊕⊕

Triple-DMARD therapy vs. Mono-DMARD therapy for patients with early RA and moderate/high disease activity who are DMARD-naive

Bibliography: Triple-DMARD vs. mono-DMARD therapy for patients with early RA and moderate/high DA who are DMARD-naive.

Outcomes	No of Participants (studies) Follow up	Quality of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects	
				Number of people who benefit with a single DMARD	Additional number of people who benefit with 3 DMARDs (95% CI)
DAS-28 (RA disease activity) (higher score indicates more severe disease activity)	786 (3 studies) 3-24 months	⊕⊕⊖⊖ **LOW**[1,2] due to risk of bias, inconsistency			The mean das-28 in the intervention groups was **0.36 lower** (0.66 to 0.05 lower)
ACR 50 response (RA disease activity)	689 (2 studies) 6-24 months	⊕⊕⊕⊕ **HIGH**	**RR 1.41** (1.18 to 1.69)	**266 per 1000**	**109 more per 1000** (from 48 more to 184 more)
Health Assessment Questionnaire (HAQ) (higher HAQ score indicates more severe physical disability)	162 (1 study)	⊕⊕⊖⊖ **LOW**[3,4] due to risk of bias, imprecision			The mean Health Assessment Questionnaire in the intervention groups was **0.17 lower** (0.35 lower to 0.01 higher)
Serious adverse events (SAEs)	981 (4 studies) 3-24 months	⊕⊕⊕⊕ **HIGH** imprecision	**RR 0.99** (0.63 to 1.53)	**96 per 1000**	**1 fewer per 1000** (from 36 fewer to 51 more)
Infections	786 (3 studies) 3-6 months	⊕⊕⊕⊕ **HIGH** imprecision	**RR 0.98** (0.71 to 1.34)	**89 per 1000**	**2 fewer per 1000** (from 26 fewer to 30 more)
Gastrointestinal adverse events	981 (4 studies) 3-24 months	⊕⊕⊕⊕ **HIGH**	**RR 1.78** (0.84 to 3.75)	**168 per 1000**	**131 more per 1000** (from 27 fewer to 461 more)
Hepatoxicity (liver enzymes >2x upper limit of normal)	470 (3 studies) 3-24 months	⊕⊕⊕⊕ **HIGH** imprecision	**RR 0.61** (0.37 to 0.99)	**162 per 1000**	**63 fewer per 1000** (from 2 fewer to 102 fewer)

[1] Two of three included trials (de Jong et al., 2013; Saunders et al., 2008) were not blinded.
[2] I-squared heterogeneity score= 74%
[3] Single-blind trial
[4] Only one moderate-sized trial (N=162) included in this analysis

Question 2 includes four RCTs:	de Jong et al., 2013[#]; Moreland et al., 2012*; Saunders et al., 2008[§]; Mottonen et al., 1999^

[#]de Jong PH, Hazes JM, Barendregt PJ, Huisman M, van Zeben D, van der Lubbe PA, et al. Induction therapy with a combination of DMARDs is better than methotrexate monotherapy: first results of the tREACH trial. Ann Rheum Dis. 2013;72(1):72-8.

*Moreland LW, O'Dell JR, Paulus HE, Curtis JR, Bathon JM, St Clair EW, et al. A randomized comparative effectiveness study of oral triple therapy versus etanercept plus methotrexate in early aggressive rheumatoid arthritis: the treatment of Early Aggressive Rheumatoid Arthritis Trial. Arthritis Rheum. 2012;64(9):2824-35.

[§]Saunders SA, Capell HA, Stirling A, Vallance R, Kincaid W, McMahon AD, et al. Triple therapy in early active rheumatoid arthritis: a randomized, single-blind, controlled trial comparing step-up and parallel treatment strategies. Arthritis Rheum. 2008;58(5):1310-7.

^Mottonen T, Hannonen P, Leirisalo-Repo M, Nissila M, Kautiainen H, Korpela M, et al. Comparison of combination therapy with single-drug therapy in early rheumatoid arthritis: a randomised trial. FIN-RACo trial group. Lancet. 1999;353(9164):1568-73.

Question 3

In patients with established RA with moderate or high disease activity, who are DMARD-naive, what is the impact of traditional DMARD combination (double or triple) therapy vs. traditional DMARD monotherapy on symptoms and AEs?

Summary: This PICO was indirectly addressed by seven RCTs in DMARD-naïve early RA patients[#⋆§^Φ≠Ω]. All of these trials compared combination therapy (either double or triple-DMARD therapy) to DMARD monotherapy. Five of the seven trials included a methotrexate monotherapy group[#⋆§^Φ], and four included a sulfasalazine monotherapy group*[§≠Ω]. Our pooled analysis demonstrated a significant benefit of combination therapy over monotherapy for reducing disease activity (as measured by DAS-28 score, ACR20, and ACR50). Hepatotoxicity was also more frequent in the combination DMARD therapy group. Physical disability (HAQ), serious adverse events (SAEs), gastrointestinal adverse events, and infections did not differ significantly between groups.

Quality of evidence across all critical outcomes: Moderate ⊕⊕⊕⊖

Combination DMARD therapy compared to DMARD monotherapy for patients with established RA with moderate/high disease activity who are DMARD-naïve.

Bibliography: Triple-DMARD vs. Mono-DMARD therapy for patients with established RA with moderate/high disease activity who are DMARD-naive.

Outcomes	No of Participants (studies) Follow up	Quality of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects	
				Number of people who benefit with a single DMARD	Additional number of people who benefit with combination DMARD therapy (95% CI)
DAS-28 (RA disease activity) higher score indicates more severe disease activity)	891 (4 studies) 3-24 months	⊕⊕⊕⊖ **MODERATE**[1] due to indirectness			The mean DAS-28 (RA disease activity) in the intervention groups was **0.27 lower** (0.52 to 0.03 lower)
ACR20 response (RA disease activity)	621 (2 studies) 6-18 months	⊕⊕⊕⊖ **MODERATE**[2] due to indirectness	**RR 1.41** (1.16 to 1.72)	**365 per 1000**	**150 more per 1000** (from 58 more to 263 more)
ACR50 response (RA disease activity)	799 (3 studies) 6-24 months	⊕⊕⊕⊖ **MODERATE**[3] due to indirectness	**RR 1.41** (1.18 to 1.68)	**246 per 1000**	**101 more per 1000** (from 44 more to 167 more)
Health Assessment Questionnaire (HAQ) (higher score indicates more severe physical disability)	267 (2 studies) 3-12 months	⊕⊖⊖⊖ **VERY LOW**[4,5,6,7] due to risk of bias, inconsistency, indirectness, imprecision			The mean health assessment questionnaire (HAQ) in the intervention groups was **1.34 lower** (3.57 lower to 0.88 higher)
Serious Adverse Events (SAEs)	981 (4 studies) 3-24 months	⊕⊕⊕⊖ **MODERATE**[8] due to indirectness	**RR 0.99** (0.63 to 1.53)	**96 per 1000**	**1 fewer per 1000** (from 36 fewer to 51 more)
Gastrointestinal Adverse Events	981 (4 studies) 4	⊕⊕⊕⊖ **MODERATE**[8] due to indirectness	**RR 1.78** (0.84 to 3.75)	**168 per 1000**	**131 more per 1000** (from 27 fewer to 461 more)
Infections	786 (3 studies) 3-6 months	⊕⊕⊕⊖ **MODERATE**[9] due to indirectness	**RR 0.98** (0.71 to 1.34)	**89 per 1000**	**2 fewer per 1000** (from 26 fewer to 30 more)

Hepatotoxicity (Liver enzymes >2x Upper Limit of Normal)	470 (3 studies) 3-24 months	⊕⊕⊕⊖ **MODERATE**[10] due to indirectness	**RR 0.61** (0.37 to 0.99)	**162 per 1000**	**63 fewer per 1000** (from 2 fewer to 102 fewer)

[1] Indirect evidence: This PICO addresses patients with established RA who were DMARD-naive. The closest available evidence was drawn from RCTs in patients with early RA who were DMARD-naive (de Jong et al., 2013; Moreland et al., 2012; Saunders et al., 2008; Haagsma et al., 1997).

[2] Indirect evidence: This PICO addresses patients with established RA who were DMARD-naive. The closest available evidence was drawn from RCTs in patients with early RA who were DMARD-naive (Moreland et al., 2012; Capell et al., 2007).

[3] Indirect evidence: This PICO addresses patients with established RA who were DMARD-naive. The closest available evidence was drawn from RCTs in patients with early RA who were DMARD-naive (Moreland et al., 2012; Capell et al., 2007; Mottonen et al., 1999).

[4] One of two included trials was only single-blinded (de Jong et al., 2013; Haagsma et al., 1997)

[5] Inconsistent: I-squared heterogeneity score=99% (de Jong et al., 2013; Haagsma et al., 1997).

[6] Indirect evidence: This PICO addresses patients with established RA who were DMARD-naive. The closest available evidence was drawn from RCTs in patients with early RA who were DMARD-naive (de Jong et al., 2013; Haagsma et al., 1997).

[7] Imprecision: wide confidence intervals around effect estimate due to small sample size (de Jong et al., 2013; Haagsma et al., 1997).

[8] Indirect evidence: This PICO addresses patients with established RA who were DMARD-naive. The closest available evidence was drawn from RCTs in patients with early RA who were DMARD-naive (de Jong et al., 2013; Moreland et al., 2012; Saunders et al., 2008; Mottonen et al., 1999).

[9] Indirect evidence: This PICO addresses patients with established RA who were DMARD-naive. The closest available evidence was drawn from RCTs in patients with early RA who were DMARD-naive (de Jong et al., 2013; Moreland et al., 2012; Saunders et al., 2008).

[10] Indirect evidence: This PICO addresses patients with established RA who were DMARD-naive. The closest available evidence was drawn from RCTs in patients with early RA who were DMARD-naive (de Jong et al., 2013; Mottonen et al., 1999; Saunders et al., 2008).

Question 3 includes seven RCTs:	de Jong et al., 2013^; Moreland et al., 2012[Φ]; Saunders et al., 2008[≠]; Capell et al., 2007[#]; Dougados et al., 1999*; Mottonen et al., 1999[Ω]; Haagsma et al., 1997[§]

[#]Capell HA, Madhok R, Porter DR, Munro RA, McInnes IB, Hunter JA, et al. Combination therapy with sulfasalazine and methotrexate is more effective than either drug alone in patients with rheumatoid arthritis with a suboptimal response to sulfasalazine: results from the double-blind placebo-controlled MASCOT study. Ann Rheum Dis. 2007;66(2):235-41.

*Dougados M, Combe B, Cantagrel A, Goupille P, Olive P, Schattenkirchner M, et al. Combination therapy in early rheumatoid arthritis: a randomised, controlled, double blind 52 week clinical trial of sulfasalazine and methotrexate compared with the single components. Ann Rheum Dis. 1999;58(4):220-5.

[§]Haagsma CJ, van Riel PL, de Jong AJ, van de Putte LB. Combination of sulfasalazine and methotrexate versus the single components in early rheumatoid arthritis: a randomized, controlled, double-blind, 52 week clinical trial. Br J Rheumatol. 1997;36(10):1082-8.

^de Jong PH, Hazes JM, Barendregt PJ, Huisman M, van Zeben D, van der Lubbe PA, et al. Induction therapy with a combination of DMARDs is better than methotrexate monotherapy: first results of the tREACH trial. Ann Rheum Dis. 2013;72(1):72-8.

[Φ]Moreland LW, O'Dell JR, Paulus HE, Curtis JR, Bathon JM, St Clair EW, et al. A randomized comparative effectiveness study of oral triple therapy versus etanercept plus methotrexate in early aggressive rheumatoid arthritis: the treatment of Early Aggressive Rheumatoid Arthritis Trial. Arthritis Rheum. 2012;64(9):2824-35.

[≠]Saunders SA, Capell HA, Stirling A, Vallance R, Kincaid W, McMahon AD, et al. Triple therapy in early active rheumatoid arthritis: a randomized, single-blind, controlled trial comparing step-up and parallel treatment strategies. Arthritis Rheum. 2008;58(5):1310-7.

[Ω]Mottonen T, Hannonen P, Leirisalo-Repo M, Nissila M, Kautiainen H, Korpela M, et al. Comparison of combination therapy with single-drug therapy in early rheumatoid arthritis: a randomised trial. FIN-RACo trial group. Lancet. 1999;353(9164):1568-73.

Question 5

In patients with established RA with moderate or high disease activity who are methotrexate-naïve, what is the impact of oral tofacitinib vs. methotrexate on symptoms and AEs?

Summary: This PICO question is directly addressed by one double-blind RCT*. In this trial, participants were randomized to receive six months of monotherapy with either methotrexate or oral tofacitinib. Statistically significant advantages of tofacitinib over methotrexate were found for all measures of RA disease activity (as measured by proportion of patients with DAS-28<2.6; ACR50 response; and EULAR "good" or "moderate" response) and for radiographic disease progression (Sharp score). No statistically significant between-group differences were found for any of the selected safety measures analyzed (including SAEs, malignancies, and serious infections).
Quality of evidence across all critical outcomes: High ⊕⊕⊕⊕

Tofacitinib compared to methotrexate for patients with established RA with moderate/high disease activity who are methotrexate-naive

Bibliography: Tofacitinib vs. methotrexate for patients with established RA with moderate/high disease activity who are DMARD-naive.

Outcomes	No of Participants (studies) Follow up	Quality of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects	
				Number of people who benefit with methotrexate	Additional number of people who benefit with tofacitinib (95% CI)
DAS-28 score < 2.6 (RA disease activity)	559 (1 study) 6 months	⊕⊕⊕⊕ **HIGH**[1]	**RR 1.92** (1.1 to 3.37)	**75 per 1000**	**69 more per 1000** (from 8 more to 178 more)
ACR 50 (RA disease activity)	559 (1 study) 6 months	⊕⊕⊕⊕ **HIGH**[1]	**RR 1.76** (1.35 to 2.29)	**263 per 1000**	**200 more per 1000** (from 92 more to 340 more)
EULAR "good" or "moderate" response	559 (1 study) 6 months	⊕⊕⊕⊕ **HIGH**[1]	**RR 1.3** (1.15 to 1.48)	**608 per 1000**	**182 more per 1000** (from 91 more to 292 more)
Sharp radiographic progression score (higher score indicates more severe disease progression)	512 (1 study) 6 months	⊕⊕⊕⊕ **HIGH**[1]			The mean sharp radiographic progression score in the intervention groups was **3.6 higher** (3.16 to 4.04 higher)
Serious adverse events (SAEs)	559 (1 study) 6 months	⊕⊕⊕⊕ **HIGH**[1] imprecision	**RR 0.91** (0.56 to 1.48)	**118 per 1000**	**11 fewer per 1000** (from 52 fewer to 57 more)
Malignancies	559 (1 study) 6 months	⊕⊕⊕⊕ **HIGH**[1] imprecision	**RR 1** (0.09 to 10.93)	**5 per 1000**	**0 fewer per 1000** (from 5 fewer to 53 more)
Serious infections	559 (1 study) 6 months	⊕⊕⊕⊕ **HIGH**[1] imprecision	**RR 1.1** (0.39 to 3.11)	**27 per 1000**	**3 more per 1000** (from 16 fewer to 57 more)

[1] Data for all outcomes was gathered from Lee et al., 2014 RCT.

Question 5 was supported by one RCT:	Lee et a., 2014*

*Lee EB, Fleischmann R, Hall S, Wilkinson B, Bradley JD, Gruben D, et al. Tofacitinib versus methotrexate in rheumatoid arthritis. N Engl J Med. 2014;370(25):2377-86.

Question 11

In patients with established RA with only low disease activity, what is the impact of tapering traditional DMARD therapy vs. continuing traditional DMARDs on symptoms and AEs?

Summary: This PICO was directly addressed by one 1-year, double-blind RCT (n=285) of established RA patients who had achieved a good therapeutic response (according to ACR criteria for clinical remission) to long-term treatment with second-line traditional DMARD therapies. Participants were randomized to either continue or discontinue DMARD therapy, with disease flare as the primary outcome of interest^. The risk of disease flare was two times higher in those who discontinued DMARD therapy vs. those who continued DMARD therapy^. No significant between-group differences were observed in quality of life (HAQ score) or withdrawal due to adverse events.

Quality of evidence across all critical outcomes: Moderate ⊕⊕⊕⊖

Discontinuing DMARDs vs. continuing DMARDs for patients with established RA with low disease activity

Bibliography: Discontinuing Traditional DMARDs vs. Continuing DMARDs in Patients with Established RA and Low Disease Activity.

Outcomes	No of Participants (studies) Follow up	Quality of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects	
				Number of people affected if continue DMARDs at same dose	Additional number of people affected if taper/discontinue DMARDs (95% CI)
Incidence of disease flare (RA disease activity)	285 (1 study) 1 years	⊕⊕⊕⊖ **MODERATE**[1] due to indirectness, imprecision	**RR 1.75** (1.2 to 2.57)	**211 flares per 1000 people**	**158 more flares per 1000 people** (from 42 more to 332 more)
Health Assessment Questionnaire (HAQ) (higher score indicates more severe physical disability)	285 (1 study) 1 years	⊕⊕⊕⊖ **MODERATE**[1] due to indirectness, imprecision			The mean health assessment questionnaire (HAQ) in the groups that discontinued DMARDs was **0.03 higher** (0.12 lower to 0.18 higher)
Withdrawal due to adverse events	285 (1 study) 1 years	⊕⊕⊕⊖ **MODERATE**[1] due to indirectness, imprecision	**RR 0.99** (0.14 to 6.95)	**14 per 1000**	**0 more per 1000** (from 12 fewer to 84 more)

[1] Wide confidence intervals due to relatively small sample size (1 trial; n=285) (ten Wolde et al., 1996).

Question 11 includes one RCT:	ten Wolde et al., 1996^

^ten Wolde S, Breedveld FC, Hermans J, Vandenbroucke JP, van de Laar MA, Markusse HM, et al. Randomised placebo-controlled study of stopping second-line drugs in rheumatoid arthritis. Lancet. 1996;347(8998):347-52.