SUPPLEMENTARY APPENDIX 1

This appendix is divided into two parts:

Part 1 details the evidence for all PICO questions that were used to support recommendation statements.*

Part 2 details the evidence for supplementary PICO questions, which were originally considered by the Voting Panel but were not used to produce recommendations due to lack of clinical relevance or redundancy with other PICO questions.

***In some instances, new PICO question-based recommendation statements were created by the voting panel during their discussion and voting on final recommendations, to clarify or improve upon the PICO questions that were originally used to guide the literature review. These new PICOs may draw from the evidence from old PICO questions, combine evidence from multiple PICO questions, or rely on expert consensus.**

PART 1: PICO Questions Supporting Recommendation Statements

Section A: Early Rheumatoid Arthritis (RA)

A.1: For early RA patients, the recommendation is strong for using a treat-to-target strategy rather than a non-targeted approach.

Voting for this statement was based on the evidence table and summary for the below PICO question:

In patients with early RA, what is the impact of using a treat-to-target strategy vs. a non-targeted approach on symptoms and AEs?

Summary: This PICO was directly addressed by one open-label RCT [1]. Patients with early RA (n=299) were randomized to two treatment groups, each of which received methotrexate monotherapy. In the treat-to-target group, patients visited the outpatient clinic monthly and methotrexate was dosed according to a computer decision program which determined whether patients had met prespecified response criteria (20% disease activity decrease from previous visit). Cyclosporine was prescribed if patients exceeded the maximum tolerable dose without achieving a sustained response. In the conventional strategy group, patients visited the outpatient clinic every three months and adjusted their methotrexate dose according to the opinion of the treating rheumatologist. Analyses of the comparative effectiveness (disease activity was measured by ACR 50 response; physical disability was measured by the HAQ Disability Index) and safety (AE withdrawals, gastrointestinal, hepatic, neurological, and pulmonary adverse events) yielded no statistically significant differences between these two treatment strategies. A second RCT provided evidence supporting the effectiveness of several treat-to-target strategies in early aggressive RA [2]. Though this trial did not include a non-targeted treatment control group, symptomatic improvement was observed among each of four different intensive treatment strategies (these strategies called for incrementally stepping up treatment at 6-week intervals if a patient's DAS28-ESR score remained $\geqq$ 3.2). The four strategies included immediate biologic therapy (MTX + etanercept), immediate triple-therapy (MTX + sulfasalazine + hydroxychloroquine), step-up biologic therapy (MTX + initial placebo etanercept), and step-up triple-therapy (MTX + initial placebo sulfasalazine + placebo hydroxychloroquine). At 24-week follow-up, the two initial combination-therapy groups demonstrated a greater reduction in DAS28-ESR scores than the initial MTX monotherapy groups**.** At week 48 and week 102 follow-up, after non-responding participants had stepped up treatment, no significant between-group differences were found in DAS28-ESR scores. Radiographic progression was statistically significantly greater at 102-week follow-up among those receiving triple-therapy than those receiving MTX + etanercept.

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

Treat-to-target strategy vs. non-targeted usual care for patients with early RA

Bibliography: Treatment-to-target strategy vs. usual care in patients with early RA.

Outcomes	No of Participants (studies) Follow up	Quality of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects	
				Risk with Non-targeted Usual Care	Risk difference with Treat-to-target strategy (95% CI)
ACR 50 response (RA disease activity)	299 (1 study) 2 years	⊕⊕⊖⊖ **LOW**[1,2,3] due to risk of bias, imprecision	**RR 1.01** (0.79 to 1.29)	**453 per 1000**	**5 more per 1000** (from 95 fewer to 131 more)
Health Assessment Questionnaire-Disability assessment (HAQ-DI) (Physical disability)	299 (1 study) 2 years	⊕⊕⊖⊖ **LOW**[2,3] due to risk of bias, imprecision			The mean health assessment questionnaire- disability assessment (HAQ-DI) (physical disability) in the intervention groups was **0.04 higher** (0.12 lower to 0.2 higher)
Study withdrawals due to adverse events	299 (1 study) 2 years	⊕⊕⊕⊖ **MODERATE**[2,3] due to imprecision	**RR 1.67** (0.79 to 3.52)	**68 per 1000**	**45 more per 1000** (from 14 fewer to 170 more)
Gastrointestinal adverse events	299 (1 study) 2 years	⊕⊕⊕⊖ **MODERATE**[2,3] due to imprecision	**RR 0.98** (0.66 to 1.46)	**250 per 1000**	**5 fewer per 1000** (from 85 fewer to 115 more)
Hepatic adverse events (AST, ALT increase above the upper limit of normal)	299 (1 study) 2 years	⊕⊕⊕⊖ **MODERATE**[3] due to imprecision	**RR 1.23** (0.79 to 1.91)	**189 per 1000**	**44 more per 1000** (from 40 fewer to 172 more)
Neurological adverse events	299 (1 study) 2 years	⊕⊕⊕⊖ **MODERATE**[3] due to imprecision	**RR 0.98** (0.61 to 1.57)	**189 per 1000**	**4 fewer per 1000** (from 74 fewer to 108 more)
Pulmonary adverse events	299 (1 study) 2 years	⊕⊕⊕⊖ **MODERATE**[3] due to imprecision	**RR 0.37** (0.1 to 1.36)	**54 per 1000**	**34 fewer per 1000** (from 49 fewer to 19 more)

*The basis for the **assumed risk** (e.g., the median control group risk across studies) is provided in footnotes. The **corresponding risk** (and its 95% confidence interval) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI).

CI: Confidence interval; **RR:** Risk ratio; **RA:** rheumatoid arthritis; **AST:** aspartate aminotransferase; **ALT:** alanine aminotransferase

GRADE Working Group grades of evidence
High quality: Further research is very unlikely to change our confidence in the estimate of effect.
Moderate quality: Further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate.
Low quality: Further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate.
Very low quality: We are very uncertain about the estimate.

[1] Participants in both groups received methotrexate (MTX). Participants randomized to the treat-to-target group visited the outpatient clinic monthly, and MTX dosage was adjusted according to a computerized decision program. Patients randomized to the non-targeted group visited the outpatient clinic every three months, and were treated according to common practice (Verstappen et al., 2007).
[2] Data for this analysis were gathered from a single open-label trial (n=299) (Verstappen et al., 2007).
[3] Wide confidence intervals due to relatively small sample size (n=299) (Verstappen et al., 2007).

This PICO includes one RCT:	Verstappen et al., 2007 [1]

A.2: For patients with early RA with low disease activity who are DMARD-naïve, the recommendation is *conditional* for using DMARD monotherapy over double DMARD therapy.

Voting for this statement was based on the evidence table and summary for the below PICO question:

In patients with early RA with only low 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 indirectly addressed by four double-blind RCTs [3-6]. These trials compared double-DMARD therapy with MTX monotherapy. Because no studies were identified for patients with early RA with low disease activity who were DMARD-naive, indirect evidence was gathered from trials including patients with early or established RA with moderate/high disease activity who had previously had an incomplete response to mono-DMARD therapy. Analysis of RA disease activity demonstrated a non-significant trend in favor of double-DMARD therapy as measured by ACR50 response. Physical disability (as measured by HAQ) did not differ significantly between groups. Double-DMARD therapy was also associated with more frequent study withdrawal due to adverse events (though this difference also did not reach statistical significance).Gastrointestinal adverse events were significantly more frequent with double-DMARD therapy, and hepatotoxicity also trended toward more frequent with combination therapy.

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

Double DMARD therapy compared to Mono-DMARD therapy for patients with early RA with low disease activity who are DMARD-naive

Bibliography: Double-DMARD therapy vs. mono-DMARD therapy in patients with early RA with low 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	
				Risk with Mono-DMARD therapy	Risk difference with Double DMARD therapy (95% CI)
Disease Activity Score (DAS) (RA disease activity) (higher score indicates more severe disease activity)	105 (1 study) 12 months	⊕⊕⊖⊖ **LOW**[1,2] due to indirectness, 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 50 response (RA disease activity)	373 (2 studies) 6-18 months	⊕⊕⊕⊖ **MODERATE**[3] due to indirectness, imprecision	**RR 2.8** (0.97 to 8.07)	**64 per 1000**	**116 more per 1000** (from 2 fewer to 454 more)

Health Assessment Questionnaire (HAQ) (higher score indicates more severe physical disability)	368 (2 studies) 6-12 months	⊕⊕⊕⊖ **MODERATE**[4] due to indirectness, imprecision			The mean health assessment questionnaire (HAQ) in the intervention groups was **0.08 lower** (0.46 lower to 0.3 higher)
Study withdrawal due to adverse events	471 (3 studies) 6-12 months	⊕⊕⊕⊖ **MODERATE**[5] due to indirectness, imprecision	**RR 1.67** (0.96 to 2.92)	**76 per 1000**	**51 more per 1000** (from 3 fewer to 146 more)
Gastrointestinal adverse events	263 (1 study) 6 months	⊕⊕⊖⊖ **LOW**[6,7] due to indirectness, imprecision	**RR 1.67** (1.17 to 2.4)	**248 per 1000**	**166 more per 1000** (from 42 more to 347 more)
Infections	263 (1 study) 6 months	⊕⊕⊖⊖ **LOW**[6,7] due to indirectness, imprecision	**RR 0.8** (0.62 to 1.04)	**519 per 1000**	**104 fewer per 1000** (from 197 fewer to 21 more)
Hepatotoxicity (ALT level >3x upper limit of normal)	263 (1 study) 6 months	⊕⊕⊖⊖ **LOW**[6,7] due to indirectness, imprecision	**RR 5.12** (0.61 to 43.19)	**8 per 1000**	**31 more per 1000** (from 3 fewer to 317 more)

*The basis for the **assumed risk** (e.g., the median control group risk across studies) is provided in footnotes. The **corresponding risk** (and its 95% confidence interval) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI).

CI: Confidence interval; **RR:** Risk ratio;

GRADE Working Group grades of evidence
High quality: Further research is very unlikely to change our confidence in the estimate of effect.
Moderate quality: Further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate.
Low quality: Further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate.
Very low quality: We are very uncertain about the estimate.

[1] Indirect evidence: this PICO addresses early RA with low disease activity, whereas the available evidence was drawn from one RCT in individuals with early RA with moderate/high disease activity (Haagsma et al., 1997).
[2] Wide confidence intervals around effect estimate due to small sample size (Haagsma et al., 1997).
[3] Indirect evidence: this PICO addresses early RA with low disease activity, whereas the available evidence was drawn from two RCTs conducted in individuals with moderate/high disease activity (Capell et al., 2007; Kremer et al., 2002). Additionally, the Kremer et al. trial was conducted in patients with established rather than early RA.
[4] Indirect evidence: this PICO addresses early RA with low disease activity, whereas the available evidence was drawn from two RCTs conducted in individuals with moderate/high disease activity (Kremer et al., 2002; Haagsma et al., 1997). Additionally, the Kremer et al. trial was conducted in patients with established rather than early RA.
[5] Indirect evidence: this PICO addresses early RA with low disease activity, whereas the available evidence was drawn from three RCTs conducted in individuals with moderate/high disease activity (Kremer et al., 2002; Dougados et al., 1999; Haagsma et al., 1997). The Kremer et al. study was additionally indirect as it randomized individuals with established rather than early RA.

[6] Indirect evidence: this PICO addresses early RA with low disease activity, whereas the available evidence was drawn from one RCT in individuals with established RA with moderate/high disease activity (Kremer et al., 2002).
[7] Wide confidence intervals around effect estimate due to small sample size (Kremer et al., 2002).

This PICO includes four RCTs:	Capell et al., 2007 [3]; Kremer et al., 2002 [4]; Dougados et al., 1999 [5]; Haagsma et al., 1997 [6]

A.3: For patients with early RA with low disease activity who are DMARD-naïve, the recommendation is strong for using DMARD monotherapy over triple DMARD therapy.

Voting for this statement was based on the evidence table and summary for the below PICO question:

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

Summary: This PICO was indirectly addressed by four RCTs [2, 7-9], one of which was double-blind [2]. All of these trials were conducted in participants with early RA and moderate to high disease activity, rather than low disease activity, so these trials only indirectly address this PICO question. Analysis of RA disease activity (measured by DAS-28 and ACR50) found a statistically significant benefit of DMARD triple-therapy over monotherapy. Comparison of physical function (Health Assessment Questionnaire) revealed a non-significant trend in favor of triple-therapy. No between-group differences were found for serious adverse events, gastrointestinal adverse events, or infection, but hepatotoxicity was significantly less frequent in patients receiving triple-therapy.

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

Traditional DMARD triple-therapy vs. traditional DMARD monotherapy for patients with early RA with low disease activity who are DMARD-naive

Bibliography: Triple-DMARD therapy vs. Mono-DMARD therapy in patients with early RA and low 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	
				Risk with Traditional DMARD monotherapy	Risk difference with Traditional DMARD triple-therapy (95% CI)
DAS-28 (RA disease activity) (higher score indicates more severe disease activity)	786 (3 studies) 3-6 months	⊕⊖⊖⊖ **VERY LOW**[1,2,3] due to risk of bias, inconsistency, indirectness			The mean DAS-28 (RA disease activity) in the intervention groups was **0.36 lower** (0.66 to 0.05 lower)
ACR50 response (RA disease activity)	689 (2 studies) 6-24 months	⊕⊕⊖⊖ **LOW**[4,5] due to risk of bias, indirectness	**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) (physical function) (higher scores indicate more severe functional deficits)	162 (1 study) 3 months	⊕⊖⊖⊖ **VERY LOW**[6,7,8] due to risk of bias, indirectness, imprecision			The mean health assessment questionnaire (HAQ) (physical function) 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	⊕⊕⊕⊖ **MODERATE**[9] 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) 3-24 months	⊕⊖⊖⊖ **VERY LOW**[9,10,11] due to risk of bias, inconsistency, 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**[3] 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	⊕⊕⊖⊖ **LOW**[12,13] due to risk of bias, indirectness	**RR 0.61** (0.37 to 0.99)	**162 per 1000**	**63 fewer per 1000** (from 2 fewer to 102 fewer)

*The basis for the **assumed risk** (e.g., the median control group risk across studies) is provided in footnotes. The **corresponding risk** (and its 95% confidence interval) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI).

CI: Confidence interval; **RR:** Risk ratio;

GRADE Working Group grades of evidence
High quality: Further research is very unlikely to change our confidence in the estimate of effect.
Moderate quality: Further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate.
Low quality: Further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate.
Very low quality: We are very uncertain about the estimate.

[1] Three RCTs were included in this analysis (de Jong et al., 2013; Moreland et al., 2012; Saunders et al., 2008), only one of which was blinded (Moreland et al., 2012).
[2] Inconsistency: I-squared score=74%
[3] Indirect evidence: included patients had moderate/high disease activity, rather than low disease activity, as specified in the PICO (de Jong et al., 2013; Moreland et al., 2012; Saunders et al., 2008).
[4] Two RCTs were included in this analysis (Moreland et al., 2012; Mottonen et al., 1999). One of these RCTs was not blinded (Mottonen et al., 1999).
[5] Indirect evidence: included patients had moderate/high disease activity, rather than low disease activity, as specified in the PICO (Moreland et al., 2012; Mottonen et al., 1999).
[6] Included RCT was only single-blinded (de Jong et al., 2013).
[7] Indirect evidence: included patients had moderate/high disease activity, rather than low disease activity, as specified in the PICO (de Jong et al., 2013).
[8] Wide confidence intervals around effect estimate due to small sample size (n=162) (de Jong et al., 2013).
[9] Indirect evidence: included patients had moderate/high disease activity, rather than low disease activity, as specified in the PICO (de Jong et al., 2013; Moreland et al., 2012; Saunders et al., 2008; Mottonen et al., 1999).
[10] Three of four included RCTs were not double-blinded (de Jong et al., 2013; Saunders et al., 2008; Mottonen et al., 1999). The Moreland et al. trial was double-blinded.
[11] Imprecision: I-squared heterogeneity score = 70%
[12] Three RCTs were included in this analysis (de Jong et al., 2013; Mottonen et al., 1999; Saunders et al., 2008). Two of these RCTs were not double-blinded (de Jong et al., 2013; Mottonen et al., 1999).
[13] Indirect evidence: included patients had moderate/high disease activity, rather than low disease activity, as specified in the PICO (de Jong et al., 2013; Saunders et al., 2008; Mottonen et al., 1999).

This PICO includes four RCTs:	de Jong et al., 2013 [7]; Moreland et al., 2012 [2]; Saunders et al., 2008 [8]; Mottonen et al., 1999 [9]

A.4: For patients with early RA who are DMARD-naïve with moderate or high disease activity, the recommendation is *conditional* for using DMARD monotherapy over double DMARD therapy.

Voting for this statement was based on the evidence table and summary for the below PICO question:

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 [5, 6] and indirectly by one double-blind RCT [3]. All three trials compared combination therapy with MTX and sulfasalazine with MTX 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 trial 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 [3]. 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 PICO 1.3. None of the three trials reported significant between-group differences in withdrawals due to adverse events [3, 5, 6].

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	
				Risk with Traditional DMARD monotherapy	Risk difference with Traditional DMARD double-therapy (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, imprecision	**RR 1.93** (0.18 to 20.65)	**19 per 1000**	**17 more per 1000** (from 15 fewer to 364 more)
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)

*The basis for the **assumed risk** (e.g., the median control group risk across studies) is provided in footnotes. The **corresponding risk** (and its 95% confidence interval) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI).

CI: Confidence interval; **RR:** Risk ratio;

GRADE Working Group grades of evidence
High quality: Further research is very unlikely to change our confidence in the estimate of effect.
Moderate quality: Further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate.
Low quality: Further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate.
Very low quality: We are very uncertain about the estimate.

[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).

This PICO includes three RCTs:	Capell et al., 2007 [3]; Dougados et al., 1999 [5]; Haagsma et al., 1997 [6]

A.5: For patients with early RA with moderate or high disease activity, who are DMARD-naïve, the recommendation is *conditional* for using DMARD monotherapy over triple DMARD therapy.

Voting for this statement was based on the evidence table and summary for the below PICO question:

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 [2, 9], and two single-blind [7, 8]. 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 [2, 7, 8]. No significant between-group differences were found for HAQ scores, serious adverse events (SAEs), infections, or GI adverse events. Hepatotoxicity was observed somewhat more frequently in those receiving DMARD monotherapy than in those receiving DMARD triple-therapy [7-9].

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	
				Risk with Mono DMARD	Risk difference with Triple DMARD (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	⊕⊕⊕⊕	**RR 0.98**	**89 per 1000**	**2 fewer per 1000**

	(3 studies) 3-6 months	**HIGH** imprecision	(0.71 to 1.34)		(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)

*The basis for the **assumed risk** (e.g., the median control group risk across studies) is provided in footnotes. The **corresponding risk** (and its 95% confidence interval) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI).

CI: Confidence interval; **RR:** Risk ratio; **RA:** rheumatoid arthritis; **HAQ:** Health assessment questionnaire; **QoL:** quality of life

GRADE Working Group grades of evidence
High quality: Further research is very unlikely to change our confidence in the estimate of effect.
Moderate quality: Further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate.
Low quality: Further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate.
Very low quality: We are very uncertain about the estimate.

[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

This PICO includes four RCTs:	de Jong et al., 2013 [7]; Moreland et al., 2012 [2]; Saunders et al., 2008 [8]; Mottonen et al., 1999 [9]

A.6: For patients with early RA and moderate or high disease activity, the recommendation is *conditional* for using low-dose glucocorticoid therapy in combination with DMARDs rather than using DMARDs alone.

Voting for this statement was based on the evidence table and summary for the below PICO question:

In patients with early RA with moderate or high disease activity, what is the impact of adding long-term low-dose glucocorticoid therapy to traditional DMARDs vs. traditional DMARDs without glucocorticoids on symptoms and AEs?

Summary: This PICO was directly addressed by seven RCTs, ranging from 6 to 24 months in duration [10-16]. All six trials compared traditional DMARDs with concomitant glucocorticoids against traditional DMARDs alone in patients with early RA. Five RCTs examined prednisolone [10, 13-16] and two examined prednisone [11, 12]. Significant benefits of additional glucocorticoids over DMARD monotherapy were found for RA disease activity (measured by DAS-28 score and proportion achieving DAS-28 remission criteria), quality of life (measured by HAQ), and radiographic progression (Sharp score). No significant between-group difference was found for serious adverse events, serious infections, hypertension, or gastrointestinal adverse events. Hypertension occurred more frequently among those receiving additional glucocorticoids, though this trend did not reach statistical significance.

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

Long-term, low dose glucocorticoids + traditional DMARDs compared to DMARDs alone for patients with early RA and moderate/high disease activity

Bibliography: Long-term, low-dose glucocorticoids + traditional DMARDs vs. DMARDs alone in patients with early RA and moderate/high disease activity.

Outcomes	No of Participants (studies) Follow up	Quality of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects	
				Risk with DMARDs alone	Risk difference with Long-term, low dose glucocorticoids + traditional DMARDs (95% CI)
DAS-28 score (RA disease activity) (higher score indicates more severe disease activity)	904 (4 studies) 6-24 months	⊕⊕⊕⊕ **HIGH**			The mean DAS-28 score (RA disease activity) in the intervention groups was **0.54 lower** (0.78 to 0.3 lower)
DAS-28 remission (RA disease activity)	396 (2 studies) 12 months	⊕⊕⊕⊖ **MODERATE**[1] due to risk of bias	**RR 1.44** (1.1 to 1.9)	**292 per 1000**	**129 more per 1000** (from 29 more to 263 more)
Health Assessment Questionnaire (HAQ)	885	⊕⊕⊕⊕			The mean health assessment questionnaire (HAQ) in

(higher score indicates more severe physical disability)	(4 studies) 6-24 months	**HIGH**			the intervention groups was **0.2 lower** (0.25 to 0.15 lower)
Sharp radiographic progression score (higher score indicates more severe radiographic progression)	533 (3 studies) 6-24 months	⊕⊕⊕⊕ **HIGH**			The mean Sharp radiographic progression score in the intervention groups was **6.06 lower** (6.71 to 5.41 lower)
Serious adverse events (SAEs)	657 (3 studies) 6-24 months	⊕⊕⊕⊕ **HIGH**	**RR 0.86** (0.62 to 1.2)	**175 per 1000**	**24 fewer per 1000** (from 66 fewer to 35 more)
Serious infections	468 (2 studies) 6-24 months	⊕⊕⊕⊕ **HIGH**	**RR 0.54** (0.18 to 1.67)	**34 per 1000**	**16 fewer per 1000** (from 28 fewer to 23 more)
Gastrointestinal adverse events	907 (4 studies) 6-24 months	⊕⊕⊕⊕ **HIGH**	**RR 0.9** (0.51 to 1.57)	**300 per 1000**	**30 fewer per 1000** (from 147 fewer to 171 more)
Hypertension	657 (3 studies) 6-24 months	⊕⊕⊕⊕ **HIGH**	**RR 2.04** (0.4 to 10.4)	**63 per 1000**	**66 more per 1000** (from 38 fewer to 595 more)

*The basis for the **assumed risk** (e.g., the median control group risk across studies) is provided in footnotes. The **corresponding risk** (and its 95% confidence interval) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI).

CI: Confidence interval; **RR:** Risk ratio;

GRADE Working Group grades of evidence
High quality: Further research is very unlikely to change our confidence in the estimate of effect.
Moderate quality: Further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate.
Low quality: Further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate.
Very low quality: We are very uncertain about the estimate.

[1] Participants and assessors were not blinded in the two RCTs that contributed to this analysis (Montecucco et al., 2012; Todoerti et al., 2010).

This PICO includes seven RCTs:	Bakker et al., 2012 [10]; Montecucco et al., 2012 [11]; Todoerti et al., 2010 [12]; Choy et al., 2008 [13]; Svensson et al., 2005 [14]; Wassenberg et al., 2005 [15]; Capell et al., 2004 [16]

A.7: For patients with early RA and moderate or high disease activity despite DMARD monotherapy, the recommendation is strong for using combination DMARD therapy *or* TNFi *or* non-TNF biologic therapy (with or without MTX).

Voting for this statement was based on the evidence tables and summaries for the below PICO questions:

In patients with early RA with moderate or high disease activity, who have failed traditional DMARD therapy, what is the impact of TNFi monotherapy vs. triple-DMARD therapy on symptoms and AEs?

Summary: This PICO was not directly addressed by any studies.

Quality of evidence across all critical outcomes: Very low ⊕⊖⊖⊖. No data were available to address this question. Recommendations were formulated based on the expertise of the voting panel.

In patients with early RA with moderate or high disease activity, who have failed traditional DMARD therapy, what is the impact of TNFi + MTX therapy vs. triple DMARD therapy on symptoms and AEs?

Summary: This PICO was directly addressed by one RCT: an open-label trial that compared TNFi therapy (infliximab) + MTX with traditional DMARD triple-therapy (MTX+HCQ+SSZ) [17]. No significant between-group differences were found for RA disease activity (measured by DAS-28 and ACR 50 response), while radiographic disease progression (Sharp score) was less severe among those receiving TNFi therapy. Infections and infestations occurred more frequently in those receiving TNFi +MTX therapy, while gastrointestinal adverse events occurred more frequently in patients receiving triple-DMARD therapy. A non-significant trend in favor of triple-DMARD therapy was found for serious adverse events.

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

TNFi therapy + MTX vs. triple-DMARD therapy for patients with early RA with moderate/high disease activity who have failed traditional DMARD therapy

Bibliography: TNFi+MTX vs Triple-DMARD therapy for patients with early RA and moderate high DA who have failed traditional DMARD therapy.

Outcomes	No of Participants (studies) Follow up	Quality of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects	
				Risk with Triple-DMARD therapy	Risk difference with TNFi therapy + MTX (95% CI)
ACR20 response (RA disease activity)	258 (1 study) 6 months	⊕⊕⊖⊖ **LOW**[1,2] due to risk of bias, imprecision	**RR 1.2** (0.87 to 1.67)	**331 per 1000**	**66 more per 1000** (from 43 fewer to 222 more)
ACR50 response (RA disease activity)	258 (1 study) 6 months	⊕⊕⊖⊖ **LOW**[1,2] due to risk of bias, imprecision	**RR 1.38** (0.9 to 2.1)	**215 per 1000**	**82 more per 1000** (from 22 fewer to 237 more)
ACR70 response (RA disease activity)	258 (1 study) 6 months	⊕⊕⊖⊖ **LOW**[1,2] due to risk of bias, imprecision	**RR 1.18** (0.66 to 2.12)	**138 per 1000**	**25 more per 1000** (from 47 fewer to 155 more)
Sharp radiographic progression score (higher score indicates more severe radiographic progression)	215 (1 study) 6 months	⊕⊕⊖⊖ **LOW**[1,2] due to risk of bias, imprecision			The mean Sharp radiographic progression score in the intervention groups was **3.23 lower** (6.29 to 0.17 lower)
Serious adverse events (SAEs)	258	⊕⊕⊖⊖	**RR 2.03**	**8 per 1000**	**8 more per 1000**

	(1 study) 6 months	**LOW**[1,2] due to risk of bias, imprecision	(0.19 to 22.12)		(from 6 fewer to 162 more)
Infections and infestations	258 (1 study) 6 months	⊕⊕⊖⊖ **LOW**[1,2] due to risk of bias, imprecision	**RR 8.12** (1.03 to 64.03)	**8 per 1000**	**55 more per 1000** (from 0 more to 485 more)
Hepatotoxicity (Swedish reporting criteria)	206 (1 study) 6 months	⊕⊕⊖⊖ **LOW**[1,2] due to risk of bias, imprecision	**RR 3.57** (0.76 to 16.77)	**19 per 1000**	**49 more per 1000** (from 5 fewer to 303 more)
Gastrointestinal adverse events	258 (1 study) 6 months	⊕⊕⊖⊖ **LOW**[1,2] due to risk of bias, imprecision	**RR 0.17** (0.05 to 0.56)	**138 per 1000**	**115 fewer per 1000** (from 61 fewer to 132 fewer)

*The basis for the **assumed risk** (e.g., the median control group risk across studies) is provided in footnotes. The **corresponding risk** (and its 95% confidence interval) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI).

CI: Confidence interval; **RR:** Risk ratio;

GRADE Working Group grades of evidence
High quality: Further research is very unlikely to change our confidence in the estimate of effect.
Moderate quality: Further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate.
Low quality: Further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate.
Very low quality: We are very uncertain about the estimate.

[1] The RCT examined was unblinded, increasing the risk of potential expectation bias, and did not adequately describe allocation procedures (van Vollenhoven et al., 2012).
[2] Wide confidence intervals around effect estimate due to small samples size (van Vollenhoven et al., 2012).

This PICO includes one RCT:	van Vollenhoven et al., 2012 [17]

In patients with early RA with moderate or high disease activity, who have failed traditional DMARD therapy, what is the impact of TNFi monotherapy vs. non-TNF biologic therapy on symptoms and AEs?

Summary: This PICO was directly addressed by one open-label RCT [18]. This small (n=60) six-month trial compared TNFi monotherapy with etanercept alone (n=22) and adalimumab alone (n=21) against non-TNF biologic monotherapy with tocilizumab (n=21). No significant differences were found for disease activity (DAS-28) or quality of life (HAQ) between TNFi and non-TNF biologic monotherapies. **The trial did not report data on adverse events, resulting in a "very low" quality of evidence across critical outcomes.**

Quality of evidence across all critical outcomes: Very low ⊕⊕⊖⊖

TNFi monotherapy vs. Non-TNF biologic therapy for patients with early RA with moderate/high disease activity who are have failed traditional DMARD therapy

Bibliography: TNFi Monotherapy vs. Non-TNF biologic therapy in patients with Early RA and moderate/high DA who have failed traditional DMARD mono or combination therapy

Outcomes	No of Participants (studies) Follow up	Quality of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects	
				Risk with Non-TNF biologic therapy	Risk difference with TNFi monotherapy (95% CI)
DAS-28 (RA disease activity)	60 (1 study) 6 months	⊕⊕⊖⊖ **LOW**[1,2] due to risk of bias, imprecision			The mean DAS-28 (RA disease activity) in the intervention groups was **0.34 lower** (1.22 lower to 0.53 higher)
Health Assessment Questionnaire (HAQ) (higher score indicates more severe physical disability)	60 (1 study) 6 months	⊕⊕⊖⊖ **LOW**[1,2] due to risk of bias, imprecision			The mean health assessment questionnaire (HAQ) in the intervention groups was **0.02 lower** (0.06 lower to 0.03 higher)

*The basis for the **assumed risk** (e.g., the median control group risk across studies) is provided in footnotes. The **corresponding risk** (and its 95% confidence interval) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI).

CI: Confidence interval;

GRADE Working Group grades of evidence
High quality: Further research is very unlikely to change our confidence in the estimate of effect.
Moderate quality: Further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate.
Low quality: Further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate.
Very low quality: We are very uncertain about the estimate.

[1] Single, small, unblinded randomized controlled trial (Kume et al., 2011).
[2] Wide confidence intervals around effect size due to small study sample (n=60) (Kume et al., 2011).

This PICO includes one RCT:	Kume et al., 2011 [18]

In patients with early RA with moderate or high disease activity, who have failed traditional DMARD therapy, what is the impact of TNFi + MTX vs. non-TNF biologic + MTX on symptoms and AEs?

Summary: This PICO was indirectly addressed by one single-blind RCT [19]. Although this PICO concerns individuals with early RA, the best available evidence was an RCT conducted in those with established RA. Patients in the trial had failed traditional DMARD therapy, but not biologic therapy, as specified in the PICO question. The trial compared adalimumab + MTX with abatacept + MTX. No statistically significant between-group differences were found for any of the selected measures of effectiveness or safety, apart from a significantly higher incidence of local injection site reactions in the TNFi + MTX group.

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

TNFi therapy + MTX vs. non-TNF biologic therapy + MTX for patients with early RA with moderate/high disease activity who have failed traditional DMARD therapy

Bibliography: TNFi + MTX vs. non-TNF + MTX in patients with early RA and moderate/high disease activity who are **have failed traditional DMARD therapy**.

Outcomes	No of Participants (studies) Follow up	Quality of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects	
				Risk with Non-TNF biologic therapy + MTX	Risk difference with TNFi therapy + MTX (95% CI)
DAS-28 (RA disease activity) (higher score indicates more severe disease activity)	646 (1 study) 12 months	⊕⊕⊖⊖ **LOW**[1,2] due to risk of bias, indirectness			The mean DAS-28 (RA disease activity) in the intervention groups was **0.03 higher** (0.19 lower to 0.25 higher)
ACR50 response (RA disease activity)	646 (1 study) 12 months	⊕⊕⊖⊖ **LOW**[1,2] due to risk of bias, indirectness	**RR 1** (0.84 to 1.18)	**462 per 1000**	**0 fewer per 1000** (from 74 fewer to 83 more)
HAQ-DI (Health Assessment Questionnaire-Disability Index) (higher score indicates more severe disability)	656 (1 study) 12 months	⊕⊕⊖⊖ **LOW**[1,2] due to risk of bias, indirectness			The mean HAQ-DI (health assessment questionnaire-disability index) in the intervention groups was **0 higher** (0.08 lower to 0.08 higher)
Sharp radiographic progression score (higher score indicates more severe disease progression)	579 (1 study) 12 months	⊕⊕⊖⊖ **LOW**[1,2] due to risk of bias, indirectness			The mean Sharp radiographic progression score in the intervention groups was **0.2 lower** (0.89 lower to 0.49 higher)
Serious Adverse Events (SAEs)	646 (1 study) 12 months	⊕⊕⊖⊖ **LOW**[1,2] due to risk of bias,	**RR 0.91** (0.57 to 1.46)	**101 per 1000**	**9 fewer per 1000** (from 43 fewer to 46 more)

		indirectness			
Serious infections	646 (1 study) 12 months	⊕⊕⊖⊖ **LOW**[1,2] due to risk of bias, indirectness	**RR 1.25** (0.47 to 3.31)	**22 per 1000**	**6 more per 1000** (from 12 fewer to 51 more)
Malignancies	646 (1 study) 12 months	⊕⊕⊖⊖ **LOW**[1,2] due to risk of bias, indirectness	**RR 0.78** (0.21 to 2.86)	**16 per 1000**	**3 fewer per 1000** (from 12 fewer to 29 more)
Local injection site reactions	646 (1 study) 12 months	⊕⊕⊖⊖ **LOW**[1,2] due to risk of bias, indirectness	**RR 2.42** (1.26 to 4.65)	**38 per 1000**	**54 more per 1000** (from 10 more to 138 more)

*The basis for the **assumed risk** (e.g., the median control group risk across studies) is provided in footnotes. The **corresponding risk** (and its 95% confidence interval) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI).

CI: Confidence interval; **RR:** Risk ratio;

GRADE Working Group grades of evidence
High quality: Further research is very unlikely to change our confidence in the estimate of effect.
Moderate quality: Further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate.
Low quality: Further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate.
Very low quality: We are very uncertain about the estimate.

[1] The RCT informing this PICO was only single-blinded, potentially introducing expectation bias (Weinblatt et al., 2013).
[2] Indirect evidence: this PICO addresses patients with early RA, however the best available evidence was an RCT in patients with established RA.

This PICO includes one RCT:	Weinblatt et al., 2013 [19]

A.8: For patients with early RA and moderate or high disease activity despite DMARD monotherapy, the recommendation is *conditional* for using TNFi monotherapy rather than tofacitinib monotherapy in patients not on background DMARDs.

Voting for this statement was based on the evidence table and summary for the below PICO question:

In patients with early RA with moderate or high disease activity, who have failed traditional DMARD therapy, what is the impact of oral tofacitinib vs. TNFi therapy on symptoms and AEs?

Summary: This PICO was indirectly addressed by one double-blind RCT [20]. Although this PICO concerns individuals with early RA, the best available evidence was an RCT conducted in patients with established RA. Patients in the trial had previously failed traditional DMARD therapy, but not biologic therapy, as specified in the PICO question. The trial compared tofacitinib with adalimumab. Patients in the adalimumab group were switched to oral tofacitinib after 12 weeks, so efficacy analyses were conducted at the 12-week time point. Safety analyses were conducted at 24-weeks; therefore, the adalimumab group had received oral tofacitinib for the final 12 weeks of the trial. ACR20 response was significantly more common with oral tofacitinib than with adalimumab, although different measures of RA disease activity demonstrated varying results (all of marginal statistical significance). Analyses of important safety outcomes (including serious adverse events, serious infections, and hepatotoxicity) revealed no statistically significant between-group differences.

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

Oral tofacitinib vs. TNFi-biologic therapy for patients with early RA with moderate/high disease activity who have failed traditional DMARD therapy

Bibliography: Oral tofacitinib vs. TNFi therapy in patients with early RA and moderate/high disease activity who are **have failed traditional DMARD therapy**.

Outcomes	No of Participants (studies) Follow up	Quality of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects	
				Risk with TNFi-biologic	Risk difference with Oral tofacitinib (95% CI)
DAS-28 score<2.6 (RA disease activity) (percentage of participants achieving DAS-28 remission)	102 (1 study) 12 weeks	⊕⊕⊖⊖ **LOW**[1,2] due to indirectness, imprecision	**RR 1.62** (0.28 to 9.3)	**38 per 1000**	**23 more per 1000** (from 27 fewer to 313 more)
ACR20 response (RA disease activity)	102	⊕⊕⊖⊖	**RR 1.65**	**358 per 1000**	**233 more per 1000**

	(1 study) 12 weeks	**LOW**[1,2] due to indirectness, imprecision	(1.08 to 2.53)		(from 29 more to 548 more)
ACR50 response (RA disease activity)	102 (1 study) 12 weeks	⊕⊕⊖⊖ **LOW**[1,2] due to indirectness, imprecision	**RR 1.95** (1 to 3.8)	**189 per 1000**	**179 more per 1000** (from 0 more to 528 more)
ACR70 response (RA disease activity)	102 (1 study) 12 weeks	⊕⊕⊖⊖ **LOW**[1,2] due to indirectness, imprecision	**RR 3.24** (0.69 to 15.33)	**38 per 1000**	**85 more per 1000** (from 12 fewer to 541 more)
Health Assessment Questionnaire-Disability Index (HAQ-DI) (higher score indicates more severe physical disability)	92 (1 study) 12 weeks	⊕⊕⊖⊖ **LOW**[1,2] due to indirectness, imprecision			The mean health assessment questionnaire-disability index (HAQ-DI) in the intervention groups was **0.19 lower** (0.49 lower to 0.11 higher)
Serious Adverse Events (SAEs)	102 (1 study) 24 weeks	⊕⊕⊖⊖ **LOW**[1,2] due to indirectness, imprecision	**RR 0.36** (0.02 to 8.63)	**19 per 1000**	**12 fewer per 1000** (from 18 fewer to 144 more)
Serious infections	102 (1 study) 24 weeks	⊕⊕⊖⊖ **LOW**[1,2] due to indirectness, imprecision	**RR 0.36** (0.02 to 8.63)	**19 per 1000**	**12 fewer per 1000** (from 18 fewer to 144 more)
Hepatotoxicity (ALT>3x upper limit of normal)	102 (1 study) 24 weeks	⊕⊕⊖⊖ **LOW**[1,2] due to indirectness, imprecision	**RR 0.36** (0.02 to 8.63)	**19 per 1000**	**12 fewer per 1000** (from 18 fewer to 144 more)

*The basis for the **assumed risk** (e.g., the median control group risk across studies) is provided in footnotes. The **corresponding risk** (and its 95% confidence interval) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI).

CI: Confidence interval; **RR:** Risk ratio;

GRADE Working Group grades of evidence

High quality: Further research is very unlikely to change our confidence in the estimate of effect.

Moderate quality: Further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate.

Low quality: Further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate.

Very low quality: We are very uncertain about the estimate.

[1] Indirect evidence: this PICO addresses early RA. The closest available evidence was an RCT in participants with established RA (Fleischmann et al., 2012).

[2] Wide confidence intervals around effect size due to small sample size (Fleischmann et al., 2012).

This PICO includes one RCT:	Fleischmann et al., 2012 [20]

A.9: For patients with early RA and moderate or high disease activity despite DMARD monotherapy, the recommendation is *conditional* for using TNFi+MTX rather than tofacitinib+MTX.

Voting for this statement was based on the evidence table and summary for the below PICO question:

In patients with early RA with moderate or high disease activity, who have failed traditional DMARD therapy, what is the impact of oral tofacitinib + MTX vs. TNFi + MTX on symptoms and AEs?

Summary: This PICO was indirectly addressed by one RCT comparing oral tofacitinib + MTX with adalimumab + MTX in patients who had previously failed treatment with methotrexate monotherapy [21]. Because the trial included participants with established RA rather than early RA, this evidence addresses this PICO question only indirectly. Analysis of RA disease activity (as measured by DAS-28 and ACR20) found no significant between-group differences, though a greater benefit for physical disability (HAQ-DI) was found among those receiving oral tofacitinib + MTX than with TNFi therapy + MTX. No significant between-group differences were found for any of the selected safety outcomes (including SAEs, serious infections, and hepatotoxicity).

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

Oral tofacitinib + MTX vs. TNFi therapy + MTX for patients with early RA who have failed traditional DMARD therapy

Bibliography: Oral tofacitinib + MTX vs. TNFi + MTX in patients with early RA with moderate/high disease activity, who **have failed traditional DMARD therapy**

.

Outcomes	No of Participants (studies) Follow up	Quality of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects	
				Risk with TNFi therapy + MTX	Risk difference with Oral tofacitinib + MTX (95% CI)
DAS-28 <2.6 (RA disease activity) (percentage of participants achieving DAS-28 remission)	355 (1 study) 6 months	⊕⊕⊖⊖ **LOW**[1,2] due to risk of bias, indirectness, and imprecision	**RR 0.92** (0.42 to 2.03)	**67 per 1000**	**5 fewer per 1000** (from 39 fewer to 69 more)
ACR20 response (RA disease activity)	395 (1 study) 6 months	⊕⊕⊖⊖ **LOW**[1,2] due to risk of bias, indirectness, and imprecision	**RR 1.09** (0.89 to 1.33)	**472 per 1000**	**43 more per 1000** (from 52 fewer to 156 more)
Health Assessment Questionnaire-	378 (1 study)	⊕⊕⊖⊖ **LOW**[1,2]			The mean health assessment questionnaire-disability index (HAQ-DI) in the intervention groups was

Disability Index (HAQ-DI) (higher score indicates more severe physical disability)	3 months	due to risk of bias, indirectness			**0.06 lower** (0.07 to 0.05 lower)
Serious Adverse Events (SAEs)	408 (1 study) 12 months	⊕⊕⊖⊖ **LOW**[1,2] due to risk of bias, indirectness, and imprecision	**RR 1.43** (0.55 to 3.68)	**34 per 1000**	**15 more per 1000** (from 15 fewer to 92 more)
Serious infections	408 (1 study) 12 months	⊕⊕⊖⊖ **LOW**[1,2] due to risk of bias, indirectness, and imprecision	**RR 2** (0.18 to 21.88)	**5 per 1000**	**5 more per 1000** (from 4 fewer to 102 more)
Hepatotoxicity (ALT>3x upper limit of normal)	28 (1 study) 12 months	⊕⊖⊖⊖ **VERY LOW**[1,2,3] due to indirectness, imprecision	**RR 1.67** (0.49 to 5.67)	**214 per 1000**	**144 more per 1000** (from 109 fewer to 1000 more)

*The basis for the **assumed risk** (e.g., the median control group risk across studies) is provided in footnotes. The **corresponding risk** (and its 95% confidence interval) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI).

CI: Confidence interval; **RR:** Risk ratio;

GRADE Working Group grades of evidence
High quality: Further research is very unlikely to change our confidence in the estimate of effect.
Moderate quality: Further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate.
Low quality: Further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate.
Very low quality: We are very uncertain about the estimate.

[1] Indirect evidence: this PICO addresses patients with early RA, while the RCT used included participants with established RA (van Vollenhoven et al., 2012).
[2] Study was unblended and allocation procedures were not adequately reported (van Vollenhoven et al., 2012).
[3] Wide confidence intervals due to very small sample size (van Vollenhoven et al., 2012).

This PICO includes one RCT:	van Vollenhoven et al., 2012 [21]

A.10: For patients with early RA experiencing an increase in joint pain and swelling (an RA flare) despite DMARD therapy, the recommendation is *conditional* for using short-term glucocorticoid therapy (< 3 months) in combination with DMARDs rather than using DMARDs without glucocorticoids.

Voting for this statement was based on the evidence table and summary for the below PICO question:

In patients with early RA with moderate or high disease activity with an acute disease flare (RA flare), what is the impact of adding short-term high-dose glucocorticoid therapy to traditional DMARDs vs. traditional DMARDs without glucocorticoids on symptoms and AEs?

Summary: This PICO was indirectly addressed by four RCTs [22-25]. While this PICO addresses those with early RA experiencing acute disease flare, the closest available evidence was gathered from RCTs in patients with early or established RA and moderate/high disease activity. Acute disease flare was not an eligibility criteria for any of these trials. The trials compared traditional DMARD therapy + short-term, high dose glucocorticoids with traditional DMARD therapy alone. No statistically significant between-group differences were found for any of the critical outcomes analyzed. One very small RCT (n=21) was not included in pooled analyses due to its short follow-up duration (2-week follow-up) and heterogeneous findings) [24]. This small, low-quality trial suggested a statistically significant benefit of additional glucocorticoids for DAS-28 score and physical function (HAQ).

Quality of evidence across all critical outcomes: Very low ⊕⊖⊖⊖

Short-term, high dose glucocorticoids + traditional DMARD therapy vs. traditional DMARDs without glucocorticoids for patients with early RA with moderate/high disease activity with an acute disease flare

Bibliography: Short-term high dose glucocorticoid therapy+ traditional DMARD therapy vs. traditional DMARD therapy without glucocorticoids in patients with early RA and moderate/high disease activity.

Outcomes	No of Participants (studies) Follow up	Quality of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects	
				Risk with Traditional DMARDs without glucocorticoids	Risk difference with Short-term, high dose glucocorticoids + traditional DMARD therapy (95% CI)
DAS-28 (RA disease activity) (higher score indicates more severe disease activity)	117 (2 studies) 1-2 years	⊕⊕⊖⊖ **LOW**[1,2] due to indirectness, imprecision			The mean DAS-28 (RA disease activity) in the intervention groups was **0.34 lower** (0.91 lower to 0.24 higher)
ACR 20 response (RA disease	26 (1 study)	⊕⊖⊖⊖ **VERY LOW**[3,4,5]	**RR 1.71** (0.94 to	**500 per 1000**	**355 more per 1000** (from 30 fewer to 1000 more)

activity)	12 months	due to risk of bias, indirectness, imprecision	3.14)		
ACR50 response (RA disease activity)	26 (1 study) 12 months	⊕⊖⊖⊖ **VERY LOW**[3,4,5] due to risk of bias, indirectness, imprecision	**RR 1.54** (0.71 to 3.35)	**417 per 1000**	**225 more per 1000** (from 121 fewer to 979 more)
ACR70 response (RA disease activity)	26 (1 study) 12 months	⊕⊖⊖⊖ **VERY LOW**[3,4,5] due to risk of bias, indirectness, imprecision	**RR 3.43** (0.89 to 13.15)	**167 per 1000**	**405 more per 1000** (from 18 fewer to 1000 more)
Health Assessment Questionnaire (HAQ) (higher score indicates more severe physical disability)	146 (3 studies) 1-2 years	⊕⊖⊖⊖ **VERY LOW**[6,7,8] due to inconsistency, indirectness, imprecision			The mean health assessment questionnaire (HAQ) in the intervention groups was **0.12 lower** (0.65 lower to 0.4 higher)
Larsen radiographic progression score (higher score indicates more severe disease progression)	91 (1 study) 2 years	⊕⊕⊖⊖ **LOW**[9,10] due to indirectness, imprecision			The mean Larsen radiographic progression score in the intervention groups was **4.76 higher** (13.4 lower to 22.92 higher)
Serious adverse events (SAEs)	120 (2 studies) 6-12 months	⊕⊕⊖⊖ **LOW**[1,2] due to indirectness, imprecision	**RR 1.79** (0.35 to 9.3)	**35 per 1000**	**28 more per 1000** (from 23 fewer to 291 more)

*The basis for the **assumed risk** (e.g., the median control group risk across studies) is provided in footnotes. The **corresponding risk** (and its 95% confidence interval) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI).

CI: Confidence interval; **RR:** Risk ratio;

GRADE Working Group grades of evidence
High quality: Further research is very unlikely to change our confidence in the estimate of effect.
Moderate quality: Further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate.
Low quality: Further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate.
Very low quality: We are very uncertain about the estimate.

[1] Indirect evidence: included trials examined patients with established RA, rather than patients with early RA with disease flare (Durez et al., 2007; Choy et al., 2005).
[2] Wide confidence intervals around effect estimate due to small sample size (Durez et al., 2007; Choy et al., 2005).
[3] Data for this analysis were gathered from an unblinded RCT (Durez et al., 2007).
[4] Indirect evidence: included trial examined patients with established RA, rather than patients with early RA with disease flare (Durez et al., 2007).
[5] Wide confidence intervals around effect estimate due to small sample size (Durez et al., 2007).
[6] I-squared heterogeneity score=71% (Durez et al., 2007; Choy et al., 2005; Ciconelli et al., 1996).
[7] Indirect evidence: included trials examined patients with established RA, rather than patients with early RA with disease flare (Durez et al., 2007; Choy et al., 2005; Ciconelli et al., 1996).
[8] Wide confidence intervals around effect estimate due to small sample size (Durez et al., 2007; Choy et al., 2005; Ciconelli et al., 1996).
[9] Indirect evidence: included trial examined patients with established RA, rather than patients with early RA with disease flare (Choy et al., 2005).

[10] Wide confidence intervals around effect estimate due to small sample size (Choy et al., 2005).

This PICO includes four RCTs:	Durez et al., 2007 [22]; Choy et al., 2005 [23]; Gerlag et al., 2004 [24]; Ciconelli et al., 1996 [25]

A.11: For patients with early RA who have an RA flare while on a TNFi or non-TNF biologic therapy, the recommendation is *conditional* for adding short-term glucocorticoid therapy rather than not adding it.

Voting for this statement was based on the evidence table and summary for the below PICO question:

In patients with established RA with moderate or high disease activity with an acute disease flare (RA flare), what is the impact of adding short-term glucocorticoid therapy to TNFi or non-TNF biologic therapy vs. not adding glucocorticoid therapy.

Summary: This PICO was not directly addressed by any studies.

Quality of evidence across all critical outcomes: Very low ⊕⊖⊖⊖. No data were available to address this question. Recommendations were formulated based on the expertise of the voting panel.

A.12: For patients with early RA and moderate or high disease activity who are on a TNFi or non-TNF biologic therapy, the recommendation is *conditional* for adding low dose glucocorticoid therapy rather than not adding it.

Voting for this statement was based on the evidence tables and summaries for the below PICO questions:

In patients with early RA with moderate or high disease activity, what is the impact of adding long-term low-dose glucocorticoid therapy to TNFi therapy vs. TNFi without glucocorticoids on symptoms and AEs?

Summary: This PICO was not directly addressed by any studies.

Quality of evidence across all critical outcomes: Very low ⊕⊖⊖⊖. No data were available to address this question.

In patients with early RA with moderate or high disease activity, what is the impact of adding long-term low-dose glucocorticoid therapy to non-TNF biologic therapy vs. non-TNF biologic therapy without glucocorticoids on symptoms and AEs?

Summary: This PICO was not directly addressed by any studies.

Quality of evidence across all critical outcomes: Very low ⊕⊖⊖⊖. No data were available to address this question.

Section B: Established Rheumatoid Arthritis (RA)

B.1: For established RA patients, the recommendation is strong for using a treat-to-target strategy rather than a non-targeted approach.

Voting for this statement was based on the evidence table and summary for the below PICO question:

In patients with established RA, what is the impact of using a treat-to-target strategy vs. a non-targeted approach on symptoms and AEs?

Summary: This PICO was directly addressed by three RCTs [26-28]. One open-label cluster-randomized trial [26] and two single-blinded trials [27, 28] compared "tight control" treatment strategies with non-targeted usual care. Each of these "tight control" strategies modified a patient's drug therapy according to a pre-determined algorithm until the patient reached a targeted disease activity score. "Usual care" groups received routine standard of care drug therapy aimed at managing RA symptoms. A statistically significant benefit of treat-to-target over usual care was found for RA disease activity (as measured by DAS-28 and ACR50 response). No significant between-group differences were found for physical disability (HAQ) or radiographic progression (Larsen). Significantly fewer gastrointestinal adverse events were observed in those receiving treat-to-target therapy, while no significant between-group differences were found for infections or hepatotoxicity.

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

Treat-to-target "tight control" strategy vs. non-targeted usual care for patients with established RA

Bibliography: Treat-to-target strategy vs. non-targeted usual care approach in patients with established RA.

Outcomes	No of Participants (studies) Follow up	Quality of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects	
				Risk with Non-targeted usual care	Risk difference with Treat-to-target strategy (95% CI)
DAS-28 (RA disease activity) (higher score indicates more severe disease activity)	103 (1 study) 18 months	⊕⊕⊕⊖ **MODERATE**[1] due to imprecision			The mean DAS-28 (RA disease activity) in the intervention groups was **1.6 lower** (2.09 to 1.11 lower)
ACR50 (RA disease activity)	110 (1 study) 18 months	⊕⊕⊕⊖ **MODERATE**[1] due to imprecision	**RR 2.09** (1.48 to 2.95)	**400 per 1000**	**436 more per 1000** (from 192 more to 780 more)
Health Assessment Questionnaire	509 (2 studies)	⊕⊕⊕⊕ **HIGH**[2]			The mean health assessment questionnaire (HAQ) in the intervention groups was

(HAQ) (higher score indicates more severe physical disability)	18-36 months	imprecision			**0.2 lower** (0.74 lower to 0.33 higher)
Larsen radiographic progression score (higher score indicates more severe disease progression)	347 (1 study) 36 months	⊕⊕⊕⊕ **HIGH**[3] imprecision			The mean Larsen radiographic progression score in the intervention groups was **0.7 lower** (9.31 lower to 7.91 higher)
Study withdrawals due to adverse events	384 (1 study) 6 months	⊕⊕⊕⊕ **HIGH**[5] due to imprecision	**RR 0.44** (0.13 to 1.57)	**111 per 1000**	**62 fewer per 1000** (from 97 fewer to 63 more)
Gastrointestinal adverse events	494 (2 studies) 6-18 months	⊕⊕⊕⊕ **HIGH**[4] imprecision	**RR 0.63** (0.4 to 0.98)	**175 per 1000**	**65 fewer per 1000** (from 4 fewer to 105 fewer)
Infections	110 (1 study) 18 months	⊕⊕⊕⊖ **MODERATE**[1] due to imprecision	**RR 0.71** (0.24 to 2.11)	**127 per 1000**	**37 fewer per 1000** (from 97 fewer to 141 more)
Abnormal liver function	110 (1 study) 18 months	⊕⊕⊕⊖ **MODERATE**[1] due to imprecision	**RR 0.5** (0.23 to 1.07)	**291 per 1000**	**145 fewer per 1000** (from 224 fewer to 20 more)

*The basis for the **assumed risk** (e.g., the median control group risk across studies) is provided in footnotes. The **corresponding risk** (and its 95% confidence interval) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI).

CI: Confidence interval; **RR:** Risk ratio;

GRADE Working Group grades of evidence
High quality: Further research is very unlikely to change our confidence in the estimate of effect.
Moderate quality: Further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate.
Low quality: Further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate.
Very low quality: We are very uncertain about the estimate.

[1] Wide confidence intervals around effect size estimate due to small sample size (Grigor et al., 2004).
[2] Symmons et al., 2005; Grigor et al., 2004
[3] Symmons et al., 005
[4] Fransen et al., 2005; Grigor et al., 2004
[5] Fransen et al., 2005.

This PICO includes three RCTs:	Fransen et al., 2005 [26]; Symmons et al., 2005 [27]; Grigor et al., 2004 [28]

B.2: For low disease activity, in DMARD-naïve patients with established RA, the recommendation is strong for using DMARD monotherapy rather than a TNFi.

Voting for this statement was based on the evidence table and summary for the below PICO question:

In patients with established RA with only low disease activity who are DMARD-naive, what is the impact of TNFi therapy vs. mono-DMARD therapy on symptoms and AEs?

Summary: This PICO was indirectly addressed by one 24-week, double-blind RCT (n=637) comparing TNFi golimumab with MTX monotherapy (published as two articles) [29, 30]. The majority of patients included within the study did have established RA (although some had disease duration of less than one year); however, included patients had active (rather than low) disease activity. All participants were methotrexate-naïve. No statistically significant between-group differences were found for any measures of RA disease activity (measured by ACR 20, 50, and 70 scores) or radiographic disease progression (Sharp score) at 24-week follow-up. Analyses of safety outcomes including serious adverse events (SAEs), serious infections, and malignancies also found no statistically significant between-group differences.

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

TNFi-biologic therapy vs. mono-DMARD therapy for patients with established RA with low disease activity who are DMARD-naive

Bibliography: TNFi therapy vs. mono-DMARD therapy in patients with established RA with low 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	
				Risk with Mono-DMARD therapy	Risk difference with TNFi-biologic therapy (95% CI)
ACR20 response (RA disease activity)	319 (1 study) 24 weeks	⊕⊕⊖⊖ **LOW**[1,2] due to indirectness, imprecision	**RR 1.04** (0.84 to 1.3)	**494 per 1000**	**20 more per 1000** (from 79 fewer to 148 more)
ACR50 response (RA disease activity)	319 (1 study) 24 weeks	⊕⊕⊖⊖ **LOW**[1,2] due to indirectness, imprecision	**RR 1.11** (0.8 to 1.55)	**294 per 1000**	**32 more per 1000** (from 59 fewer to 162 more)
ACR70 response (RA disease activity)	319 (1 study) 24 weeks	⊕⊕⊖⊖ **LOW**[1,2] due to indirectness, imprecision	**RR 0.89** (0.52 to 1.5)	**156 per 1000**	**17 fewer per 1000** (from 75 fewer to 78 more)
Sharp radiographic progression score	159	⊕⊕⊖⊖			The mean Sharp radiographic progression score in

(higher score indicates more severe disease progression)	(1 study) 24 weeks	**LOW**[1,2] due to indirectness, imprecision			the intervention groups was **0.53 lower** (1.49 lower to 0.43 higher)
Serious adverse events (SAEs)	317 (1 study) 24 weeks	⊕⊕⊖⊖ **LOW**[1,2] due to indirectness, imprecision	**RR 0.46** (0.16 to 1.3)	**69 per 1000**	**37 fewer per 1000** (from 58 fewer to 21 more)
Serious infections	317 (1 study) 24 weeks	⊕⊕⊖⊖ **LOW**[1,2] due to indirectness, imprecision	**RR 0.68** (0.12 to 4.01)	**19 per 1000**	**6 fewer per 1000** (from 16 fewer to 56 more)
Malignancies	317 (1 study) 24 weeks	⊕⊕⊖⊖ **LOW**[1,2] due to indirectness, imprecision	**RR 0.2** (0.01 to 4.21)	**12 per 1000**	**10 fewer per 1000** (from 12 fewer to 40 more)

*The basis for the **assumed risk** (e.g., the median control group risk across studies) is provided in footnotes. The **corresponding risk** (and its 95% confidence interval) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI).

CI: Confidence interval; **RR:** Risk ratio;

GRADE Working Group grades of evidence
High quality: Further research is very unlikely to change our confidence in the estimate of effect.
Moderate quality: Further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate.
Low quality: Further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate.
Very low quality: We are very uncertain about the estimate.

[1] The trial from which data are reported included patients with active RA, rather than low disease activity (Emery et al., 2009).
[2] Wide confidence intervals around effect size due to small sample.

This PICO includes one RCT, published separately in two articles:	Ostergaard et al., 2011 [29]; Emery et al., 2009 [30]

B.3: In patients with established RA and moderate or high disease activity, the recommendation is *conditional* for using DMARD monotherapy rather than tofacitinib when disease activity is moderate or high.

Voting for this statement was based on the evidence table and summary for the below PICO question:

In patients with established RA with moderate or high disease activity who are MTX-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 [31]. In this trial, participants were randomized to receive six months of monotherapy with either MTX 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 MTX for patients with established RA with moderate/high disease activity who are MTX-naive

Bibliography: Tofacitinib vs. MTX 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	
				Risk with MTX	Risk difference 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)

*The basis for the **assumed risk** (e.g., the median control group risk across studies) is provided in footnotes. The **corresponding risk** (and its 95% confidence interval) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI).

CI: Confidence interval; **RR:** Risk ratio;

GRADE Working Group grades of evidence
High quality: Further research is very unlikely to change our confidence in the estimate of effect.
Moderate quality: Further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate.
Low quality: Further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate.
Very low quality: We are very uncertain about the estimate.

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

This PICO was supported by one RCT:	Lee et a., 2014 [31]

B.4: For moderate or high disease activity in DMARD-naïve patients with established RA, the recommendation is *conditional* for using DMARD monotherapy over combination DMARD therapy.

Voting for this statement was based on the evidence table and summary for the below PICO question:

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 [2, 3, 5-9]. All of these trials compared combination therapy (either double or triple-DMARD therapy) to DMARD monotherapy. Five of the seven trials included a MTX monotherapy group [2, 3, 5-7], and four included a sulfasalazine monotherapy group [5, 6, 8, 9]. 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 less frequent in the combination DMARD therapy group. Physical disability (HAQ), SAEs, GI 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	
				Risk with Mono DMARD therapy	Risk difference 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	267 (2 studies)	⊕⊖⊖⊖ **VERY LOW**[4,5,6,7]			The mean health assessment questionnaire (HAQ) in the intervention groups was

(HAQ) (higher score indicates more severe physical disability)	3-12 months	due to risk of bias, inconsistency, indirectness, imprecision			**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)

*The basis for the **assumed risk** (e.g., the median control group risk across studies) is provided in footnotes. The **corresponding risk** (and its 95% confidence interval) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI).

CI: Confidence interval; **RR:** Risk ratio;

GRADE Working Group grades of evidence
High quality: Further research is very unlikely to change our confidence in the estimate of effect.
Moderate quality: Further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate.
Low quality: Further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate.
Very low quality: We are very uncertain about the estimate.

[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).

This PICO includes seven RCTs:	de Jong et al., 2013 [7]; Moreland et al., 2012 [2]; Saunders et al., 2008 [8]; Capell et al., 2007 [3]; Dougados et al., 1999 [5]; Mottonen et al., 1999 [9]; Haagsma et al., 1997 [6]

B.5: For patients with established RA and moderate or high disease activity despite DMARD monotherapy, the recommendation is strong for using combination DMARDs *or* adding a TNFi *or* a non-TNF biologic *or* tofacitinib (all choices with or without methotrexate), rather than continuing DMARD monotherapy alone.

Voting for this statement was based on the evidence tables and summaries for the below PICO questions:

In patients with established RA with moderate or high disease activity, who have failed traditional DMARD therapy, what is the impact of TNFi therapy vs. non-TNF biologic therapy on symptoms and AEs?

Summary: This PICO was directly addressed by one high-quality six-month double-blind RCT (n=326) comparing TNFi adalimumab with non-TNF biologic tocilizumab in patients who had tried and failed methotrexate treatment [32]. The group randomized to receive non-TNF biologic therapy demonstrated lower RA disease activity (DAS-28) and higher quality of life (HAQ) compared with those receiving TNFi therapy. Among each of the safety domains analyzed (including SAEs, cancers, hepatotoxicity, and cardiovascular toxicity), no statistically significant between-group differences were found.

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

TNFi therapy vs. non-TNF biologic therapy for patients with established RA with moderate/high disease activity who have failed traditional mono- or double-therapy

Bibliography: TNFi therapy vs. non-TNF biologic therapy in patients with established RA with moderate/high disease activity who have failed DMARD mono- or double-therapy.

Outcomes	No of Participants (studies) Follow up	Quality of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects	
				Risk with Non-TNF biologic therapy	Risk difference with TNFi therapy (95% CI)
DAS-28 (RA disease activity)	325 (1 study) 6 months	⊕⊕⊕⊕ **HIGH**			The mean DAS-28 (RA disease activity) in the intervention groups was **1.4 higher** (1.2 to 1.6 higher)
Health Assessment Questionnaire (HAQ) (QoL)	325 (1 study) 6 months	⊕⊕⊕⊕ **HIGH**			The mean health assessment questionnaire (HAQ) in the intervention groups was **0.2 higher** (0.07 to 0.33 higher)

ACR 50 response (RA disease activity)	325 (1 study) 6 months	⊕⊕⊕⊕ **HIGH**	**RR 0.59** (0.44 to 0.79)	**472 per 1000**	**194 fewer per 1000** (from 99 fewer to 265 fewer)
Serious Adverse Events (SAEs)	324 (1 study) 6 months	⊕⊕⊕⊕ **HIGH** imprecision	**RR 1.1** (0.63 to 1.9)	**130 per 1000**	**13 more per 1000** (from 48 fewer to 117 more)
Serious infections	324 (1 study) 6 months	⊕⊕⊕⊕ **HIGH** imprecision	**RR 0.86** (0.29 to 2.5)	**43 per 1000**	**6 fewer per 1000** (from 31 fewer to 65 more)
Cancers	324 (1 study) 6 months	⊕⊕⊕⊕ **HIGH**	**RR 1** (0.06 to 15.85)	**6 per 1000**	**0 fewer per 1000** (from 6 fewer to 92 more)
Hepatotoxicity (ALT > 2.5x upper normal limit)	324 (1 study) 6 months	⊕⊕⊕⊕ **HIGH** imprecision	**RR 0.45** (0.16 to 1.28)	**68 per 1000**	**37 fewer per 1000** (from 57 fewer to 19 more)
Cardiovascular toxicity	324 (1 study) 6 months	⊕⊕⊕⊕ **HIGH** imprecision	**RR 1** (0.14 to 7.01)	**12 per 1000**	**0 fewer per 1000** (from 11 fewer to 74 more)

*The basis for the **assumed risk** (e.g., the median control group risk across studies) is provided in footnotes. The **corresponding risk** (and its 95% confidence interval) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI).

CI: Confidence interval; **RR:** Risk ratio; **RA:** rheumatoid arthritis; **QoL:** quality of life

GRADE Working Group grades of evidence
High quality: Further research is very unlikely to change our confidence in the estimate of effect.
Moderate quality: Further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate.
Low quality: Further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate.
Very low quality: We are very uncertain about the estimate.

This PICO includes one RCT:	Gabay et al., 2013 [32]

In patients with established RA with moderate or high disease activity, who have failed traditional DMARD therapy, what is the impact of TNFi therapy + MTX vs. non-TNF biologic therapy + MTX on symptoms and AEs?

Summary: This PICO was directly addressed by two RCTs, one double-blind trial comparing infliximab + MTX with abatacept + MTX [33] and one single-blind trial comparing adalimumab + methotrexate with abatacept + methotrexate [34]. Analysis of these trials demonstrated no statistically significant between-group differences for any measures of RA disease activity or radiographic disease progression (measured by DAS-28, ACR 50, and Sharp score). Infusion reactions or injection site reactions were significantly more frequent in the TNFi + methotrexate group than in the non-TNF biologic + methotrexate group. No statistically significant between-group differences were found for incidence of serious adverse events, malignancies, or gastrointestinal adverse events, though each trended in favor of non-TNF biologic therapy.

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

TNFi therapy + MTX vs. non-TNF biologic therapy + MTX for patients with established RA with moderate/high disease activity who have failed traditional DMARD mono- or double-therapy

Bibliography: TNFi therapy + MTX vs. non-TNF biologic therapy + MTX in patients with established RA with moderate/high disease activity who have failed traditional DMARD mono- or double therapy.

Outcomes	No of Participants (studies) Follow up	Quality of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects	
				Risk with Non-TNF biologic therapy + MTX	Risk difference with TNFi therapy + MTX (95% CI)
DAS-28 (RA disease activity) (higher score indicates more severe disease activity)	967 (2 studies) 1-2 years	⊕⊕⊕⊕ **HIGH**[1]			The mean DAS-28 (RA disease activity) in the intervention groups was **0.32 higher** (0.1 lower to 0.74 higher)
ACR50 response (RA disease activity)	967 (2 studies) 1-2 years	⊕⊕⊕⊕ **HIGH**[1]	**RR 0.93** (0.72 to 1.21)	**449 per 1000**	**31 fewer per 1000** (from 126 fewer to 94 more)
Sharp radiographic progression score (higher score indicates more severe disease progression)	517 (1 study) 2 years	⊕⊕⊕⊖ **MODERATE**[2] due to risk of bias			The mean sharp radiographic progression score in the intervention groups was **0.36 lower** (6.41 lower to 5.69 higher)
Serious Adverse Events (SAEs)	967 (2 studies) 1-2 years	⊕⊕⊕⊕ **HIGH**[1]	**RR 1.42** (0.91 to 2.2)	**124 per 1000**	**52 more per 1000** (from 11 fewer to 149 more)

Serious Infections	967 (2 studies) 1-2 years	⊕⊕⊕⊕ **HIGH**[1]	**RR 2.3** (0.83 to 6.35)	**32 per 1000**	**41 more per 1000** (from 5 fewer to 169 more)
Malignancies	967 (2 studies) 1-2 years	⊕⊕⊕⊕ **HIGH**[1]	**RR 1.08** (0.42 to 2.79)	**17 per 1000**	**1 more per 1000** (from 10 fewer to 30 more)
Gastrointestinal adverse events	646 (1 study) 1-2 years	⊕⊕⊕⊕ **HIGH**[1]	**RR 0.97** (0.06 to 15.43)	**3 per 1000**	**0 fewer per 1000** (from 3 fewer to 45 more)
Infusion reactions/injection site reactions	967 (2 studies) 1-2 years	⊕⊕⊕⊕ **HIGH**[1]	**RR 3.08** (1.98 to 4.79)	**50 per 1000**	**103 more per 1000** (from 49 more to 188 more)

*The basis for the **assumed risk** (e.g., the median control group risk across studies) is provided in footnotes. The **corresponding risk** (and its 95% confidence interval) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI).

CI: Confidence interval; **RR:** Risk ratio;

GRADE Working Group grades of evidence
High quality: Further research is very unlikely to change our confidence in the estimate of effect.
Moderate quality: Further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate.
Low quality: Further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate.
Very low quality: We are very uncertain about the estimate.

[1] Two RCTs, one double-blinded (Schiff et al., 2008) and one single-blinded (Schiff et al., 2014) contributed to this analysis.
[2] Patients were unblinded to treatment group in the randomized controlled trial contributing to this analysis (Schiff et al., 2014)

This PICO includes two RCTs:	Schiff et al., 2014 [34]; Schiff et al., 2008 [33]

In patients with established RA with moderate or high disease activity, who have failed traditional DMARD therapy, what is the impact of TNFi therapy vs. oral tofacitinib therapy on symptoms and AEs?

Summary: This PICO was directly addressed by one 24-week, double-blind RCT (n=646) comparing TNFi monotherapy (adalimumab) with oral tofacitinib monotherapy [20]. A significantly greater proportion of oral tofacitinib patients experienced a 20% reduction in RA disease activity (ACR 20 response score), though this advantage was only marginally significant for a 50% reduction (ACR 50) and non-significant for a 70% reduction (ACR 70). No significant between-group difference was detected for HAQ disability score, as well as for each of the safety parameters analyzed (serious adverse events, serious infections, and hepatotoxicity).

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

TNFi therapy vs. Oral tofacitinib for patients with established RA with moderate/high disease activity who have failed traditional DMARD therapy

Bibliography: TNFi therapy vs Oral tofacitinib in established RA, DMARD failure.

Outcomes	No of Participants (studies) Follow up	Quality of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects	
				Risk with Oral tofacitinib	Risk difference with TNFi therapy (95% CI)
ACR 20 response (RA disease activity)	102 (1 study) 12 weeks	⊕⊕⊕⊖ **MODERATE**[1] due to imprecision	**RR 0.61** (0.39 to 0.93)	**592 per 1000**	**231 fewer per 1000** (from 41 fewer to 361 fewer)
ACR 50 response (RA disease activity)	102 (1 study) 12 weeks	⊕⊕⊕⊖ **MODERATE**[1] due to imprecision	**RR 0.51** (0.26 to 1)	**367 per 1000**	**180 fewer per 1000** (from 272 fewer to 0 more)
ACR 70 response (RA disease activity)	102 (1 study) 12 weeks	⊕⊕⊕⊖ **MODERATE**[1] due to imprecision	**RR 0.31** (0.07 to 1.46)	**122 per 1000**	**84 fewer per 1000** (from 114 fewer to 56 more)
Health Assessment Questionnaire - Disability Index (HAQ-DI) (Physical disability) (higher score indicates more severe disability)	92 (1 study) 12 weeks	⊕⊕⊕⊖ **MODERATE**[1] due to imprecision			The mean health assessment questionnaire - disability index (HAQ-DI) (physical disability) in the intervention groups was **0.19 higher** (0.11 lower to 0.49 higher)
Serious adverse events (SAEs)	102 (1 study) 24 weeks	⊕⊕⊕⊖ **MODERATE**[1] due to imprecision	**RR 0.36** (0.02 to 8.63)	**19 per 1000**	**12 fewer per 1000** (from 18 fewer to 144 more)
Serious infections	102 (1 study) 24 weeks	⊕⊕⊕⊖ **MODERATE**[1] due to imprecision	Not estimable	**N/A**	No serious infections reported in either treatment group.

Hepatotoxicity (ALT > 3X upper normal limit)	102 (1 study) 24 weeks	⊕⊕⊕⊖ **MODERATE**[1] due to imprecision	**RR 0.36** (0.02 to 8.63)	**19 per 1000**	**12 fewer per 1000** (from 18 fewer to 144 more)

*The basis for the **assumed risk** (e.g., the median control group risk across studies) is provided in footnotes. The **corresponding risk** (and its 95% confidence interval) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI).

CI: Confidence interval; **RR:** Risk ratio; **RA:** rheumatoid arthritis

GRADE Working Group grades of evidence
High quality: Further research is very unlikely to change our confidence in the estimate of effect.
Moderate quality: Further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate.
Low quality: Further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate.
Very low quality: We are very uncertain about the estimate.

[1] Wide confidence intervals due to small sample size. Only one RCT (n=102) reported data for this outcome (Fleischmann et al., 2012).

This PICO includes one RCT:	Fleischmann et al., 2012 [20]

In patients with established RA with moderate or high disease activity, who have failed traditional DMARD therapy, what is the impact of TNFi therapy + MTX vs. oral agent oral tofacitinib therapy + MTX on symptoms and AEs?

Summary: This PICO was directly addressed by one 52-week, double-blind RCT (n=717) comparing TNFi adalimumab + MTX with oral tofacitinib + methotrexate [21]. No statistically significant between-group differences were found for any measures of RA disease activity (measured by DAS-28 and ACR20 response), yet physical disability was found to be less severe in the group receiving oral tofacitinib + methotrexate (measured by Health Assessment Questionnaire-Disability Index). Analyses of safety outcomes including serious adverse events (SAEs), serious infections, and hepatotoxicity found no statistically significant between-group differences.

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

TNFi + MTX vs. oral tofacitinib + MTX for patients with established RA with moderate/high disease activity who have failed traditional DMARD mono- or double therapy

Bibliography: TNFi therapy + MTX vs. oral tofacitinib + MTX in those with established RA moderate/high DA who have failed traditional DMARD mono or double therapy

Outcomes	No of Participants (studies) Follow up	Quality of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects	
				Risk with Oral tofacitinib + MTX	Risk difference with TNFi + MTX (95% CI)
DAS-28 score < 2.6 (RA disease activity)	355 (1 study) 6 months	⊕⊕⊕⊖ **MODERATE**[1] due to risk of bias, imprecision	**RR 1.08** (0.49 to 2.39)	**62 per 1000**	**5 more per 1000** (from 32 fewer to 86 more)
ACR20 response (RA disease activity)	395 (1 study) 6 months	⊕⊕⊕⊖ **MODERATE** due to risk of bias, imprecision	**RR 0.92** (0.75 to 1.12)	**515 per 1000**	**41 fewer per 1000** (from 129 fewer to 62 more)
Health Assessment Questionnaire-Disability index (HAQ-DI)	378 (1 study) 3 months	⊕⊕⊕⊖ **MODERATE**[1] due to risk of bias			The mean health assessment questionnaire- disability index (HAQ-DI) in the intervention groups was **0.06 higher** (0.05 to 0.07 higher)
Serious adverse events (SAEs)	408 (1 study) 12 months	⊕⊕⊕⊖ **MODERATE**[1] due to risk of bias, imprecision	**RR 0.7** (0.27 to 1.8)	**49 per 1000**	**15 fewer per 1000** (from 36 fewer to 39 more)
Serious Infections	408 (1 study) 12 months	⊕⊕⊕⊖ **MODERATE**[1] due to risk of bias, imprecision	**RR 0.5** (0.05 to 5.47)	**10 per 1000**	**5 fewer per 1000** (from 9 fewer to 44 more)
Hepatoxicity (ALT>3X upper limit of normal)	28 (1 study)	⊕⊖⊖⊖ **VERY LOW**[1,2]	**RR 0.6** (0.18 to	**357 per 1000**	**143 fewer per 1000** (from 293 fewer to 371 more)

	12 months	due to risk of bias, imprecision	2.04)	

*The basis for the **assumed risk** (e.g., the median control group risk across studies) is provided in footnotes. The **corresponding risk** (and its 95% confidence interval) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI).

CI: Confidence interval; **RR:** Risk ratio;

GRADE Working Group grades of evidence
High quality: Further research is very unlikely to change our confidence in the estimate of effect.
Moderate quality: Further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate.
Low quality: Further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate.
Very low quality: We are very uncertain about the estimate.

[1] Study was unblended and allocation procedures were not adequately reported (van Vollenhoven et al., 2012).
[2] Very small sample size (n=28) (van Vollenhoven et al., 2012).

This PICO includes one RCT:	van Vollenhoven et al., 2012 [21]

In patients with <u>established</u> RA with <u>moderate or high disease</u> activity, who have failed traditional DMARD therapy, what is the impact of <u>TNFi</u> therapy vs. <u>combination triple DMARD</u> therapy on symptoms and AEs?

<u>Summary</u>: This PICO was not directly addressed by any studies.

<u>Quality of evidence across all critical outcomes</u>: Very low ⊕⊖⊖⊖. No data were available to address this question.

In patients with established RA with moderate or high disease activity, who have failed traditional DMARD therapy, what is the impact of TNFi therapy + MTX vs. combination triple DMARD therapy on symptoms and AEs?

Summary: This PICO was directly addressed by one 48-week, double-blind RCT (n=353) comparing TNFi etanercept + MTX with triple-DMARD therapy (methotrexate, sulfasalazine, and hydroxychloroquine) [35]. A statistically significant advantage of TNFi+MTX therapy over DMARD triple-therapy was found for RA disease activity as measured by DAS-28, though no significant between-group difference was found for ACR50 response or Sharp radiographic progression score. Analyses of safety outcomes including serious adverse events (SAEs), serious infections, and mortality found no statistically significant between-group differences. Gastrointestinal adverse events were marginally more frequent among those receiving DMARD triple-therapy.

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

TNFi + MTX vs. triple DMARD therapy for patients with established RA with moderate/high disease activity who have failed traditional DMARD mono- or double therapy

Bibliography: TNFi-biologic therapy + MTX vs. triple-DMARD therapy in those with established RA with moderate/high disease activity who **have failed traditional DMARD therapy**.

Outcomes	No of Participants (studies) Follow up	Quality of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects	
				Risk with Triple DMARD therapy	Risk difference with TNFi-biologic + MTX (95% CI)
DAS-28 (RA disease activity) (higher score indicates more severe disease activity)	309 (1 study) 48 weeks	⊕⊕⊖⊖ **MODERATE**[1] due to risk of bias			The mean DAS-28 (RA disease activity) in the intervention groups was **0.16 lower** (0.22 to 0.1 lower)
ACR50 response (RA disease activity)	310 (1 study) 48 weeks	⊕⊕⊖⊖ **MODERATE**[1] due to risk of bias, imprecision	**RR 1.2** (0.91 to 1.59)	**355 per 1000**	**71 more per 1000** (from 32 fewer to 209 more)
Sharp radiographic progression score (higher score indicates more severe radiographic progression)	304 (1 study) 48 weeks	⊕⊕⊖⊖ **MODERATE**[1] due to risk of bias, imprecision			The mean Sharp radiographic progression score in the intervention groups was **0.25 lower** (0.86 lower to 0.36 higher)
Serious adverse events (SAEs)	441 (1 study) 48 weeks	⊕⊕⊖⊖ **MODERATE**[2] due to risk of bias, imprecision	**RR 1.05** (0.63 to 1.77)	**113 per 1000**	**6 more per 1000** (from 42 fewer to 87 more)
Serious infections	441 (1 study) 48 weeks	⊕⊕⊖⊖ **MODERATE**[2] due to risk of bias, imprecision	**RR 2.28** (0.71 to 7.3)	**18 per 1000**	**23 more per 1000** (from 5 fewer to 114 more)
Gastrointestinal adverse events	441	⊕⊕⊖⊖	**RR 0.72**	**297 per 1000**	**83 fewer per 1000**

	(1 study) 48 weeks	**MODERATE**[2] due to risk of bias, imprecision	(0.52 to 1)		(from 143 fewer to 0 more)
Mortality	441 (1 study) 48 weeks	⊕⊕⊖⊖ **MODERATE**[1] due to risk of bias, imprecision	**RR 3.04** (0.12 to 74.24)	**0 per 1000**	**-**

*The basis for the **assumed risk** (e.g., the median control group risk across studies) is provided in footnotes. The **corresponding risk** (and its 95% confidence interval) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI).

CI: Confidence interval; **RR:** Risk ratio;

GRADE Working Group grades of evidence
High quality: Further research is very unlikely to change our confidence in the estimate of effect.
Moderate quality: Further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate.
Low quality: Further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate.
Very low quality: We are very uncertain about the estimate.

[1] Data for this PICO were drawn from one double-blind RCT (n=353) (O'Dell et al., 2013). Patients from each treatment group were able to switch to the opposite treatment after 24 weeks if they did not receive an adequate therapeutic response. Therefore, the primary outcomes at 48 weeks (which only include medication-continuers) are susceptible to attrition bias.
[2] Patients from each treatment group were able to switch to the opposite study treatment after 24 weeks if they did not receive an adequate therapeutic response on their original study medication. Therefore, patients who switched treatment groups were counted towards the N of both safety groups. Adverse events were attributed to the patients' current therapy at the time of AE incidence, which may incorrectly attribute some AEs caused by switiching patients' former drug therapy (O'Dell et al., 2013).

This PICO includes one RCT:	O'Dell et al., 2013 [35]

In patients with established RA with moderate or high disease activity who have failed traditional DMARD therapy and are continuing MTX, what is the impact of adding tofacitinib vs. not adding tofacitinib on symptoms and AEs?*

Summary: This PICO question is directly addressed by eight RCTs, ranging from 3 to 6 months in duration [20, 21, 36-41]. All seven trials compared tofacitinib with concomitant DMARD therapy against DMARD therapy alone in DMARD-experienced patients with established RA. Six of eight studies used methotrexate as the concomitant DMARD [21, 36-38, 40, 41]. In two studies, participants were taking concomitant anti-malarial medication [20, 39]. Significant benefits of tofacitinib over DMARD monotherapy were found for RA disease activity (measured by DAS-28 score and proportion achieving ACR50 improvement criteria) and quality of life (measured by HAQ). None of the seven studies reported information regarding radiographic progression over the course of tofacitinib therapy with concomitant DMARDs. A modest non-significant benefit of tofacitinib combination therapy over DMARD therapy were found for serious adverse events. No significant between group differences were found for serious infections or gastrointestinal adverse events. Hepatotoxicity (defined as ALT level >3 times upper limit of normal) occurred more frequently among those receiving tofacitinib and DMARD combination therapy, though this difference was not statistically significant.

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

Tofacitinib + MTX compared to MTX alone for patients with established RA with moderate/high disease activity who have failed traditional DMARD therapy

Bibliography: Tofacitinib + MTX vs. MTX alone in patients with established RA with moderate/high disease activity who have failed traditional DMARD therapy.

Outcomes	No of Participants (studies) Follow up	Quality of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects	
				Risk with MTX	Risk difference with Tofacitinib + MTX (95% CI)
DAS-28 score < 2.6 (RA disease activity)	1960 (7 studies) 3-6 months	⊕⊕⊕⊕ **HIGH**	**RR 2.69** (1.64 to 4.43)	**27 per 1000**	**46 more per 1000** (from 17 more to 94 more)
ACR 20 (RA disease activity)	2109 (8 studies) 3-6 months	⊕⊕⊕⊕ **HIGH**	**RR 1.96** (1.64 to 2.34)	**272 per 1000**	**261 more per 1000** (from 174 more to 364 more)
ACR 50 (RA disease activity)	371 (2 studies) 3 months	⊕⊕⊕⊕ **HIGH**	**RR 4.72** (1.87 to 33.39)	**73 per 1000**	**273 more per 1000** (from 36 more to 1000 more)
Health Assessment Questionnaire-Disability Index (HAQ-DI) (higher score indicates more severe physical disability)	1677 (7 studies) 3-6 months	⊕⊕⊕⊕ **HIGH**			The mean Health Assessment Questionnaire-Disability Index (HAQ-DI) in the intervention groups was **0.26 lower** (0.38 to 0.15 lower)
Serious adverse events (SAEs)	1663	⊕⊕⊕⊕	**RR 0.69**	**38 per**	**12 fewer per 1000**

	(6 studies) 3-6 months	**HIGH** imprecision	(0.23 to 2.1)	**1000**	(from 29 fewer to 42 more)
Serious infections	1116 (5 studies) 3-6 months	⊕⊕⊕⊕ **HIGH**	**RR 1.01** (0.17 to 6.12)	**2 per 1000**	**0 more per 1000** (from 2 fewer to 12 more)
Hepatotoxicity (ALT>3x upper limit of normal)	1014 (5 studies) 3-6 months	⊕⊕⊕⊕ **HIGH** imprecision	**RR 3.8** (0.3 to 47.98)	**5 per 1000**	**13 more per 1000** (from 3 fewer to 214 more)
Gastrointestinal adverse events	195 (2 studies) 3 months	⊕⊕⊖⊖ **LOW**[1] due to imprecision	**RR 1.08** (0.53 to 2.2)	**124 per 1000**	**10 more per 1000** (from 58 fewer to 148 more)

*The basis for the **assumed risk** (e.g., the median control group risk across studies) is provided in footnotes. The **corresponding risk** (and its 95% confidence interval) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI).

CI: Confidence interval; **RR:** Risk ratio;

GRADE Working Group grades of evidence
High quality: Further research is very unlikely to change our confidence in the estimate of effect.
Moderate quality: Further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate.
Low quality: Further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate.
Very low quality: We are very uncertain about the estimate.

[1] Wide confidence intervals around effect estimate due to small sample size (n=195) (Kremer et al., 2012; Tanaka et al., 2011).

This PICO was supported by eight RCTs:	Burmester et al., 2013 [36]; Kremer et al., 2013 [37]; van der Heijde et al., 2013 [38]; Fleischmann et al., 2012a [20]; Kremer et al., 2012 [41]; Fleischmann et al., 2012b [39]; van Vollenhoven et al., 2012 [21]; Tanaka et al., 2011 [40]

B.6: For patients with established RA and moderate or high disease activity despite TNFi therapy, not currently on DMARD therapy, the recommendation is strong for adding one or two DMARDs in combination with TNFi therapy rather than TNFi therapy alone.

Voting for this statement was based on the evidence table and summary for the below PICO question:

In patients with established RA with moderate or high disease activity, what is the impact of adding a mono-or double DMARD therapy to TNFi therapy vs. the same TNFi therapy alone on symptoms and AEs?

Summary: This PICO question is directly addressed by six RCTs [42-47]. Patients randomized to receive DMARD therapy in addition to TNFi therapy demonstrated statistically significantly superior control of disease activity (as measured by DAS-28 and ACR50 response), physical disability (HAQ score), and structural disease progression (Sharp radiographic score) vs. TNFi therapy alone. No significant between-group differences were found for serious adverse events (SAEs), serious infections, or malignancies.

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

TNFi + traditional DMARD therapy compared to TNFi therapy alone for patients with established RA with moderate/high disease activity

Bibliography: TNFi + DMARD therapy vs. TNFi therapy alone in Patients with established RA and moderate/high disease activity.

Outcomes	No of Participants (studies) Follow up	Quality of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects	
				Risk with TNFi therapy alone	Risk difference with TNFi + traditional DMARD therapy (95% CI)
DAS-28 (RA disease activity) (higher score indicates more severe disease activity)	800 (3 studies) 6-12 months	⊕⊕⊕⊖ **MODERATE**[1] due to inconsistency			The mean DAS-28 (RA disease activity) in the intervention groups was **0.5 lower** (0.98 to 0.01 lower)
ACR50 response (RA disease activity)	1479 (6 studies) 4-12 months	⊕⊕⊕⊕ **HIGH**	**RR 1.28** (1.09 to 1.5)	**395 per 1000**	**110 more per 1000** (from 36 more to 197 more)
Health Assessment Questionnaire (HAQ) (higher score indicates more severe physical disability)	658 (2 studies) 6-12 months	⊕⊕⊕⊕ **HIGH**[2]			The mean health assessment questionnaire (HAQ) in the intervention groups was **0.16 lower** (0.27 to 0.05 lower)
Sharp radiographic progression score (higher score indicates more severe disease	454 (1 study)	⊕⊕⊕⊕ **HIGH**[3]			The mean Sharp radiographic progression score in the intervention groups was

progression)	6 months				**1.06 lower** (1.84 to 0.28 lower)
Serious Adverse Events (SAEs)	1009 (4 studies) 4-12 months	⊕⊕⊕⊕ **HIGH**[4] imprecision	**RR 1.27** (0.8 to 2.02)	**59 per 1000**	**16 more per 1000** (from 12 fewer to 60 more)
Serious infections	1316 (4 studies) 4-12 months	⊕⊕⊕⊕ **HIGH**[4] imprecision	**RR 0.83** (0.46 to 1.51)	**36 per 1000**	**6 fewer per 1000** (from 19 fewer to 18 more)
Malignancies	692 (2 studies) 6-12 months	⊕⊕⊕⊕ **HIGH**[5] imprecision	**RR 0.37** (0.07 to 1.88)	**17 per 1000**	**11 fewer per 1000** (from 16 fewer to 15 more)

*The basis for the **assumed risk** (e.g., the median control group risk across studies) is provided in footnotes. The **corresponding risk** (and its 95% confidence interval) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI).

CI: Confidence interval; **RR:** Risk ratio;

GRADE Working Group grades of evidence
High quality: Further research is very unlikely to change our confidence in the estimate of effect.
Moderate quality: Further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate.
Low quality: Further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate.
Very low quality: We are very uncertain about the estimate.

[1] I-squared heterogeneity score=86% (Kameda et al., 2010; Combe et al., 2006; & Klareskog et al., 2004).
[2] Combe et al. 2006; Klareskog et al., 2004
[3] Klareskog et al., 2004
[4] Kameda et al., 2010; Kremer et al., 2010; Keystone et al., 2009; Riel et al., 2006
[5] Keystone et al., 2009; Klareskog et al., 2004

This PICO includes six RCTs:	Kameda et al., 2010 [42]; Kremer et al., 2010 [43]; Keystone et al., 2009 [44]; Combe et al., 2006 [45]; Riel et al., 2006 [46]; Klareskog et al., 2004 [47]

B.7: For patients with established RA and moderate or high disease activity despite use of a single TNFi, the recommendation is *conditional* for using another TNFi rather than not using a TNFi.

Voting for this statement was based on the below PICO question:

In patients with established RA with moderate or high disease activity despite use of a single TNFi, what is the impact of using another TNFi vs. not using a TNFi on symptoms and AEs?

Summary: This PICO was not directly addressed by any studies.

Quality of evidence across all critical outcomes: Very low ⊕⊖⊖⊖. No data were available to address this question. Recommendations were formulated based on the expertise of the voting panel. This recommendation is related to therapy instead of no therapy. [For additional recommendations related to this patient population, see B.12, B.13, B.14, B.15, B.23, and B.24.]

B.8: For patients with established RA and disease activity is still moderate or high despite using multiple (2+) TNFi therapies, the recommendation is conditional for using a non-TNF biologic therapy rather than another TNFi.

Voting for this statement was based on the evidence table and summary for the below PICO question:

In patients with established RA with moderate or high disease activity, who have failed multiple TNFi therapies, what is the impact of non-TNF biologic therapy vs. another TNFi on symptoms and AEs?

Summary: This PICO was addressed by indirect observational evidence; three longitudinal cohort studies (two retrospective analyses [48, 49] and one prospective cohort study [50]) compared non-TNF biologic therapies with alternate TNFi therapies in individuals who had failed prior TNFi therapies. This evidence applies to this PICO only indirectly, as the majority of patients in each of these studies were receiving concomitant therapy with traditional DMARDs. Non-TNF biologic therapy was more effective than TNFi therapies at reducing RA disease activity, as measured by percentage of participants achieving EULAR "good response" criteria, though no statistically significant between-group difference was found for DAS-28 or adverse events (reported in only 8% of all patients) [49]. The incidence of severe infections was not significantly different between treatments [48].

Quality of evidence across all critical outcomes: Very low ⊕⊖⊖⊖

Non-TNF biologic therapy vs. TNFi therapy for patients with established RA with moderate/high disease activity who have failed multiple TNFis

Bibliography: Non-TNF biologics vs TNFis in patients with established RA with moderate/high disease activity who have failed multiple TNFis.

Outcomes	No of Participants (studies) Follow up	Quality of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects	
				Risk with TNFi	Risk difference with Non-TNF biologic (95% CI)
DAS-28 (RA disease activity) (lower score indicates less severe disease activity)	411 (2 studies) 11-12 months	⊕⊖⊖⊖ **VERY LOW**[1,2] due to risk of bias, indirectness			The mean DAS-28 (RA disease activity) in the intervention groups was **0.01 lower** (0.39 lower to 0.38 higher)
EULAR "good response" (RA disease activity)	303 (1 study) 12 months	⊕⊖⊖⊖ **VERY LOW**[1] due to risk of bias	**RR 1.6** (1.23 to 2.1)	**330 per 1000**	**198 more per 1000** (from 76 more to 363 more)
Severe infections	4332 (1 study) 12 months	⊕⊖⊖⊖ **VERY LOW**[3] due to indirectness	**RR 1.28** (0.96 to 1.71)	**93 per 1000**	**26 more per 1000** (from 4 fewer to 66 more)

*The basis for the **assumed risk** (e.g., the median control group risk across studies) is provided in footnotes. The **corresponding risk** (and its 95% confidence interval) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI).

CI: Confidence interval; **RR:** Risk ratio;

GRADE Working Group grades of evidence
High quality: Further research is very unlikely to change our confidence in the estimate of effect.
Moderate quality: Further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate.
Low quality: Further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate.
Very low quality: We are very uncertain about the estimate.

[1] High risk of selection bias: patients taking rituximab had statistically significantly more severe disease activity, and had failed a greater number of prior therapies (Gomez-Reino et al., 2012).
[2] Evidence was indirect, due to a number of included patients in one included study not having previously failed multiple TNFi therapies (Finckh et al., 2009). All patients in the Gomez-Reino study had failed multiple TNFis (Gomez-Reino et al., 2012).
[3] Indirect evidence: the majority of the population examined in this study were taking concomitant DMARDs with their TNFi or non-TNF biologic therapies (60-72% were taking concomitant MTX, substantial numbers were taking other concomitant DMARDs) (Johnston et al., 2013).

This PICO includes three observational studies:	Johnston et al., 2013 [48]; Gomez-Reino et al., 2012 [50]; Finckh et al., 2010 [49]

B.9: For patients with established RA and disease activity is still moderate or high despite using multiple (2+) TNFi therapies, the recommendation is conditional for using a non-TNF biologic therapy (with methotrexate) rather than another TNFi (with methotrexate).

Voting for this statement was based on the evidence table and summary for the below PICO question:

In patients with established RA with moderate or high disease activity, who have failed multiple TNFi therapies, what is the impact of non-TNF biologic therapy + MTX vs. another TNFi + MTX on symptoms and AEs?

Summary: This PICO was addressed by indirect observational evidence; two retrospective cohort studies compared non-TNF biologic therapies with alternate TNFi therapies in individuals who had failed prior TNFi therapies [48, 49]. This evidence applies to this PICO only indirectly, as the majority of patients—though not all patients—in each of these studies were receiving concomitant therapy with traditional DMARDs such as MTX. No statistically significant between-group difference was found for RA disease activity (measured by DAS-28) or for adverse events (reported in only 8% of all patients) [49]. The incidence of severe infections was also not significantly different between treatments [48].

Quality of evidence across all critical outcomes: Very low ⊕⊖⊖⊖

Non-TNF biologic therapy + MTX vs. TNFi-biologic therapy + MTX for patients with established RA with moderate/high disease activity who have failed multiple TNFis

Bibliography: Non-TNF biologics + MTX vs. TNFis + MTX in patients with established RA with moderate/high disease activity who have failed multiple TNFis.

Outcomes	No of Participants (studies) Follow up	Quality of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects	
				Risk with TNFi-biologic therapy +MTX	Risk difference with Non-TNF biologic therapy +MTX (95% CI)
DAS-28 (RA disease activity) (higher score indicates more severe disease activity)	108 (1 study) 11 months	⊕⊖⊖⊖ **VERY LOW**[1,2] due to indirectness, imprecision			The mean DAS-28 (RA disease activity) in the intervention groups was **0.35 higher** (0.1 lower to 0.8 higher)
Severe infections	4332 (4 studies) 12 months	⊕⊖⊖⊖ **VERY LOW**[3] due to indirectness	**RR 1.28** (0.96 to 1.71)	**93 per 1000**	**26 more per 1000** (from 4 fewer to 66 more)

*The basis for the **assumed risk** (e.g., the median control group risk across studies) is provided in footnotes. The **corresponding risk** (and its 95% confidence interval) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI).

CI: Confidence interval; **RR:** Risk ratio;

GRADE Working Group grades of evidence
High quality: Further research is very unlikely to change our confidence in the estimate of effect.
Moderate quality: Further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate.
Low quality: Further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate.
Very low quality: We are very uncertain about the estimate.

[1] Indirect evidence: the majority of the population examined in this study-but not the entire population-were taking concomitant DMARDs with their TNFi or non-TNF biologic therapies (~53% were taking concomitant MTX, substantial numbers were taking other concomitant DMARDs) (Finckh et al., 2010).
[2] Wide confidence intervals around risk difference due to small sample size (N=108) (Finckh et al., 2010).
[3] Indirect evidence: the majority of the population examined in this study-but not the entire population-were taking concomitant DMARDs with their TNFi or non-TNF biologic therapies (60-72% were taking concomitant MTX, substantial numbers were taking other concomitant DMARDs) (Johnston et al., 2013).

This PICO includes three observational studies:	Johnston et al., 2013 [48]; Finckh et al., 2010 [49]

B.10: For patients with established RA and disease activity is still moderate or high despite using multiple (2+) TNFi therapies, the recommendation is conditional for using a non-TNF biologic therapy rather than tofacitinib.

Voting for this statement was based on the below PICO question:

In patients with established RA with moderate or high disease activity, who have failed multiple TNFi therapies, what is the impact of non-TNF biologic therapy vs. oral tofacitinib on symptoms and AEs?

Summary: This PICO was not directly addressed by any studies.

Quality of evidence across all critical outcomes: Very low ⊕⊖⊖⊖. No data were available to address this question.

B.11: For patients with established RA and disease activity is still moderate or high despite using multiple (2+) TNFi therapies, the recommendation is conditional for using a non-TNF biologic therapy rather than tofacitinib.

Voting for this statement was based on the below PICO question:

In patients with established RA with moderate or high disease activity, who have failed multiple TNFi therapies, what is the impact of non-TNF biologic therapy + MTX vs. oral tofacitinib + MTX on symptoms and AEs?

Summary: This PICO was not directly addressed by any studies.

Quality of evidence across all critical outcomes: Very low ⊕⊖⊖⊖. No data were available to address this question.

B.12: For patients with established RA and moderate or high disease activity despite use of a single TNFi, not currently on DMARD therapy, the recommendation is *conditional* for using a non-TNF biologic rather than another TNFi.

Voting for this statement was based on the evidence table and summary for the below PICO question:

In patients with established RA with moderate or high disease activity, who have failed a single TNFi therapy, what is the impact of non-TNF biologic therapy vs. another TNFi on symptoms and AEs?

Summary: This PICO was directly addressed by three six-month, non-randomized retrospective cohort studies comparing non-TNF biologic rituximab therapy with a second-line TNFi in patients who had previously failed therapy with one TNFi [51-53]. No statistically significant between-group difference was found for RA disease activity (as measured by DAS-28). Greater improvement in physical ability was observed in patients receiving TNFi therapy relative to those receiving non-TNF rituximab therapy (as measured by the Health Assessment Questionnaire). **One study (total n=196) specified that no deaths or serious adverse events were observed during follow-up, and that adverse events were infrequent and similar between groups [52].**

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

Non-TNF biologic therapy compared to another TNFi therapy for patients with established RA with moderate/high disease activity who have failed a single TNFi therapy

Bibliography: Non-TNF biologic therapy vs. another TNFi therapy in patients with established RA and moderate/high disease activity who have failed a single anti-TNF biologic.

Outcomes	No of Participants (studies) Follow up	Quality of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects	
				Risk with Another TNFi therapy	Risk difference with Non-TNF biologic therapy (95% CI)
DAS-28 (RA disease activity) (higher score indicates more severe disease activity)	1740 (3 studies) 6 months	⊕⊕⊖⊖ **LOW**			The mean DAS-28 (RA disease activity) in the intervention groups was **0.02 standard deviations higher** (0.16 lower to 0.2 higher)
Health Assessment Questionnaire (HAQ) (higher score indicates more severe physical disability)	1198 (3 studies) 6 months	⊕⊕⊖⊖ **LOW**			The mean health assessment questionnaire (HAQ) in the intervention groups was **0.3 standard deviations higher** (0.02 lower to 0.63 higher)

*The basis for the **assumed risk** (e.g., the median control group risk across studies) is provided in footnotes. The **corresponding risk** (and its 95% confidence interval) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI).

CI: Confidence interval;

GRADE Working Group grades of evidence
High quality: Further research is very unlikely to change our confidence in the estimate of effect.
Moderate quality: Further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate.
Low quality: Further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate.
Very low quality: We are very uncertain about the estimate.

This PICO includes three retrospective cohort studies:	Chatzidionysiou et al., 2013 [51]; Kekow et al., 2012 [52]; Soliman et al., 2012 [53]

B.13: For patients with established RA with moderate or high disease activity, the recommendation is *conditional* for using a non-TNF biologic rather than tofacitinib monotherapy.

Voting for this statement was based on the the below PICO question:

In patients with established RA with moderate or high disease activity, who have failed a single TNFi therapy, what is the impact of non-TNF biologic therapy vs. oral tofacitinib on symptoms and AEs?

Summary: This PICO was not directly addressed by any studies.

Quality of evidence across all critical outcomes: Very low ⊕⊖⊖⊖. No data were available to address this question. Recommendations were formulated based on the expertise of the voting panel.

B.14: For patients with established RA and moderate or high disease activity despite use of a single TNFi and methotrexate, currently on DMARD therapy, the recommendation is *conditional* for using a non-TNF biologic rather than another TNFi.

Voting for this statement was based on the evidence table and summary for the below PICO question:

In patients with established RA with moderate or high disease activity, who have failed a single TNFi therapy, what is the impact of non-TNF biologic therapy + MTX vs. another TNFi + MTX on symptoms and AEs?

Summary: This PICO was addressed by five observational cohort studies [52, 54-57]. The evidence was slightly indirect: a majority of participants in each trial—though not all participants—were taking MTX (approx. 52%, 50%, 85%, and 66% in the Emery et al.,[54] Kekow et al., [52] Wakabayashi et al., [56] and Finckh et al. [57] studies, respectively). One study matched patients switching to abatacept (n=431 at 6 months, n=311 at 12 months) with those switching to other TNFi agents (n=746 at 6 months; n=493 at 12 months) after TNFi failure [55]. This study demonstrated no statistically significant between group differences in modified ACR20, ACR50, ACR70, and HAQ scores at either time point in adjusted analyses. Pooled analysis of four other cohort studies indicated that RA disease activity (measured by DAS-28) improved more in those receiving non-TNF biologic therapy. In contrast, one small study found that patients receiving TNFi therapy demonstrated significantly greater improvement in physical function (measured by HAQ) than patients receiving non-TNF biologic therapy. No significant between-group difference was found for serious adverse events or injection site reactions, though serious infections were significantly more frequent among those receiving non-TNF biologics**.**

Quality of evidence across all critical outcomes: Very low ⊕⊖⊖⊖

Non-TNF biologic therapy + MTX compared to another TNFi + MTX for patients with established RA with moderate/high disease severity who have failed a single TNFi therapy

Bibliography: Non-TNF biologic + MTX vs. another TNFi + MTX in patients with established RA with moderate/high disease activity who have failed a single TNFi therapy.

Outcomes	No of Participants (studies) Follow up	Quality of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects	
				Risk with Another TNFi + MTX	Risk difference with Non-TNF biologic therapy + MTX (95% CI)
DAS-28 (RA disease activity) (higher score indicates more severe disease activity)	1079 (4 studies) 6-31 months	⊕⊖⊖⊖ **VERY LOW**[1,2] due to risk of bias, indirectness			The mean DAS-28 (RA disease activity) in the intervention groups was **0.37 lower** (0.52 to 0.21 lower)

Health Assessment Questionnaire (HAQ) (higher score indicates more severe physical disability)	47 (1 study) 6 months	⊕⊖⊖⊖ **VERY LOW**[3,4,5] due to risk of bias, indirectness, imprecision			The mean health assessment questionnaire (HAQ) in the intervention groups was **0.36 higher** (0.08 to 0.64 higher)
Serious adverse events (SAEs)	1111 (1 study) 6 months	⊕⊖⊖⊖ **VERY LOW**[6] due to indirectness	**RR 1.23** (0.89 to 1.69)	**110 per 1000**	**25 more per 1000** (from 12 fewer to 76 more)
Injection site reactions/Infusion reaction	1227 (2 studies) 6 months	⊕⊖⊖⊖ **VERY LOW**[7] due to indirectness	**RR 0.75** (0.04 to 13.86)	**51 per 1000**	**13 fewer per 1000** (from 49 fewer to 651 more)
Serious infections	1111 (1 study) 6 months	⊕⊖⊖⊖ **VERY LOW**[6] due to indirectness	**RR 2.15** (1 to 4.59)	**18 per 1000**	**20 more per 1000** (from 0 more to 64 more)

*The basis for the **assumed risk** (e.g., the median control group risk across studies) is provided in footnotes. The **corresponding risk** (and its 95% confidence interval) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI).

CI: Confidence interval; **RR:** Risk ratio;

GRADE Working Group grades of evidence
High quality: Further research is very unlikely to change our confidence in the estimate of effect.
Moderate quality: Further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate.
Low quality: Further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate.
Very low quality: We are very uncertain about the estimate.

[1] High risk for confounding bias; measures to adjust for confounding covariates not described in three (Kekow et al., 2012; Wakabayashi et al., 2011; Finckh et al., 2007) of four included studies (analysis also included Emery et al., 2014).
[2] Not all patients were administered concomitant MTX (approx. 52%, 50%, 85%, and 66% received MTX in Emery et al., Kekow et al., Wakabayashi et al., and Finckh et al. studies, respectively).
[3] High risk for confounding bias; measures to adjust for confounding covariates not described (Kekow et al., 2012).
[4] Not all patients were administered concomitant MTX (approx. 50% in Kekow et al., study received MTX).
[5] Wide confidence intervals around effect size due to small samples size (n=47) (Kekow et al., 2012).
[6] Not all patients were administered concomitant MTX (approx. 52%, received MTX in Emery et al., study).
[7] Not all patients were administered concomitant MTX (approx. 52% and 66% received MTX in Emery et al., and Finckh et al. studies, respectively).

This PICO includes five observational studies:	Emery et al., 2014 [54]; Harrold et al., 2014 [55]; Kekow et al., 2012 [52]; Wakabayashi et al., 2011 [56]; Finckh et al., 2007 [57]

B.15: For patients established RA and with moderate or high disease activity despite use of a single TNFi and methotrexate, currently on DMARD therapy, the recommendation is *conditional* for using a non-TNF biologic rather than another tofacitinib.

Voting for this statement was based on the below PICO question:

In patients with established RA with moderate or high disease activity, who have failed a single TNFi therapy, what is the impact of non-TNF biologic therapy + MTX on vs. oral tofacitinib + MTX on symptoms and AEs?

Summary: This PICO was not directly addressed by any studies.

Quality of evidence across all critical outcomes: Very low ⊕⊖⊖⊖. No data were available to address this question. Recommendations were formulated based on the expertise of the voting panel.

B.16: For patients established RA and disease activity is still moderate or high despite a non-TNF biologic therapy, the recommendation is conditional for using another non-TNF biologic rather than tofacitinib.

Voting for this statement was based on the below PICO question:

In patients with established RA with moderate or high disease activity, who have failed non-TNF biologic therapy, what is the impact of oral tofacitinib therapy vs. another non-TNF biologic on symptoms and AEs?

Summary: This PICO was not directly addressed by any studies.

Quality of evidence across all critical outcomes: Very low ⊕⊖⊖⊖. No data were available to address this question. Recommendations were formulated based on the expertise of the voting panel.

B.17: For patients established RA and disease activity is still moderate or high despite a non-TNF biologic therapy, the recommendation is conditional for using another non-TNF biologic, with methotrexate, rather than tofacitinib with methotrexate.

Voting for this statement was based on the below PICO question:

In patients with established RA with moderate or high disease activity, who have failed non-TNF biologic therapy, what is the impact of oral tofacitinib therapy + MTX vs. another non-TNF biologic + MTX on symptoms and AEs?

Summary: This PICO was not directly addressed by any studies.

Quality of evidence across all critical outcomes: Very low ⊕⊖⊖⊖. No data were available to address this question. Recommendations were formulated based on the expertise of the voting panel.

B.18: For patients established RA and has moderate or high disease activity and has failed multiple non-TNF biologics and is TNFi-naïve, the recommendation is *conditional* for using TNFi rather than not using TNFi*.*

Voting for this statement was based on the below PICO question:

In a patient with established RA with moderate-high disease activity, who has failed multiple non-TNF biologics <u>but is TNFi-naïve</u>, what is the impact of using TNFi vs. not using TNFi?

<u>Summary</u>: This PICO was not directly addressed by any studies.

<u>Quality of evidence across all critical outcomes</u>: Very low ⊕⊖⊖⊖. No data were available to address this question. Recommendations were formulated based on the expertise of the voting panel.

B.19: In patients with established RA with moderate or high disease activity, the recommendation is conditional for using tofacitinib rather than another TNFi.

Voting for this statement was based on the evidence table and summary for the below PICO question:

In patients with established RA with moderate or high disease activity, who have failed both TNFi and non-TNF biologic therapy, what is the impact of oral tofacitinib therapy vs. another TNFi on symptoms and AEs?

Summary: This PICO was indirectly addressed by one RCT comparing oral tofacitinib with adalimumab in patients who had previously failed treatment with traditional DMARD therapy [20]. Because the trial's inclusion criteria did not include prior failure of TNFi or non-TNF biologic therapy, the evidence addresses this PICO question only indirectly. Analysis of RA disease activity (as measured by ACR20, 50, and 70 responses) found greater benefit with oral tofacitinib than with TNFi therapy. No between-group differences were found for physical disability (HAQ-DI) or any of the selected safety outcomes (including SAEs, serious infections, and hepatotoxicity).

Quality of evidence across all critical outcomes: Very low ⊕⊖⊖⊖

Oral tofacitinib vs. TNFi for patients with established RA with moderate/high disease activity who have failed both TNFi and non-TNF biologic therapy

Bibliography: Oral tofacitinib therapy vs. alternate TNFi in patients with established RA and moderate/high disease activity who have failed TNFi and non-TNF biologic therapy.

Outcomes	No of Participants (studies) Follow up	Quality of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects	
				Risk with TNFi-biologic	Risk difference with Oral tofacitinib (95% CI)
ACR20 response (RA disease activity)	102 (1 study) 12 weeks	⊕⊖⊖⊖ **VERY LOW**[1,2] due to indirectness, imprecision	**RR 1.65** (1.08 to 2.53)	**358 per 1000**	**233 more per 1000** (from 29 more to 548 more)
ACR50 response (RA disease activity)	102 (1 study) 12 weeks	⊕⊖⊖⊖ **VERY LOW**[1,2] due to indirectness, imprecision	**RR 1.95** (1 to 3.8)	**189 per 1000**	**179 more per 1000** (from 0 more to 528 more)
ACR70 response (RA disease activity)	102 (1 study) 12 weeks	⊕⊖⊖⊖ **VERY LOW**[1,2] due to indirectness, imprecision	**RR 15.68** (3.95 to 62.29)	**38 per 1000**	**554 more per 1000** (from 111 more to 1000 more)
Health Assessment Questionnaire-	92 (1 study)	⊕⊖⊖⊖ **VERY LOW**[1,2]			The mean HAQ-DI (health assessment questionnaire-disability index) in the intervention groups was

Disability Index (HAQ-DI) (higher score indicates more severe physical disability)	12 weeks	due to indirectness, imprecision			**0.19 lower** (0.49 lower to 0.11 higher)
Serious Adverse Events (SAEs)	102 (1 study) 24 weeks	⊕⊖⊖⊖ **VERY LOW**[1,2] due to indirectness, imprecision	**RR 0.36** (0.02 to 8.63)	**19 per 1000**	**12 fewer per 1000** (from 18 fewer to 144 more)
Serious infections	102 (1 study) 24 weeks	⊕⊖⊖⊖ **VERY LOW**[1,2] due to indirectness, imprecision	Not estimable	See comment	The between-group difference in serious infections incidence was not statistically significant.
Hepatotoxicity (ALT>3x Upper Limit of Normal)	102 (1 study) 24 weeks	⊕⊖⊖⊖ **VERY LOW**[1,2] due to indirectness, imprecision	**RR 0.36** (0.02 to 8.63)	**19 per 1000**	**12 fewer per 1000** (from 18 fewer to 144 more)

*The basis for the **assumed risk** (e.g., the median control group risk across studies) is provided in footnotes. The **corresponding risk** (and its 95% confidence interval) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI).

CI: Confidence interval; **RR:** Risk ratio;

GRADE Working Group grades of evidence
High quality: Further research is very unlikely to change our confidence in the estimate of effect.
Moderate quality: Further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate.
Low quality: Further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate.
Very low quality: We are very uncertain about the estimate.

[1] Indirect evidence: randomized patients had previously failed traditional DMARD therapy, but failure of TNFi or non-TNF biologic therapy was not a selection criteria (Fleischmann et al., 2012).
[2] Wide confidence intervals around estimate due to small sample size (Fleischmann et al., 2012).

This PICO includes one RCT:	Fleischmann et al., 2012 [20]

B.20: If a patient with established RA still has moderate or high disease activity, the recommendation is conditional for using tofacitinib (with methotrexate) rather than another TNFi (with methotrexate).

Voting for this statement was based on the evidence table and summary for the below PICO question:

In patients with established RA with moderate or high disease activity, who have failed both TNFi and non-TNF biologic therapy, what is the impact of oral tofacitinib + MTX therapy vs. another TNFi + MTX on symptoms and AEs?

Summary: This PICO was indirectly addressed by one RCT comparing oral tofacitinib + MTX with adalimumab + MTX in patients who had previously failed treatment with methotrexate monotherapy [21]. Because the trial's inclusion criteria did not include prior failure of TNFi or non-TNF biologic therapy, this evidence addresses this PICO question only indirectly. Analysis of RA disease activity (as measured by DAS-28 and ACR20) found no significant between-group differences, though a greater benefit for physical disability (HAQ-DI) was found among those receiving oral tofacitinib + MTX than with TNFi therapy + MTX. No significant between-group differences were found for any of the selected safety outcomes (including SAEs, serious infections, and hepatotoxicity).

Quality of evidence across all critical outcomes: Very low ⊕⊖⊖⊖

Oral tofacitinib + MTX vs. TNFi-biologic + MTX for patients with established RA with moderate/high disease activity who have failed TNFi and non-TNF biologic therapy

Bibliography: Oral tofacitinib + MTX vs. TNFi + MTX in patients with established RA with moderate/high disease activity who have failed TNFi and non-TNF biologic therapy.

Outcomes	No of Participants (studies) Follow up	Quality of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects	
				Risk with TNFi + MTX	Risk difference with Oral tofacitinib + MTX (95% CI)
DAS-28 score <2.6 (RA disease activity)	355 (1 study) 6 months	⊕⊖⊖⊖ **VERY LOW**[1,2] due to risk of bias, indirectness, and imprecision	**RR 0.92** (0.42 to 2.03)	**67 per 1000**	**5 fewer per 1000** (from 39 fewer to 69 more)
ACR20 response (RA disease activity)	395 (1 study) 6 months	⊕⊖⊖⊖ **VERY LOW**[1,2] due to risk of bias, indirectness, and imprecision	**RR 1.09** (0.89 to 1.33)	**472 per 1000**	**43 more per 1000** (from 52 fewer to 156 more)
HAQ-DI (Health Assessment Questionnaire) (Physical disability)	378 (1 study) 3 months	⊕⊖⊖⊖ **VERY LOW**[1,2] due to risk of bias, indirectness			The mean HAQ-DI (Health Assessment Questionnaire-Disability Index) in the intervention groups was **0.06 lower** (0.07 to 0.05 lower)

Serious Adverse Events (SAEs)	408 (1 study) 12 months	⊕⊖⊖⊖ **VERY LOW**[1,2] due to risk of bias, indirectness, and imprecision	**RR 1.43** (0.55 to 3.68)	**34 per 1000**	**15 more per 1000** (from 15 fewer to 92 more)
Serious infections	408 (1 study) 12 months	⊕⊖⊖⊖ **VERY LOW**[1,2] due to risk of bias, indirectness, and imprecision	**RR 2** (0.18 to 21.88)	**5 per 1000**	**5 more per 1000** (from 4 fewer to 102 more)
Hepatotoxicity (AST >3x upper limit of normal)	407 (1 study) 3 months	⊕⊖⊖⊖ **VERY LOW**[1,2] due to risk of bias, indirectness	**RR 3.01** (0.12 to 73.57)	**0 per 1000**	**-**
Hepatotoxicity (ALT >3x upper limit of normal)	407 (1 study) 3 months	⊕⊖⊖⊖ **VERY LOW**[1,2] due to risk of bias, indirectness	**RR 5.02** (0.24 to 104.01)	**0 per 1000**	**-**

*The basis for the **assumed risk** (e.g., the median control group risk across studies) is provided in footnotes. The **corresponding risk** (and its 95% confidence interval) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI).

CI: Confidence interval; **RR:** Risk ratio;

GRADE Working Group grades of evidence
High quality: Further research is very unlikely to change our confidence in the estimate of effect.
Moderate quality: Further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate.
Low quality: Further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate.
Very low quality: We are very uncertain about the estimate.

[1] The RCT examined was unblinded, increasing the risk of potential expectation bias, and did not adequately describe allocation procedures (van Vollenhoven et al., 2012).
[2]Indirect evidence: randomized participants had not failed previous TNFis or non-TNF biologic agents (van Vollenhoven et al., 2012).

This PICO includes one RCT:	van Vollenhoven et al., 2012 [21]

B.21: For patients with established RA with moderate or high disease activity after using at least one TNFi biologic and at least one non-TNF-biologic, the recommendation is conditional for first using another non-TNF biologic (with or without methotrexate) rather than tofacitinib.

Voting for this statement was based on the below PICO question:

In patients with established RA with moderate or high disease activity, who have failed both TNFi and non-TNF biologic therapy, what is the impact of oral tofacitinib therapy vs. another non-TNF biologic on symptoms and AEs?

Summary: This PICO was not directly addressed by any studies.

Quality of evidence across all critical outcomes: Very low ⊕⊖⊖⊖. No data were available to address this question. Recommendations were formulated based on the expertise of the voting panel.

B.22: For patients with established RA with moderate or high disease activity after using at least one TNFi biologic and at least one non-TNF-biologic, the recommendation is conditional for first using another non-TNF biologic (with or without methotrexate) rather than tofacitinib.

Voting for this statement was based on the below PICO question:

In patients with established RA with moderate or high disease activity, who have failed both TNFi and non-TNF biologic therapy, what is the impact of oral tofacitinib therapy + MTX vs. another non-TNF biologic +MTX on symptoms and AEs?

Summary: This PICO was not directly addressed by any studies.

Quality of evidence across all critical outcomes: Very low ⊕⊖⊖⊖. No data were available to address this question. Recommendations were formulated based on the expertise of the voting panel.

B.23: For patients with established RA with moderate or high disease activity after failing TNFi therapy and for whom non-TNF biologic therapy is not an option, the recommendation is conditional for using tofacitinib (with or without methotrexate) rather than another TNFi.

Voting for this statement was based on the evidence table and summary for the below PICO question:

In patients with established RA with moderate or high disease activity, who have failed multiple TNFi therapies, what is the impact of oral tofacitinib therapy vs. another TNFi on symptoms and AEs?

Summary: This PICO was indirectly addressed by one RCT comparing oral tofacitinib with adalimumab in patients who had previously failed treatment with traditional DMARD [20]. Because the trial's inclusion criteria did not include prior failure of any TNFi therapies, this evidence addresses this PICO question only indirectly. Analysis of RA disease activity (as measured by ACR20, 50, and 70 responses) found greater benefit with oral tofacitinib than with TNFi therapy. No between-group differences were found for physical disability (HAQ-DI) or any of the selected safety outcomes (including SAEs, serious infections, and hepatotoxicity).

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

Oral tofacitinib vs. TNFi-biologic for patients with established RA with moderate/high disease activity who have failed TNFi therapy

Bibliography: Oral tofacitinib vs. another TNFi in those with established RA with moderate/high disease activity who have failed TNFi-biologic therapy.

Outcomes	No of Participants (studies) Follow up	Quality of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects	
				Risk with TNFi-biologic	Risk difference with Oral tofacitinib (95% CI)
ACR20 response (RA disease activity)	102 (1 study) 12 weeks	⊕⊕⊖⊖ **LOW**[1,2] due to indirectness, imprecision	**RR 1.65** (1.08 to 2.53)	**358 per 1000**	**233 more per 1000** (from 29 more to 548 more)
ACR50 response (RA disease activity)	102 (1 study) 12 weeks	⊕⊕⊖⊖ **LOW**[1,2] due to indirectness, imprecision	**RR 1.95** (1 to 3.8)	**189 per 1000**	**179 more per 1000** (from 0 more to 528 more)
ACR70 response (RA disease activity)	102 (1 study) 12 weeks	⊕⊕⊖⊖ **LOW**[1,2] due to indirectness, imprecision	**RR 15.68** (3.95 to 62.29)	**38 per 1000**	**554 more per 1000** (from 111 more to 1000 more)
Health Assessment Questionnaire-Disability Index (HAQ-DI) (physical disability)	92 (1 study)	⊕⊕⊖⊖ **LOW**[1,2]			The mean health assessment questionnaire-disability index (HAQ-DI) in the intervention groups was

(higher score indicates more severe disability)	12 weeks	due to indirectness, imprecision			**0.19 lower** (0.49 lower to 0.11 higher)
Serious adverse events (SAE)	102 (1 study) 12 weeks	⊕⊕⊖⊖ **LOW**[1,2] due to indirectness, imprecision	**RR 0.36** (0.02 to 8.63)	**19 per 1000**	**12 fewer per 1000** (from 18 fewer to 144 more)
Serious infections	102 (1 study) 12 weeks	⊕⊕⊖⊖ **LOW**[1,2] due to indirectness, imprecision	Not estimable	See comment	The between-group difference in serious infections incidence was not statistically significant.
Hepatotoxicity (ALT>3X upper limit of normal)	102 (1 study) 12 weeks	⊕⊕⊖⊖ **LOW**[1,2] due to indirectness, imprecision	**RR 0.36** (0.02 to 8.63)	**19 per 1000**	**12 fewer per 1000** (from 18 fewer to 144 more)

*The basis for the **assumed risk** (e.g., the median control group risk across studies) is provided in footnotes. The **corresponding risk** (and its 95% confidence interval) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI).

CI: Confidence interval; **RR:** Risk ratio;

GRADE Working Group grades of evidence
High quality: Further research is very unlikely to change our confidence in the estimate of effect.
Moderate quality: Further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate.
Low quality: Further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate.
Very low quality: We are very uncertain about the estimate.

[1] Indirect evidence: participants included in the Fleischmann et al., 2012 trial had failed traditional DMARD therapy, but prior TNFi failure was not specified as a criterion for study inclusion.
[2] Wide confidence intervals around estimate due to small sample size (Fleischmann et al., 2012).

This PICO includes one RCT:	Fleischmann et al., 2012 [20]

B.24: For patients with established RA with moderate or high disease activity after failing TNFi therapy and for whom non-TNF biologic therapy is not an option, the recommendation is conditional for using tofacitinib (with methotrexate) rather than another TNFi (with methotrexate).

Voting for this statement was based on the evidence table and summary for the below PICO question:

In patients with established RA with moderate or high disease activity, who have failed multiple TNFi therapies, what is the impact of oral tofacitinib therapy + MTX vs. another TNFi + MTX on symptoms and AEs?

Summary: This PICO was indirectly addressed by one RCT comparing oral tofacitinib + MTX with adalimumab + MTX in patients who had previously failed treatment with methotrexate monotherapy [21]. Because the trial's inclusion criteria did not include prior failure of any TNFi therapies, this evidence addresses this PICO question only indirectly. Analysis of RA disease activity (as measured by DAS-28 and ACR20) found no significant between-group differences, though a greater benefit for physical disability (HAQ-DI) was found among those receiving oral tofacitinib + MTX than with TNFi therapy + MTX. No significant between-group differences were found for any of the selected safety outcomes (including SAEs, serious infections, and hepatotoxicity).

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

Oral tofacitinib + MTX compared to TNFi + MTX for patients with established RA with moderate/high disease activity who have failed prior TNFi therapy

Bibliography: Oral tofacitinib + MTX vs. TNFi + MTX in patients with established RA with moderate/high disease activity who have failed TNFi therapy.

Outcomes	No of Participants (studies) Follow up	Quality of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects	
				Risk with TNFi + MTX	Risk difference with Oral tofacitinib + MTX (95% CI)
DAS-28 score <2.6 (RA disease activity)	355 (1 study) 6 months	⊕⊕⊖⊖ **LOW**[1,2] due to indirectness, imprecision	**RR 0.92** (0.42 to 2.03)	**67 per 1000**	**5 fewer per 1000** (from 39 fewer to 69 more)
ACR20 response (RA disease activity)	395 (1 study) 6 months	⊕⊕⊖⊖ **LOW**[1,2] due to indirectness, imprecision	**RR 1.09** (0.89 to 1.33)	**472 per 1000**	**43 more per 1000** (from 52 fewer to 156 more)
Health Assessment Questionnaire-	378	⊕⊕⊖⊖			The mean HAQ-DI (health assessment questionnaire-

Disability Index (HAQ-DI) (higher score indicates more severe disability)	(1 study) 3 months	**LOW**[1,2] due to indirectness, imprecision			disability index) (physical disability) in the intervention groups was **0.06 lower** (0.07 to 0.05 lower)
Serious Adverse Events (SAEs)	408 (1 study) 12 months	⊕⊕⊖⊖ **LOW**[1,2] due to indirectness, imprecision	**RR 1.43** (0.55 to 3.68)	**34 per 1000**	**15 more per 1000** (from 15 fewer to 92 more)
Serious infections	408 (1 study) 12 months	⊕⊕⊖⊖ **LOW**[1,2] due to indirectness, imprecision	**RR 2** (0.18 to 21.88)	**5 per 1000**	**5 more per 1000** (from 4 fewer to 102 more)
Hepatotoxicity (AST >3x upper limit of normal)	407 (1 study) 3 months	⊕⊕⊖⊖ **LOW**[1,2] due to indirectness, imprecision	**RR 3.01** (0.12 to 73.57)	**0 per 1000**	**-**
Hepatotoxicity (ALT >3x upper limit of normal)	407 (1 study) 3 months	⊕⊕⊖⊖ **LOW**[1,2] due to indirectness, imprecision	**RR 5.02** (0.24 to 104.01)	**0 per 1000**	**-**

*The basis for the **assumed risk** (e.g., the median control group risk across studies) is provided in footnotes. The **corresponding risk** (and its 95% confidence interval) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI).

CI: Confidence interval; **RR:** Risk ratio;

GRADE Working Group grades of evidence
High quality: Further research is very unlikely to change our confidence in the estimate of effect.
Moderate quality: Further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate.
Low quality: Further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate.
Very low quality: We are very uncertain about the estimate.

[1] The RCT examined was unblinded, increasing the risk of potential expectation bias, and did not adequately describe allocation procedures (van Vollenhoven et al., 2012).
[2] Indirect evidence: randomized participants had not failed previous TNFi agents (van Vollenhoven et al., 2012).

This PICO includes one RCT:	van Vollenhoven et al., 2012 [21]

B.26: In patients with established RA and moderate or high disease activity, the recommendation is *conditional* for adding a short-term, low dose glucocorticoid therapy in combination with DMARD, TNFi, or non-TNF biologic therapy rather than using DMARD, TNFi, or non-TNF biologic therapies without glucocorticoids.

Voting for this statement was based on the evidence table and summary for the below PICO question:

In patients with established RA with moderate or high disease activity, what is the impact of adding long-term low-dose glucocorticoid therapy to traditional DMARD therapy vs. traditional DMARDs without glucocorticoids?

Summary: This PICO was directly addressed by three RCTs: two double-blind trials [23, 58] and one open-label trial [59]. All three trials compared traditional DMARDs and concomitant glucocorticoids with traditional DMARDs alone in patients with established RA. Significant benefits of additional glucocorticoids over DMARD monotherapy were found for RA disease activity (measured by DAS-28 score and proportion achieving DAS-28 remission criteria), quality of life (measured by HAQ), and physical function (SF-36 physical component). The difference in SF-36 mental component score did not reach statistical significance. No significant between-group differences were found for any safety domains analyzed (including serious adverse events, cardiovascular adverse events, and incident osteoporosis).

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

Long-term, low-dose glucocorticoids with traditional DMARDs vs. traditional DMARDs alone for patients with established rheumatoid arthritis with moderate/high disease activity

Bibliography: Long-term low-dose GC therapy + traditional DMARDs vs. traditional DMARDs without GCs in those with established RA moderate/high disease activity.

Outcomes	No of Participants (studies) Follow up	Quality of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects	
				Risk with Traditional DMARDs alone	Risk difference with Long-term low-dose glucocorticoids with traditional DMARDs (95% CI)
DAS-28 (RA disease activity)	410 (2 studies) 3-24 months	⊕⊕⊕⊕ **HIGH**			The mean das-28 (ra disease activity) in the intervention groups was **0.39 lower** (0.71 to 0.06 lower)
ACR 20 response (RA disease activity)	348 (1 study) 3 months	⊕⊕⊕⊕ **HIGH**	**RR 1.63** (1.2 to 2.23)	**294 per 1000**	**185 more per 1000** (from 59 more to 362 more)

Health Assessment Questionnaire (HAQ) (QoL) (higher scores indicate poorer QoL/physical function)	486 (3 studies) 3-24 months	⊕⊕⊕⊕ **HIGH**			The mean health assessment questionnaire (HAQ) in the intervention groups was **0.18 lower** (0.28 to 0.08 lower)
SF-36 (Physical component) (lower scores indicate greater disability)	348 (1 study) 3 months	⊕⊕⊕⊖ **MODERATE**[1] due to risk of bias			The mean sf-36 (physical component) in the intervention groups was **2.4 higher** (0.74 to 4.06 higher)
SF-36 (Mental component) (lower scores indicate greater disability)	348 (1 study) 3 months	⊕⊕⊕⊖ **MODERATE**[1] due to risk of bias			The mean sf-36 (mental component) in the intervention groups was **1 higher** (0.94 lower to 2.94 higher)
Serious Adverse Events (SAEs)	350 (1 study) 3 months	⊕⊕⊕⊕ **HIGH** imprecision	**RR 0.26** (0.02 to 2.81)	**17 per 1000**	**12 fewer per 1000** (from 16 fewer to 30 more)
Cardiovascular AEs (Hypertension)	441 (2 studies) 3-24 months	⊕⊕⊕⊕ **HIGH** imprecision	**RR 3.03** (0.67 to 13.82)	**12 per 1000**	**25 more per 1000** (from 4 fewer to 158 more)
Osteoporosis	91 (1 study) 24 months	⊕⊕⊖⊖ **LOW**[2] due to risk of bias, imprecision	**RR 4.49** (0.22 to 90.99)	**0 per 1000**	**-**

*The basis for the **assumed risk** (e.g., the median control group risk across studies) is provided in footnotes. The **corresponding risk** (and its 95% confidence interval) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI).

CI: Confidence interval; **RR:** Risk ratio; **RA:** rheumatoid arthritis; **QoL:** quality of life

GRADE Working Group grades of evidence
High quality: Further research is very unlikely to change our confidence in the estimate of effect.
Moderate quality: Further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate.
Low quality: Further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate.
Very low quality: We are very uncertain about the estimate.

[1] Data were gathered from one trial which did not adequately describe randomization and blinding procedures (Buttgereit et al., 2013).
[2] Wide confidence intervals for effect estimate due to small sample size (n=91) (Choy et al., 2005).

This PICO includes three RCTs:	Buttgereit et al., 2013 [58]; Choy et al., 2005 [23]; Hansen et al., 1999 [59]

B.27: In patients with established RA and moderate or high disease activity, the recommendation is conditional for adding low dose glucocorticoid therapy rather than without glucocorticoids.

Voting for this statement was based on the evidence tables and summaries for the below PICO questions:

In patients with established RA with moderate or high disease activity, what is the impact of adding long-term low-dose glucocorticoid therapy to TNFi therapy vs. TNFi without glucocorticoids on symptoms and AEs?

Summary: This PICO was indirectly addressed by one open-label RCT [12]. This trial found no statistically significant between-group difference in patients achieving DAS-28 criteria for low disease activity. Because this trial was conducted in patients with early rather than established RA, this trial only addresses this PICO indirectly. **This trial did not address the relative safety of the studied treatments.**

Quality of evidence across all critical outcomes: Very low ⊕⊖⊖⊖

TNFi therapy +long-term, low dose glucocorticoids vs. TNFi therapy alone for patients with established RA with moderate/high disease activity

Bibliography: TNFi therapy + long-term, low dose glucocorticoids vs. TNFi therapy alone in patients with established RA and moderate/high disease activity.

Outcomes	No of Participants (studies) Follow up	Quality of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects	
				Risk with TNFi therapy alone	Risk difference with TNFi therapy +long-term, low dose glucocorticoids (95% CI)
DAS-28 remission (DAS-28 score < 1.6) (RA disease activity)	210 (1 study) 12 months	⊕⊖⊖⊖ **VERY LOW**[1,2,3] due to risk of bias, indirectness, imprecision	**RR 1.31** (0.9 to 1.9)	**305 per 1000**	**94 more per 1000** (from 30 fewer to 274 more)

*The basis for the **assumed risk** (e.g., the median control group risk across studies) is provided in footnotes. The **corresponding risk** (and its 95% confidence interval) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI).

CI: Confidence interval; **RR:** Risk ratio;

GRADE Working Group grades of evidence
High quality: Further research is very unlikely to change our confidence in the estimate of effect.
Moderate quality: Further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate.

Low quality: Further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate.
Very low quality: We are very uncertain about the estimate.

[1] Data were drawn from an open-label RCT, thereby introducing the possibility of expectation bias (Todoerti et al., 2010).
[2] Indirect evidence: included patients had early RA, rather than the established RA specified in the PICO question (Todoerti et al., 2010).
[3] Wide confidence intervals around effect estimate due to small sample size (Todoerti et al., 2010).

This PICO includes one RCT:	Todoerti et al., 2010 [12]

In patients with <u>established</u> RA with <u>moderate or high disease</u> activity, what is the impact of <u>adding long-term low-dose glucocorticoid therapy to non-TNF biologic therapy</u> vs. <u>non-TNF biologic therapy without glucocorticoids</u> on symptoms and AEs?

<u>Summary</u>: This PICO was not directly addressed by any studies.

<u>Quality of evidence across all critical outcomes</u>: Very low ⊕⊖⊖⊖. No data were available to address this question.

B.28: In patients with established RA experiencing an acute disease flare, the recommendation is *conditional* for using short-term glucocorticoid therapy in combination with DMARD, TNFi, or non-TNF biologic therapy over any of these therapies without glucocorticoids.

Voting for this statement was based on the evidence table and summary for the below PICO question:

In patients with established RA with moderate or high disease activity with an acute disease flare (RA flare), what is the impact of adding short-term high-dose glucocorticoid therapy to traditional DMARDs vs. traditional DMARDs without glucocorticoids on symptoms and AEs?

Summary: This PICO was indirectly addressed by four RCTs [22-25]. While this PICO addresses those with established RA experiencing acute disease flare, the closest available evidence was gathered from RCTs in patients with early or established RA and moderate/high disease activity. Acute disease flare was not an eligibility criteria for any of these trials. The trials compared traditional DMARD therapy + short-term, high dose glucocorticoids with traditional DMARD therapy alone. No statistically significant between-group differences were found for any of the critical outcomes analyzed. One very small RCT (n=21) was not included in pooled analyses due to its short follow-up duration (2-week follow-up) and heterogeneous findings) [24]. This small, low-quality trial suggested a statistically significant benefit of additional glucocorticoids for DAS-28 score and physical function (HAQ).

Quality of evidence across all critical outcomes: Very low ⊕⊖⊖⊖

Short-term, high dose glucocorticoids + traditional DMARD therapy vs. traditional DMARDs without glucocorticoids for patients with established RA with moderate/high disease activity with an acute disease flare

Bibliography: Short-term high dose glucocorticoid therapy+ traditional DMARD therapy vs. traditional DMARD therapy without glucocorticoids in patients with established RA and moderate/high disease activity with an acute disease flare.

Outcomes	No of Participants (studies) Follow up	Quality of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects	
				Risk with Traditional DMARDs without glucocorticoids	Risk difference with Short-term, high dose glucocorticoids + traditional DMARD therapy (95% CI)
DAS-28 (RA disease activity) (higher score indicates more severe disease activity)	117 (2 studies) 1-2 years	⨁⨁◯◯ **LOW**[1,2] due to indirectness, imprecision			The mean DAS-28 (RA disease activity) in the intervention groups was **0.34 lower** (0.91 lower to 0.24 higher)
ACR 20 response (RA disease activity)	26 (1 study) 12 months	⨁◯◯◯ **VERY LOW**[3,4,5] due to risk of bias, indirectness, imprecision	**RR 1.71** (0.94 to 3.14)	**500 per 1000**	**355 more per 1000** (from 30 fewer to 1000 more)
ACR50 response (RA disease activity)	26 (1 study) 12 months	⨁◯◯◯ **VERY LOW**[3,4,5] due to risk of bias, indirectness, imprecision	**RR 1.54** (0.71 to 3.35)	**417 per 1000**	**225 more per 1000** (from 121 fewer to 979 more)
ACR70 response (RA disease activity)	26 (1 study) 12 months	⨁◯◯◯ **VERY LOW**[3,4,5] due to risk of bias, indirectness, imprecision	**RR 3.43** (0.89 to 13.15)	**167 per 1000**	**405 more per 1000** (from 18 fewer to 1000 more)
Health Assessment Questionnaire (HAQ) (higher score indicates more severe physical disability)	146 (3 studies) 1-2 years	⨁◯◯◯ **VERY LOW**[6,7,8] due to inconsistency, indirectness, imprecision			The mean health assessment questionnaire (HAQ) in the intervention groups was **0.12 lower** (0.65 lower to 0.4 higher)
Larsen radiographic progression score (higher score indicates more severe disease progression)	91 (1 study) 2 years	⨁⨁◯◯ **LOW**[9,10] due to indirectness, imprecision			The mean Larsen radiographic progression score in the intervention groups was **4.76 higher** (13.4 lower to 22.92 higher)
Serious adverse events (SAEs)	120 (2 studies) 6-12 months	⨁⨁◯◯ **LOW**[1,2] due to indirectness, imprecision	**RR 1.79** (0.35 to 9.3)	**35 per 1000**	**28 more per 1000** (from 23 fewer to 291 more)

*The basis for the **assumed risk** (e.g., the median control group risk across studies) is provided in footnotes. The **corresponding risk** (and its 95% confidence interval) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI).

CI: Confidence interval; **RR:** Risk ratio;

GRADE Working Group grades of evidence

High quality: Further research is very unlikely to change our confidence in the estimate of effect.

Moderate quality: Further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate.

Low quality: Further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate.

Very low quality: We are very uncertain about the estimate.

[1] Indirect evidence: included trials examined patients with established RA, but disease flare was not an eligibility criteria in these trials (Durez et al., 2007; Choy et al., 2005).

[2] Wide confidence intervals around effect estimate due to small sample size (Durez et al., 2007; Choy et al., 2005).

[3] Data for this analysis were gathered from an unblinded RCT (Durez et al., 2007).

[4] Indirect evidence: included trial examined patients with established RA, but disease flare was not an eligibility criteria in these trials (Durez et al., 2007).

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

[6] I-squared heterogeneity score=71% (Durez et al., 2007; Choy et al., 2005; Ciconelli et al., 1996).

[7] Indirect evidence: included trials examined patients with established RA, but disease flare was not an eligibility criteria in these trials (Durez et al., 2007; Choy et al., 2005; Ciconelli et al., 1996).

[8] Wide confidence intervals around effect estimate due to small sample size (Durez et al., 2007; Choy et al., 2005; Ciconelli et al., 1996).

[9] Indirect evidence: included trial examined patients with established RA, but disease flare was not an eligibility criteria in these trials (Choy et al., 2005).

[10] Wide confidence intervals around effect estimate due to small sample size (Choy et al., 2005).

This PICO includes four RCTs:	Durez et al., 2007 [22]; Choy et al., 2005 [23]; Gerlag et al., 2004 [24]; Ciconelli et al., 1996 [25]

B.29: In patients with established RA experiencing an acute disease flare, the recommendation is conditional for using short-term glucocorticoid therapy over without glucocorticoids.

Voting for this statement was based on the evidence table and summary for B.28.

B.30: In patients with established RA with low disease activity (but not remission), we strongly recommend continuing DMARD therapy.

Voting for this statement was based on the evidence table and summary for the below PICO question:

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 [60]. The risk of disease flare was two times higher in those who discontinued DMARD therapy vs. those who continued DMARD therapy [60]. 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	
				Risk with Continuing DMARDs	Risk difference with Discontinuing 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 per 1000**	**158 more per 1000** (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 intervention groups 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 fewer per 1000** (from 12 fewer to 84 more)

*The basis for the **assumed risk** (e.g., the median control group risk across studies) is provided in footnotes. The **corresponding risk** (and its 95% confidence interval) is based on the

assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI).

CI: Confidence interval; **RR:** Risk ratio; **RA:** rheumatoid arthritis; **QoL:** quality of life

GRADE Working Group grades of evidence
High quality: Further research is very unlikely to change our confidence in the estimate of effect.
Moderate quality: Further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate.
Low quality: Further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate.
Very low quality: We are very uncertain about the estimate.

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

This PICO includes one RCT:	ten Wolde et al., 1996 [60]

B.31: In patients with established RA, currently in remission, we *conditionally* recommend tapering DMARD therapy.

Voting for this statement was based on the evidence table and summary for the below PICO question:

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

Summary: This PICO was addressed indirectly 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. The evidence is indirect due to included participants having achieved low disease activity, but not full disease remission. Upon achieving a "good response," participants were randomized to either continue or discontinue DMARD therapy, with disease flare as the primary outcome of interest [60]. The risk of disease flare was two times higher in those who discontinued DMARD therapy vs. those who continued DMARD therapy [60]. 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: Low ⊕⊕⊖⊖

Discontinuing traditional DMARD therapy vs. continuing DMARD therapy for patients with established RA in disease remission

Bibliography: Discontinuing traditional DMARD therapy vs. continuing DMARDs in patients with established RA in disease remission.

Outcomes	No of Participants (studies) Follow up	Quality of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects	
				Risk with Continuing DMARDs	Risk difference with Discontinuing traditional DMARD therapy (95% CI)
Incidence of disease flare (RA disease activity)	285 (1 study) 1 years	⊕⊕⊖⊖ **LOW**[1,2] due to indirectness, imprecision	**RR 1.75** (1.2 to 2.57)	**211 per 1000**	**158 more per 1000** (from 42 more to 332 more)
Health Assessment Questionnaire (HAQ) (higher score indicates more severe physical disability)	285 (1 study) 1 years	⊕⊕⊖⊖ **LOW**[1,2] due to indirectness, imprecision			The mean health assessment questionnaire (haq) in the intervention groups was **0.03 higher** (0.12 lower to 0.18 higher)
Withdrawal due to adverse events	285 (1 study) 1 years	⊕⊕⊖⊖ **LOW**[1,2] due to indirectness, imprecision	**RR 0.99** (0.14 to 6.95)	**14 per 1000**	**0 fewer per 1000** (from 12 fewer to 84 more)

*The basis for the **assumed risk** (e.g., the median control group risk across studies) is provided in footnotes. The **corresponding risk** (and its 95% confidence interval) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI).

CI: Confidence interval; **RR:** Risk ratio;

GRADE Working Group grades of evidence
High quality: Further research is very unlikely to change our confidence in the estimate of effect.
Moderate quality: Further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate.
Low quality: Further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate.
Very low quality: We are very uncertain about the estimate.

[1] Indirect evidence: participants in the included evidence were randomized upon achieving the criteria for low disease activity, rather than full disease remission (ten Wolde et al., 1996).
[2] Wide confidence intervals due to relatively small sample size (1 trial; n=285) (ten Wolde et al., 1996).

This PICO includes one RCT:	ten Wolde et al., 1996 [60]

B.32: In patients with established RA and low disease activity (but not remission) who are continuing methotrexate in combination with a biologic or tofacitinib, we strongly recommend continuing TNFi rather than discontinuing these medications.

Voting for this statement was based on the evidence table and summary for the below PICO question:

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

Summary: This PICO was directly addressed by two 52-week, double-blind RCTs (n=285) including established RA patients who had achieved low disease activity (DAS-28 < 3.2) on either a regimen of adalimumab and methotrexate [61] or etanercept and methotrexate [62]. Upon achieving low disease activity, participants in each trial were randomized to either continue or discontinue their TNFi therapy. No significant between-group differences were found for RA disease activity (measured by DAS-28; ACR 50 response) or radiographic disease progression (Sharp score), though overall quality of life (HAQ score) was rated as modestly superior among those who continued TNFi therapy. No significant between-group differences were detected for any of the safety domains analyzed (serious adverse events, serious infections, and malignancies).

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

TNFi discontinuation vs. TNFi continuation for patients with established RA with low disease activity

Bibliography: TNFi discontinuation vs. TNFi continuation in established RA with low disease activity.

Outcomes	No of Participants (studies) Follow up	Quality of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects	
				Risk with TNFi continuation	Risk difference with TNFi discontinuation (95% CI)
DAS-28 low disease activity (DAS-28 score < 3.2) (RA disease activity)	605 (2 studies) 1 years	⊕⊕⊕⊕ **HIGH** imprecision	**RR 0.68** (0.36 to 1.28)	**856 per 1000**	**274 fewer per 1000** (from 548 fewer to 240 more)
ACR 50 response (RA disease activity)	604 (2 studies) 1 years	⊕⊕⊕⊕ **HIGH** imprecision	**RR 0.63** (0.2 to 1.97)	**715 per 1000**	**264 fewer per 1000** (from 572 fewer to 693 more)
Sharp radiographic progression score	351 (1 study) 1 years	⊕⊕⊕⊕ **HIGH** imprecision			The mean Sharp radiographic progression score in the intervention groups was **0.2 higher** (11.02 lower to 11.42 higher)

Health Assessment Questionnaire-Disability Index (HAQ-DI) (higher score indicates poorer physical function)	402 (1 study) 1 years	⊕⊕⊕⊕ **HIGH** imprecision			The mean health assessment questionnaire-disability index (HAQ-DI) in the intervention groups was **0.3 higher** (0.19 to 0.41 higher)
Serious Adverse Events (SAEs)	532 (2 studies) 1 years	⊕⊕⊕⊕ **HIGH** imprecision	**RR 0.85** (0.5 to 1.45)	**104 per 1000**	**16 fewer per 1000** (from 52 fewer to 47 more)
Serious Infections	609 (2 studies) 1 years	⊕⊕⊕⊕ **HIGH**	**RR 0.79** (0.3 to 2.11)	**29 per 1000**	**6 fewer per 1000** (from 21 fewer to 33 more)
Malignancies	609 (2 studies) 1 years	⊕⊕⊕⊕ **HIGH**	**RR 0.97** (0.14 to 6.57)	**7 per 1000**	**0 fewer per 1000** (from 6 fewer to 36 more)

*The basis for the **assumed risk** (e.g., the median control group risk across studies) is provided in footnotes. The **corresponding risk** (and its 95% confidence interval) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI).

CI: Confidence interval; **RR:** Risk ratio; **RA:** rheumatoid arthritis; **QoL:** quality of life

GRADE Working Group grades of evidence
High quality: Further research is very unlikely to change our confidence in the estimate of effect.
Moderate quality: Further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate.
Low quality: Further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate.
Very low quality: We are very uncertain about the estimate.

This PICO includes two RCTs:	Smolen et al., 2014 [61]; Smolen et al., 2013 [62]

B.33: In a patient with established RA is in remission and continuing MTX, we *conditionally* recommend tapering TNFi rather than not tapering.

Voting for this statement was based on the evidence table and summary for the below PICO question:

In patients with established RA in disease remission, what is the impact of tapering TNFi therapy vs. continuing TNFi therapy on symptoms and AEs?

Summary: This PICO was indirectly addressed by two 52-week, double-blind RCTs (n=285) including established RA patients who had achieved low disease activity (DAS-28 < 3.2) on either a regimen of adalimumab and methotrexate [61] or etanercept and methotrexate [62]. Because included participants in both trials were included upon reaching low disease activity (DAS-28 < 3.2) rather than full disease remission, this evidence addresses this PICO only indirectly. Participants in each trial—upon achieving low disease activity—were randomized to either continue or discontinue their TNFi therapy. No significant between-group differences were found for RA disease activity (measured by DAS-28; ACR 50 response) or radiographic disease progression (Sharp score), though overall quality of life (HAQ score) was rated as modestly superior among those who continued TNFi therapy. No significant between-group differences were detected for any of the safety domains analyzed (serious adverse events, serious infections, and malignancies).

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

TNFi discontinuation vs. TNFi continuation for patients with established RA in disease remission

Bibliography: Sullivan MC. 5.6 TNFi discontinuation vs. TNFi continuation in established RA in disease remission.

Outcomes	No of Participants (studies) Follow up	Quality of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects	
				Risk with TNFi continuation	Risk difference with TNFi discontinuation (95% CI)
DAS-28 low disease activity (DAS-28 score < 3.2) (RA disease activity)	605 (2 studies) 12 months	⊕⊕⊕⊖ **MODERATE**[1] due to indirectness, imprecision	**RR 0.68** (0.36 to 1.28)	**856 per 1000**	**274 fewer per 1000** (from 548 fewer to 240 more)
ACR 50 response (RA disease activity)	604 (2 studies) 12 months	⊕⊕⊕⊖ **MODERATE**[1] due to indirectness, imprecision	**RR 0.63** (0.2 to 1.97)	**715 per 1000**	**264 fewer per 1000** (from 572 fewer to 693 more)
Sharp radiographic progression score (higher score indicates more severe disease	351 (1 study)	⊕⊕⊕⊖ **MODERATE**[1]			The mean Sharp radiographic progression score in the intervention groups was

progression)	12 months	due to indirectness, imprecision			**0.2 higher** (11.02 lower to 11.42 higher)
Health Assessment Questionnaire-Disability Index (HAQ-DI) (higher score indicates more severe physical disability)	402 (1 study) 12 months	⊕⊕⊕⊖ **MODERATE**[1] due to indirectness			The mean health assessment questionnaire-disability index (HAQ-DI) in the intervention groups was **0.3 higher** (0.19 to 0.41 higher)
Serious Adverse Events (SAEs)	532 (2 studies) 12 months	⊕⊕⊕⊖ **MODERATE**[1] due to indirectness, imprecision	**RR 0.85** (0.5 to 1.45)	**104 per 1000**	**16 fewer per 1000** (from 52 fewer to 47 more)
Serious Infections	609 (2 studies) 12 months	⊕⊕⊕⊖ **MODERATE**[1] due to indirectness, imprecision	**RR 0.79** (0.3 to 2.11)	**29 per 1000**	**6 fewer per 1000** (from 21 fewer to 33 more)
Malignancy	609 (2 studies) 12 months	⊕⊕⊕⊖ **MODERATE**[1] due to indirectness, imprecision	**RR 0.97** (0.14 to 6.57)	**7 per 1000**	**0 fewer per 1000** (from 6 fewer to 36 more)

*The basis for the **assumed risk** (e.g., the median control group risk across studies) is provided in footnotes. The **corresponding risk** (and its 95% confidence interval) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI).

CI: Confidence interval; **RR:** Risk ratio;

GRADE Working Group grades of evidence
High quality: Further research is very unlikely to change our confidence in the estimate of effect.
Moderate quality: Further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate.
Low quality: Further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate.
Very low quality: We are very uncertain about the estimate.

[1] Indirect evidence: this PICO question concerns patients with RA in remission. The closest evidence available was two RCTs including patients who had low disease activity (DAS-28 < 3.2), though not necessarily in remission (Smolen et al., 2014; Smolen et al., 2013).

This PICO includes two RCTs:	Smolen et al., 2014 [61]; Smolen et al., 2013 [62]

B.34: In patients with established RA and low disease activity (but not remission) who are continuing methotrexate in combination with a biologic or tofacitinib, we strongly recommend continuing non-TNF biologic rather than discontinuing these medications

Voting for this statement was based on the below PICO question:

In patients with established RA with only low disease activity, what is the impact of discontinuing non-TNF biologic therapy vs. continuing non-TNF biologic therapy on symptoms and AEs?

Summary: This PICO was not directly addressed by any studies.

Quality of evidence across all critical outcomes: Very low ⊕⊖⊖⊖. No data were available to address this question. Recommendations were formulated based on the expertise of the voting panel.

B.35: In a patient with established RA and is in remission and continuing MTX, we *conditionally* recommend tapering non-TNF biologic rather than not tapering.

Voting for this statement was based on the below PICO question:

In patients with established RA in disease remission, what is the impact of discontinuing non-TNF biologic therapy vs. continuing non-TNF biologic therapy on symptoms and AEs?

Summary: This PICO was not directly addressed by any studies.

Quality of evidence across all critical outcomes: Very low ⊕⊖⊖⊖. No data were available to address this question. Recommendations were formulated based on the expertise of the voting panel.

B.36: In patients with established RA and low disease activity (but not remission) who are continuing methotrexate in combination with a biologic or tofacitinib, we strongly recommend continuing tofacitinib rather than discontinuing these medications.

Voting for this statement was based on the below PICO question:

In patients with established RA with only low disease activity, what is the impact of discontinuing oral tofacitinib vs. continuing oral tofacitinib on symptoms and AEs?

Summary: This PICO was not directly addressed by any studies.

Quality of evidence across all critical outcomes: Very low ⊕⊖⊖⊖. No data were available to address this question. Recommendations were formulated based on the expertise of the voting panel.

B.37: In a patient with established RA and is in remission and continuing MTX, we *conditionally* recommend tapering tofacitinib rather than not tapering.

Voting for this statement was based on the below PICO question:

In patients with established RA in disease remission, what is the impact of discontinuing oral tofacitinib vs. continuing oral tofacitinib on symptoms and AEs?

Summary: This PICO was not directly addressed by any studies.

Quality of evidence across all critical outcomes: Very low ⊕⊖⊖⊖. No data were available to address this question. Recommendations were formulated based on the expertise of the voting panel.

B.38: In patients with established RA in remission, we also strongly recommend continuing at least a DMARD, TNFi, non-TNF biologic or tofacitinib rather than discontinuing all of these therapies, i.e., we strongly recommend ***not*** discontinuing all therapies in patients with established RA in disease remission.

Voting for this statement was based on the below PICO question:

In patients with established RA in disease remission, what is the impact of discontinuing all therapies vs. continuing at least traditional DMARDs or TNFi or non-TNF biologics or oral tofacitinib on symptoms and AEs?

Summary: This PICO was not directly addressed by any studies.

Quality of evidence across all critical outcomes: Very low ⊕⊖⊖⊖. No data were available to address this question. Recommendations were formulated based on the expertise of the voting panel.

Section C: Safety in patients with congestive heart failure risk

C.1: For patients with established RA, moderate or high disease activity and New York Heart Association (NYHA) class III or IV congestive heart failure (CHF) (Table 1), we *conditionally* recommend using combination DMARD therapy rather than a TNFi.

Voting for this statement was based on the evidence table and summary for the below PICO question:

In patients with established RA with moderate or high disease activity, is it safer to use TNFi therapy or combination DMARD therapy in the presence of CHF NYHA class III or IV?

Summary: This PICO was addressed by three double-blind, placebo-controlled RCTs, two in patients with CHF NYHA class II-IV [63], and another in CHF NYHA patients class III-IV [64]. The evidence therefore addresses this PICO only indirectly, as no traditional DMARD comparison group was included. Pooled analyses for mortality, serious infections, and CHF hospitalization revealed no significant between-group differences, with non-significant trends in favor of placebo in all three groups. Injection site reactions occurred more frequently in those receiving TNFi therapy than in those receiving placebo. One trial found that high dose infliximab therapy (10 mg/kg) was associated with increased risk of death from any cause or hospitalization for heart failure through 28 weeks (hazard ratio 2.84, 95% CI 1.01 to 7.97), while lower dose infliximab (5 mg/kg) was not associated with a significantly increased risk [64].

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

TNFi therapy vs. combination DMARD therapy for patients with established RA with moderate/high disease activity in the presence of CHF NYHA class III or IV

Bibliography: In patients with established RA with moderate/high disease activity, is it safer to use TNFi therapy in the presence of CHF NYHA III or IV vs. combination DMARD therapy?

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 TNFi therapy (95% CI)
Injection site reactions	1360 (2 studies) 6 months	⊕⊕⊕⊖ **MODERATE**[1] due to indirectness, imprecision	**RR 2.25** (0.98 to 5.13)	**65 per 1000**	**81 more per 1000** (from 1 fewer to 267 more)
Mortality	1464 (3 studies) 6 months	⊕⊕⊕⊖ **MODERATE**[2] due to indirectness, imprecision	**RR 1.07** (0.8 to 1.42)	**111 per 1000**	**8 more per 1000** (from 22 fewer to 47 more)
Serious infections	1360 (2 studies) 6 months	⊕⊕⊕⊖ **MODERATE**[1] due to indirectness, imprecision	**RR 1.16** (0.61 to 2.23)	**62 per 1000**	**10 more per 1000** (from 24 fewer to 76 more)
CHF hospitalization	99 (1 study) 6 months	⊕⊕⊕⊖ **LOW**[3] due to indirectness, imprecision	**RR 0.59** (0.15 to 2.33)	**102 per 1000**	**42 fewer per 1000** (from 87 fewer to 136 more)

*The basis for the **assumed risk** (e.g., the median control group risk across studies) is provided in footnotes. The **corresponding risk** (and its 95% confidence interval) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI).

CI: Confidence interval; **RR:** Risk ratio;

GRADE Working Group grades of evidence
High quality: Further research is very unlikely to change our confidence in the estimate of effect.
Moderate quality: Further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate.
Low quality: Further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate.
Very low quality: We are very uncertain about the estimate.

[1] Indirect evidence: This study compares risk with TNFi therapy vs. risk with placebo. Combination DMARD therapy was not examined (Mann et al., 2004).
[2] Indirect evidence: These studies compare risk with TNFi therapy vs. risk with placebo. Combination DMARD therapy was not examined in either study (Mann et al., 2004; Chung et al., 2003).
[3] Indirect evidence: This study compares risk with TNFi therapy vs. risk with placebo. Combination DMARD therapy was not examined in this trial (Mann et al., 2004; Chung et al., 2003).

This PICO includes three RCTs published in two articles:	Mann et al., 2004 [63]; Chung et al., 2003 [64]

C.2: For patients with established RA, moderate or high disease activity and New York Heart Association (NYHA) class III or IV congestive heart failure (CHF) (Table 1), we *conditionally* recommend using combination a non-TNF biologic rather than a TNFi.

Voting for this statement was based on the below PICO question:

In patients with established RA with moderate or high disease activity, is it safer to use TNFi therapy or non-TNF biologic therapy in the presence of CHF NYHA class III or IV?

Summary: This PICO was not directly addressed by any studies.

Quality of evidence across all critical outcomes: Very low ⊕⊖⊖⊖. No data were available to address this question. Recommendations were formulated based on the expertise of the voting panel.

C.3 For patients with established RA, moderate or high disease activity and New York Heart Association (NYHA) class III or IV congestive heart failure (CHF) (Table 1), we *conditionally* recommend using combination tofacitinib rather than a TNFi.

Voting for this statement was based on the evidence table and summary for the below PICO question:

In patients with established RA with moderate or high disease activity, is it safe to use TNFi therapy or oral tofacitinib in the presence of CHF NYHA class III or IV?

Summary: This PICO was not directly addressed by any studies.

Quality of evidence across all critical outcomes: Very low ⊕⊖⊖⊖. No data were available to address this question. Recommendations were formulated based on the expertise of the voting panel.

C.4: If patients with established RA with moderate or high disease activity are treated with a TNFi and their CHF worsens, we *conditionally* recommend switching to combination DMARD therapy rather than a different TNFi.

Voting for this statement was based on the below PICO question:

In patients with established RA with moderate or high disease activity, if the CHF worsened while on TNFi therapy, is it safer to use a different TNFi or combination DMARD therapy?

Summary: This PICO was not directly addressed by any studies.

Quality of evidence across all critical outcomes: Very low ⊕⊖⊖⊖. No data were available to address this question. Recommendations were formulated based on the expertise of the voting panel.

C.5: If patients with established RA with moderate or high disease activity are treated with a TNFi and their CHF worsens, we *conditionally* recommend switching to combination a non-TNF biologic rather than a different TNFi.

Voting for this statement was based on the below PICO question:

In patients with established RA with moderate or high disease activity, if the CHF worsened while on TNFi therapy, is it safer to use a different TNFi or a non-TNF biologic?

Summary: This PICO was not directly addressed by any studies.

Quality of evidence across all critical outcomes: Very low ⊕⊖⊖⊖. No data were available to address this question. Recommendations were formulated based on the expertise of the voting panel.

C.6: If patients with established RA are treated with a TNFi and their CHF worsens, we *conditionally* recommend switching to a tofacitinib rather than a different TNFi.

Voting for this statement was based on the below PICO question:

In patients with established RA with moderate or high disease activity, if the CHF worsened while on TNFi therapy, is it safer to use a different TNFi or oral tofacitinib?

Summary: This PICO was not directly addressed by any studies.

Quality of evidence across all critical outcomes: Very low ⊕⊖⊖⊖. No data were available to address this question. Recommendations were formulated based on the expertise of the voting panel.

Section D: Safety in patients with Hepatitis B

D.1: In patients with established RA with moderate or high disease activity and evidence of chronic hepatitis B infection (hepatitis surface antigen (HbsAg) positive > 6 months), who are receiving effective antiviral treatment, we strongly recommend treating them the same as patients without this condition (DMARD, TNFi, non-TNF biologic or tofacitinib).

Voting for this statement was based on the evidence table and summary for the below PICO question:

In patients with established RA with moderate or high disease activity in the presence of hepatitis B infection (hepatitis surface antigen positive) who are receiving effective antiviral treatment, is it safer to use DMARD or biologic therapy, according to which therapy would be given to a patient *without* evidence of a hepatitis B infection, or use neither DMARD nor biologic therapy?

Quality of evidence across all critical outcomes: Very low ⊕⊖⊖⊖ (Evidence for this PICO is indirect: addresses chronic hepatitis B)

Summary: D.1 was addressed by the American Association for the Study of Liver Diseases' (AASLD) practice guidelines for chronic hepatitis B [65, 66]. The PICOs were also indirectly addressed by four observational studies [67-70] and two case series [71, 72] (Table D).

AASLD Guidelines: Regarding the use of immunosuppressive therapy in hepatitis B carriers, the AASLD's clinical practice guidelines recommend that patients administered immunosuppressive therapy should receive prophylactic antiviral therapy at the onset of treatment, and maintain this prophylaxis for 6 months after the conclusion of treatment [65]. Testing for hepatitis B surface antigen prior to initiation of immunosuppressive treatment is also recommended. The AASLD notes that HBV reactivation is more common in treatment regimens including corticosteroid use. For patients with serum HBV DNA levels > 2,000 IU/ml prior to immunosuppressive therapy, the AASLD recommended continuation of antiviral therapy until therapeutic endpoints for chronic HBV are reached.

RA-specific evidence:

Non-biologic DMARDs: One retrospective, non-comparative study addressed the safety of traditional non-biologic DMARDs in the presence of chronic hepatitis B virus (HBV) infection [67]. Of 20 RA patients included, eight (40%) experienced a viral load increase during the course of the six-year study period. The study authors advocated for periodic monitoring of serum ALT and liver function

tests while using immunosuppressive therapy in the presence of chronic HBV, and concluded that the use of antiviral prophylaxis during immunosuppressive therapy is still controversial.

TNFi therapy: Four studies examined the safety of TNFi therapies in the presence of chronic HBV [68, 70-72]. Across two cohort studies, seven of 23 RA patients with chronic HBV experienced disease reactivation following therapy with TNFi therapy (mean follow-up durations of 12 months and 23 months, respectively) [68, 70]. Two case series examined ALT and AST levels in a total of five RA patients with chronic HBV undergoing TNFi therapy [71, 72]. Neither study reported a significant increase in HBV viral load. All four studies recommended antiviral prophylaxis prior to TNFi therapy in patients with chronic HBV.

Non-TNF biologic therapy: One retrospective study examined the safety of non-TNF biologic therapy, with or without antiviral prophylaxis, in RA patients who were HBV carriers or had chronic HBV [69]. During follow-up for abatacept therapy (treatment duration ranging from 3-33 months), four of eight participants experienced HBV reactivation during the course of abatacept treatment. The four patients who experienced reactivation were the only four who did not receive antiviral prophylaxis prior to non-TNF biologic treatment. The study authors concluded that non-TNF biologic therapy is feasible in patients with RA and chronic HBV if antiviral prophylaxis is given concurrently.

Tofacitinib: No evidence was found regarding the use of tofacitinib in RA patients with chronic HBV.

Table D: Use of Biologics in Patients with Chronic Hepatitis B

Author, year	Study Type	Duration	Population Description	Treatment given to relevant population	Results
Thong, 2007[67]	Retrospective, non-comparative study	6 years	TOTAL: 38 chronic hepatitis B patients with rheumatic diseases. PICO: 20 chronic HBV patients with RA	Traditional DMARD therapy	ALT/AST elevation: 20 (52.6%) patients developed ALT >2x ULN. Viral reactivation: 7 patients in total experienced HBV reactivation. 1/7 patients treated for HBV reactivation was confirmed as having RA. Viral load increase: 8 (40%) patients experienced HBV DNA elevation. 6 (30%) were negative for HBV DNA, levels were not tested in 6 (30%) patients. RA Efficacy: N/A
Lan, 2011[68]	Retrospective study	12 months	TOTAL: 88 RA HBcAb + patients. PICO: 18 (20.5%) RA patients with chronic HBV	TNFi (+/- antiviral prophylaxis)	ALT/AST elevation: N/A Viral reactivation: 5/18 chronic HBV patients experienced reactivation. Observed a higher risk for reactivation with high baseline viral load. Viral load increase: N/A RA Efficacy: N/A
Kim, 2012[69]	Retrospective study	Min 3 months, Max 33 months	TOTAL: 8 RA patients with HBV (6 inactive carriers) PICO: 2 RA patients with chronic HBV	Abatacept (+/- antiviral prophylaxis)	ALT/AST elevation: Decline in both ALT and AST in patients receiving Abatacept and prophylaxis. Viral reactivation: 4 patients experienced reactivation. Viral load increase: N/A RA Efficacy: Statistically significant improvement in DAS-28.

Author, year	Study Type	Duration	Population Description	Treatment given to relevant population	Results
Tamori, 2011[70]	Prospective, non-comparative study	23 months (mean)	TOTAL: 50 RA patients who were Anti-HBc positive. PICO: 5 RA patients with chronic HBV	TNFi (+/- antiviral prophylaxis)	ALT/AST elevation: N/A Viral reactivation: 2/5 HBsAg positive patients experienced reactivation of HBV. Prophylactic antiviral treatment recommended during TNFi/MTX therapy Viral load increase: N/A RA Efficacy: N/A
Roux, 2006[71]	Case series	Min 3 months, Max 39 months	TOTAL: 6 cases of patients with rheumatic diseases and chronic HBV or HCV PICO: 2 RA patients with chronic HBV	TNFi (+/- antiviral prophylaxis)	ALT/AST elevation: ALT/AST remained normal for both patients of interest. Viral reactivation: N/A Viral load increase: In one patient, viral load remained normal. In another (not taking antiviral), viral load decreased. RA Efficacy: N/A
Li, 2009[72]	Case series	Min 3 months, Max 60 months	TOTAL: 11 cases of RA patients with chronic HBV or HCV PICO: 3 RA patients with chronic HBV	TNFi	ALT/AST elevation: 1/3 patients experienced a transient rise in ALT during TNFi treatment (returned to normal within 24 hours). All patients' ALT/AST within 1x ULN at the end of the study period. Viral reactivation: N/A Viral load increase: No chronic HBV patients experienced a significant increase in viral load, but one patient experienced a decrease over the course of the study period. RA Efficacy: N/A

Section E: Safety in patients with Hepatitis C

PICO E.1: For patients with established RA with moderate or high disease activity and evidence of chronic hepatitis C virus (HCV) infection, who are receiving effective antiviral treatment, we *conditionally* recommend treating them the same as the patients without this condition (DMARD, TNFi, non-TNF biologic or tofacitinib).

E.2: If the same patient is not requiring or receiving antiviral treatment for their hepatitis C, we *conditionally* recommend using DMARD therapy rather than TNFi.

Voting for these statements was based on the summary and evidence table below:

Summary: E.1 and E.2 were indirectly addressed by four studies evaluating TNFi safety in patients with hepatitis C virus (HCV) who were receiving immunosuppression for a variety of medical conditions (Table E). One retrospective review examined 216 HCV-positive patients who had received TNFi immunosuppressive therapy for various conditions in the fields of rheumatology, dermatology, and gastroenterology [73]. Additionally, a placebo-controlled RCT found that etanercept was safe and effective as an adjuvant to interferon and ribavirin in the treatment of chronic HCV [74]. These studies, along with two case series (one in HCV patients with rheumatological manifestations and one in patients with inflammatory bowel disease) [75, 76], each concluded that short-term TNFi biologic treatment is safe in patients with chronic HCV. The presence or absence of concurrent antiviral therapy varied from patient to patient in each of these studies. One long-term follow-up observational study followed 32 patients with HCV-related vasculitis [77]. The study compared 20 patients receiving rituximab and interferon-alpha antiviral therapy with 12 patients receiving rituximab alone due to antiviral-intolerance. Clinical and immunologic relapses were observed in 22% and 34% of patients, respectively, and all relapses were related to the absence of antiviral therapy. HCV viral load and ALT levels both decreased significantly in the antiviral group, while neither decreased significantly (and ALT levels slightly increased) in the rituximab-only group.

A clinical practice guideline on the treatment of HCV in patients with psoriasis also concluded that that TNFi therapy was safe in the short-term in individuals with chronic HCV, based on evidence from a number of case series and case reports [78]. The guideline concluded that inadequate evidence is currently available to assess the long-term safety of TNFi use in individuals with HCV.

RA-specific evidence:

Within RA patients, one open-label RCT [79], three retrospective cohort studies [72, 80, 81], and three case series [82-84] indirectly addressed these PICOs (Table E).

Non-biologic DMARDs: One small open-label RCT compared MTX monotherapy, etanercept monotherapy, and etanercept + MTX combination therapy in 29 patients with active RA and mild hepatitis C virus (HCV) infection [79]. AST and ALT levels did not change significantly in any of the treatment arms during 54-week follow-up, nor did HCV viral load. DAS44 and HAQ scores were significantly reduced from baseline across all treatment groups. The study authors concluded that patients with RA and chronic, mild HCV can be successfully treated with MTX and etanercept without increasing hepatotoxicity or HCV activity.

TNFi therapy: One retrospective study examined the safety of TNFi treatment in 216 patients with HCV [73], over a total of 260 cumulative patient-years of treatment. Of these patients, only three experienced HCV recrudescence. The study authors concluded that TNFi treatment is safe in the short-term for patients with HCV. The existing data was deemed insufficient to establish long-term safety. One double-blind RCT compared etanercept with placebo in addition to interferon and ribavirin for patients with chronic HCV.

Seven studies examined TNFi therapy in patients with RA and HCV. One small open-label RCT (n=29; described above under Non-biologic DMARDs) supported the safety and efficacy of etanercept with or without methotrexate therapy in patients with RA and mild chronic HCV [79]. Three cohort studies (total n=63) also examined use of TNFi therapy in RA patients with HCV with varying viral load [72, 80, 81]. Across these studies, one patient experienced a worsening HCV viral load, and two other patients who had a greater than tenfold variation between their maximum and minimum HCV levels experienced their highest level during TNFi therapy. In three case series examining RA patients with HCV receiving TNFi therapy (total n=16) [82-84], two series found no discernible pattern in HCV viral load, while one series observed viral load increase in two of three participants [84]. Four of five studies that examined TNFi efficacy reported benefits for RA disease activity [79-81, 83], while one case series described two of five patients discontinuing therapy due to lack of efficacy [82].

Non-TNF biologic therapy: No evidence was found regarding the use of non-TNF biologic therapy in RA patients with HCV.

Tofacitinib: No evidence was found regarding the use of tofacitinib in RA patients with HCV.

Table E: Use of Biologics in Patients with Hepatitis C and a High or Low Viral Load

Author, year	Study Type	Duration	Population Description	Treatment given to relevant population	Results
Pompili et al., 2013 [73]	Retrospective study	14 months (median) 260 cumulative patient-years	TOTAL/PICO: 216 HCV-positive individuals treated with one or more TNFi (derived from small observational studies in rheumatology, dermatology, & gastroenterology)	TNFis	Among 216 patients with HCV treated with TNFis, only three instances of drug withdrawal due to liver toxicity were observed. AST/ALT elevation: Five patients experienced elevation in AST/ALT serum level > 3 times the upper limit of normal. Viral load increase: Nine patients experienced an elevation in HCV-RNA (>1 log above baselines).
Lin et al., 2013 [75]	Case series	27 months (mean)	TOTAL: 37 patients with HCV & inflammatory bowel disease (IBD) PICO: 5 of these patients received TNFi	4 received etanercept, 1 received adalimumab	ALT/AST/Other liver enzyme elevation: IBD treatment with TNFi resulted in no hepatic flares among 5 patients. Mean viral load pre-TNFi (5.3 MM IU/ml) Mean viral load post-TNFi (3.8 MM IU/ml)
Marotte et al., 2007 [76]	Open prospective study	3 months	TOTAL/PICO: 9 patients with HCV & rheumatological manifestations (5 had positive viral load, 4 negative at entry)	Etanercept	Among five patients with a detectable HCV viral load, no variation in viral load was observed during three months of etanercept treatment. In the four patients with no detectable viral load at baseline, no reactivation of viral load occurred. Serum AST, ALT, & PT tests did not differ significantly. Six of nine patients had received previous HCV therapy with interferon-alpha or ribavirin. Efficacy: the one patient meeting ACR RA diagnosis experienced an ACR20 response at three months.

Author, year	Study Type	Duration	Population Description	Treatment given to relevant population	Results
Zein et al., 2005 [74]	RCT	72 weeks	TOTAL/PICO: 50 patients with detectable HCV-RNA, elevated serum ALT, & a liver biopsy specimen indicating chronic HCV infection	(Etanercept or placebo) + Interferon, & ribavirin	At 24 weeks, HCV RNA was absent in 63% of etanercept group vs. 32% of placebo group (p=0.04). At 72 weeks, HCV RNA absent in 42% of etanercept group vs. 32% of placebo group (non-significant). Most AEs were more frequent in the placebo group, with the exception of hemotologic, musculoskeletal, & genitourinary AEs (between-group differences were not statistically significant).
Terrier et al., 2009 [77]	Prospective observational cohort	24 months	TOTAL/PICO: 32 patients with HCV-related vasculitis (with or without antiviral intolerance)	Rituximab + interferon or Rituximab only	At 24 months, HCV load showed significant decrease from 5.8 ± 0.5 log copies/mL at baseline to 2.3 ± 2.7 log copies/mL in the antiviral patients ($p<0.001$). In patients receiving rituximab alone, HCV load was 6.1 ± 0.8 at baseline and 6.0 ± 0.5 at 24 months (p not significant). From baseline to 24 months, ALT levels decreased from 1.3 ± 0.7-fold the upper normal limit to 1.1 ± 0.4 ULN in the antiviral patients, while ALT increased from 1.5 ± 1.4 to 1.7 ± 1.4-fold ULN in the rituximab-only patients.
Iannone, 2014[79]	Open-label, randomized trial	54 weeks	TOTAL/PICO: 29 patients with RA and mild Hepatitis C infection (viral load unspecified) receiving TNFi+/- DMARDs	Etanercept (+/- MTX) or MTX	ALT/AST/Other liver enzyme elevation: No significant differences in ALT, ALP, bilirubin, or albumin levels between groups. Worsening of infectious symptoms/adverse events (AEs): Only one AE, unrelated to treatment, occurred. No significant changes in disease activity. Viral load increase: N/A RA Efficacy: DAS44 and HAQ showed significant improvement over time in all groups.

Author, year	Study Type	Duration	Population Description	Treatment given to relevant population	Results
Ferri, 2008[80]	Retrospective study	20 months (mean)	TOTAL/PICO: 31 RA patients who are positive for Hepatitis C (viral load unspecified)	TNFis	ALT/AST/Other liver enzyme elevation: Liver enzymes remained stable for most patients throughout study duration. 6 patients discontinued between 7-40 months due to ALT levels remaining consistently 4x above ULN. Worsening of infectious symptoms/adverse events (AEs): 3 patients experienced a significant increase in viremia. Viral load increase: HCV viral load remained stable or reduced in the majority of patients. RA Efficacy: Significant improvement in DAS28 was observed even after only 3 months of treatment.
Peterson, 2003[81]	Retrospective study/Prospective study	34 months/4 months	TOTAL/PICO: 16 (retrospective) and 8 (prospective) patients with RA and chronic Hepatitis C (moderate/high viral load at baseline: mean log VL= 6.476).	TNFis	Liver enzyme elevation: No significant changes in ALT, AST, or albumin. Worsening of infectious symptoms/adverse events (AEs): N/A Viral load increase: 7/8 (prospective) patients experienced a decrease in viral load. 10/22 patients with repeated HCV measurement had a 1-5X difference between min & max viral load. 3/5 patients with a >10X difference experienced their maximum value while taking an TNFi. RA Efficacy: Efficacy data only available for patients participating in prospective study. ACR20 was achieved in 7 of 8 patients, ACR50 in 5, & ACR70 in 3.
Li, 2009[72]	Retrospective study	20 months (mean)	TOTAL: 11 RA patients with Hepatitis C or B receiving TNFis. PICO: 8 RA patients with Hepatitis C (baseline viral load varied) receiving TNFis	TNFis	ALT/AST/Other liver enzyme elevation: In all HCV patients, AST and ALT levels remained within 1x ULN at the study's conclusion. On patient experienced a permanent rise in both AST and ALT. Two patients with baseline elevation in ALT/AST at baseline experienced a mild decline at follow up. Worsening of infectious symptoms/adverse events (AEs): N/A Viral load increase: Only one patient experienced a significant rise in viral load. RA Efficacy: N/A

Author, year	Study Type	Duration	Population Description	Treatment given to relevant population	Results
Parke, 2004[82]	Case series	41 months (mean)	TOTAL/PICO: 5 RA patients with Hepatitis C (viral load not specified)	TNFis (+/- DMARDs)	ALT/AST/Other liver enzyme elevation: No significant changes in ALT occurred throughout. Worsening of infectious symptoms/adverse events (AEs): No patients experienced severe AEs related to Hepatitis C. Viral load increase: Trends in viral load were variable. No consistent pattern between patients. RA Efficacy: Two patients discontinued TNFi due to lack of efficacy.
Cavazzana, 2008[83]	Case series	14 months (median)	TOTAL: 6 patients with chronic HCV (viral load not specified) and rheumatic diseases receiving TNFis after combo DMARD failure. PICO: 4 RA patients with Hepatitis C receiving TNFis after DMARD failure.	Etanercept	ALT/AST/Other liver enzyme elevation: Liver enzymes remained stable throughout study period. Worsening of infectious symptoms/adverse events (AEs): No patient experienced a worsening of HCV symptoms. Viral load increase: Viral load remained stable throughout study duration. RA Efficacy: Significant improvement of DAS28 during ETN therapy. HAQ and ESR remained stable.
Cansu, 2008[84]	Case series	21 months (median)	TOTAL: 5 patients with rheumatic diseases and Hepatitis C or Hepatitis B receiving TNFis after combo DMARD failure. PICO: 3 RA patients with HCV (moderate/high viral load in one patient, other two patients not specified) receiving TNFis after combo DMARD failure.	TNFis	ALT/AST/Other liver enzyme elevation: Fluctuations in liver enzymes were observed, but significant changes in liver enzyme levels were only observed in one patient. Worsening of infectious symptoms/adverse events (AEs): Hepatitis C reactivation was experienced by two patients while receiving ETN. Viral load increase: Two patients experienced an increase in viral load, while one experienced a decrease in viral load during the study period, Authors concluded that ETN+DMARD without antiviral prophylaxis might result in an increased viral load. RA Efficacy: N/A

Section F: Safety in patients with skin cancer risk

F.1: In patients with established RA and moderate or high disease activity and a history of previously treated or untreated skin cancer (melanoma), we *conditionally* recommend the use of DMARD therapy over biologics.

Voting for this statement was based on the evidence table and summaries for the below PICO questions:

In patients with established RA with moderate or high disease activity, is it safer to use TNFi therapy or combination DMARD therapy in the presence of previously treated or untreated melanoma skin cancer?

Summary: This PICO was addressed by two retrospective cohort studies including patients with rheumatoid arthritis who have had a prior malignancy [85, 86]. One study examined 54 RA patients with a history of TNFi treatment and prior melanoma skin cancer. These patients were compared with 295 non-biologic treated patients with a history of melanoma [85]. Three vs. 10 participants in the TNFi and non-TNFi groups developed a new melanoma during follow-up (hazard ratio 3.2, 95% CI 0.8 to 13.1). A second study included 27 patients who had previously had melanoma skin cancer [86]. Among 17 patients who had previously received TNFi therapy, three (18%) developed a subsequent malignancy (the study did not specify whether this malignancy was a melanoma). Among 10 patients who had received only traditional DMARD therapy, none (0%) developed subsequent malignancies. This between-group difference was not statistically significant. The authors of the second study concluded that the current manner of prescribing TNFis to those with prior malignancy in the UK is not resulting in an increased risk of incident malignancy, but that this finding should not indicate that it is safe to treat all RA patients with prior malignancy with TNFi therapy.

Quality of evidence across all critical outcomes: Very low ⊕⊖⊖⊖

TNFi therapy vs. combination DMARD therapy for patients with established RA with moderate/high disease activity in presence of previously treated or untreated melanoma skin cancer

Bibliography: Safety of TNFi therapy vs. combination DMARD therapy in patients with established RA with moderate/high disease activity in the presence of previously treated or untreated melanoma skin cancer.

Outcomes	No of Participants (studies) Follow up	Quality of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects	
				Risk with Combination DMARD therapy	Risk difference with TNFi therapy (95% CI)
Incident malignancies	27 (1 study) 1	⊕⊖⊖⊖ **VERY LOW**[1] due to imprecision	**RR 4.28** (0.24 to 75.2)	**0 per 1000**	**-**

*The basis for the **assumed risk** (e.g., the median control group risk across studies) is provided in footnotes. The **corresponding risk** (and its 95% confidence interval) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI).

CI: Confidence interval; **RR:** Risk ratio;

GRADE Working Group grades of evidence
High quality: Further research is very unlikely to change our confidence in the estimate of effect.
Moderate quality: Further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate.
Low quality: Further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate.
Very low quality: We are very uncertain about the estimate.

[1] Wide confidence intervals around risk estimate due to very small sample size (Dixon et al., 2010).

This PICO includes one retrospective cohort study:	Raaschou et al., 2013 [85]; Dixon et al., 2010 [86]

In patients with <u>established</u> RA with <u>moderate or high disease</u> activity, is it safer to use <u>TNFi therapy</u> or <u>non-TNF biologic therapy</u> in the presence of previously treated or untreated melanoma skin cancer?

<u>Summary</u>: This PICO was not directly addressed by any studies.

<u>Quality of evidence across all critical outcomes</u>: Very low ⊕⊖⊖⊖. No data were available to address this question. Recommendations were formulated based on the expertise of the voting panel.

F.2: In patients with established RA and moderate or high disease activity and a history of previously treated or untreated skin cancer (melanoma), we *conditionally* recommend the use of DMARD therapy over tofacitinib.

Voting for this statement was based on the below PICO question:

In patients with established RA with moderate or high disease activity and a history of previously treated or untreated melanoma skin cancer, is it safer to use traditional DMARD therapy or tofacinitib therapy?

Voting for this PICO was based on the evidence for F.1.

F.3: In patients with established RA and moderate or high disease activity and a history of previously treated or untreated skin cancer (non-melanoma), we *conditionally* recommend the use of DMARD therapy over biologics.

Voting for this statement was based on the evidence tables and summaries for the below PICO questions:

In patients with established RA with moderate or high disease activity, is it safer to use TNFi therapy or combination DMARD therapy in the presence of previously treated or untreated non-melanoma skin cancer?

Summary: This PICO was addressed by one retrospective cohort study of patients with rheumatoid arthritis who have had a prior malignancy [87]. The study examines the association between TNFi therapy and incident non-melanoma skin cancer. Participants taking TNFi therapy may or may not have received concomitant traditional DMARD therapy. Use of TNFi therapy was associated with a slight but non-significant increase in risk of developing non-melanoma skin cancer (hazard ratio: 1.24, p=0.089). Associations between combination DMARD therapy and non-melanoma skin cancer incidence were not examined.

Quality of evidence across all critical outcomes: Very low ⊕⊖⊖⊖

TNFi therapy vs. combination DMARD therapy for patients with established RA with moderate/high disease activity in the presence of previously treated or untreated non-melanoma skin cancer

Bibliography: Safety of TNFi therapy vs. combination DMARD therapy in patients with established RA with moderate/high disease activity in the presence of previously treated or untreated non-melanoma skin cancer.

Outcomes	No of Participants (studies) Follow up	Quality of the evidence (GRADE)	Hazard ratio (p-value)	Anticipated absolute effects	
				Risk with Combination DMARD therapy	Risk difference with TNFi therapy (95% CI)
Incident non-melanoma skin cancer	15789 (1 study)	⊕⊖⊖⊖ **VERY LOW**[1] due to indirectness	1.24 (p=0.089)		--

*The basis for the **assumed risk** (e.g., the median control group risk across studies) is provided in footnotes. The **corresponding risk** (and its 95% confidence interval) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI).

CI: Confidence interval;

GRADE Working Group grades of evidence

High quality: Further research is very unlikely to change our confidence in the estimate of effect.
Moderate quality: Further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate.
Low quality: Further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate.
Very low quality: We are very uncertain about the estimate.

[1] Indirect evidence: this study examines the association between TNFi therapy and non-melanoma skin cancer incidence (with or without concomitant DMARD therapy). The study does not examine the association between DMARD therapy alone and skin cancer (Chakravarty et al., 2005).

This PICO includes one retrospective cohort study:	Chakravarty et al., 2005 [87]

In patients with <u>established</u> RA with <u>moderate or high disease</u> activity, is it safer to use <u>TNFi therapy</u> or <u>non-TNF biologic therapy</u> in the presence of previously treated or untreated non-melanoma skin cancer?

<u>Summary</u>: This PICO was not directly addressed by any studies.

<u>Quality of evidence across all critical outcomes</u>: Very low ⊕⊖⊖⊖. No data were available to address this question. Recommendations were formulated based on the expertise of the voting panel.

F.4: In patients with established RA and moderate or high disease activity and a history of previously treated or untreated skin cancer (non-melanoma), we *conditionally* recommend the use of DMARD therapy over tofacitinib.

Voting for this statement was based on the evidence table and summary for the below PICO question:

In patients with established RA with moderate or high disease activity and a history of previously treated or untreated non-melanoma skin cancer, is it safer to use traditional DMARD therapy or tofacitinib therapy?

Quality of evidence across all critical outcomes: Very low ⊕⊖⊖⊖. No data were available to address this question. Recommendations were formulated based on the expertise of the voting panel.

Section G: Safety in patients with lymphoproliferative disorder risk

G.1: In patients with established RA with moderate or high disease activity and a history of a previously treated lymphoproliferative disorder, we strongly recommend using rituximab rather than TNFi.

Voting for this statement was based on the evidence for the below PICO question, as well as on the expertise of the voting panel:

In patients with established RA with moderate or high disease activity, is it safer to use TNFi therapy or non-TNF biologic therapy in the presence of previously treated lymphoproliferative disorder?

Summary: This PICO was not directly addressed by any studies.

Quality of evidence across all critical outcomes: Very low ⊕⊖⊖⊖. No data were available to address this question. Recommendations were formulated based on the expertise of the voting panel.

G.2: In patients with established RA with moderate or high disease activity and history of a previously treated lymphoproliferative disorder, we conditionally recommend using combination DMARD therapy over TNFi.

Voting for this statement was based on the evidence table and summary for the below PICO question:

In patients with established RA with moderate or high disease activity, is it safer to use TNFi therapy or combination DMARD therapy in the presence of previously treated lymphoproliferative disorder?

Summary: This PICO was addressed by two observational studies. One prospective cohort study examined patients with rheumatoid arthritis who had had a prior malignancy [86]. The study compared patients who had received TNFi therapy with patients who had received only traditional DMARD therapy. Among 24 patients who had previously treated lymphoproliferative disorder (LPD), no subsequent malignancy incidence was observed in either those receiving TNFi or traditional DMARD therapy. Another case-control study examined clinical features of patients who were diagnosed with LPD during MTX therapy and discontinued treatment, compared with patients who were not diagnosed with an LPD (N= 125) during MTX therapy and continued to receive MTX [88]. Multivariate analysis of risk factors revealed that mean MTX dosage was significantly different between the two groups after adjusting for age, RA duration, and functional class (P=0.001). The study concluded that mean MTX dosage was an independent risk factor regarding MTX-LPD onset in RA patients. Results suggest that a higher MTX dose may promote LPD onset in RA patients.

Quality of evidence across all critical outcomes: Very low ⊕⊖⊖⊖

TNFi-biologic therapy vs. combination DMARD therapy for patients with established RA with moderate/high disease activity in presence of previously treated lymphoproliferative disorder

Bibliography: Safety of TNFi therapy vs. combination DMARD therapy in patients with established RA and moderate/high disease activity in the presence of previously treated lymphoproliferative disorder.

Outcomes	No of Participants (studies) Follow up	Quality of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects	
				Risk with Combination DMARD therapy	Risk difference with TNFi-biologic therapy (95% CI)
Incident malignancies	24 (1 study)	⨁⊖⊖⊖ **VERY LOW**[1] due to imprecision	Not estimable	No LPD incidence observed	No LPD incidence observed

*The basis for the **assumed risk** (e.g., the median control group risk across studies) is provided in footnotes. The **corresponding risk** (and its 95% confidence interval) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI).

CI: Confidence interval;

GRADE Working Group grades of evidence
High quality: Further research is very unlikely to change our confidence in the estimate of effect.
Moderate quality: Further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate.
Low quality: Further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate.
Very low quality: We are very uncertain about the estimate.

[1] Imprecise estimate due to small sample size (Dixon et al., 2010).

This PICO includes one retrospective cohort study:	Kameda et al., 2014 [88]; Dixon et al., 2010 [86]

G.3: In patients with established RA with moderate or high disease activity and a history of a previously treated lymphoproliferative disorder, we *conditionally* recommend using abatacept rather than TNFi.

Voting for G.3 was based in part on the evidence for G.1 and G.2, as well as on the expertise of the voting panel.

G.4: In patients with established RA with moderate or high disease activity and a history of a previously treated lymphoproliferative disorder, we *conditionally* recommend using tocilizumab rather than TNFi.

Voting for G.4 was based in part on the evidence for G.1 and G.2, as well as on the expertise of the voting panel.

Section H: Safety in patients with solid organ cancer risk

H.1: In patients with established RA with moderate or high disease activity and previously appropriately treated solid organ cancer, we *conditionally* recommend that they be treated for RA just as one would treat an RA patient without a history of solid organ cancer

Voting for this statement was based on the evidence table and summary for the below PICO question:

In patients with established RA with moderate or high disease activity, is it safer to use TNFi therapy or combination DMARD therapy in the presence of previously treated solid organ cancer?

Summary: This PICO was addressed by two retrospective cohort studies of patients with rheumatoid arthritis who have had a prior malignancy [86]. One study compared patients who had received TNFi therapy with patients who had received only traditional DMARD therapy. Among 243 patients with previously treated solid organ cancer, the incidence of malignancies was not statistically significantly different between patients receiving TNFi vs. traditional DMARD therapy. A second study examined 143 RA patients with breast cancer prior to TNFi therapy (median 9.4 years prior to TNFi treatment/start of follow-up) [89]. Over a median followup of 4.9 years, 9 TNFi-treated patients developed breast cancer recurrence (crude incidence rate 15/1000 person-years) compared with 9 among 120 disease-matched biologic-naïve patients (16/1000 person-years). The adjusted hazard ratio for those receiving TNFi therapy was 1.1 (95% CI: 0.4 to 2.8).

Quality of evidence across all critical outcomes: Very low ⊕⊖⊖⊖

TNFi therapy vs. combination DMARD therapy for patients with established RA with moderate/high disease activity in the presence of previously treated solid organ cancer

Bibliography: Safety of TNFi therapy vs. combination DMARD therapy in patients with established RA with moderate/high disease activity in the presence of previously treated solid organ cancer.

Outcomes	No of Participants (studies) Follow up	Quality of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects	
				Risk with Combination DMARD therapy	Risk difference with TNFi therapy (95% CI)
Incident malignancies	243 (1 study)	⊕⊖⊖⊖ **VERY LOW**[1] due to imprecision	**RR 0.58** (0.23 to 1.45)	**94 per 1000**	**39 fewer per 1000** (from 72 fewer to 42 more)

*The basis for the **assumed risk** (e.g., the median control group risk across studies) is provided in footnotes. The **corresponding risk** (and its 95% confidence interval) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI).

CI: Confidence interval; **RR:** Risk ratio;

GRADE Working Group grades of evidence
High quality: Further research is very unlikely to change our confidence in the estimate of effect.
Moderate quality: Further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate.
Low quality: Further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate.
Very low quality: We are very uncertain about the estimate.

[1] Wide confidence intervals around risk estimate due to small sample size (Dixon et al., 2010).

This PICO includes one retrospective cohort study:	Dixon et al., 2010 [86]; Raaschou et al., 2014 [89]

In patients with <u>established</u> RA with <u>moderate or high disease</u> activity, is it safer to use <u>TNFi therapy</u> or <u>non-TNF biologic therapy</u> in the presence of previously treated solid organ cancer?

<u>Summary</u>: This PICO was not directly addressed by any studies.

<u>Quality of evidence across all critical outcomes</u>: Very low ⊕⊖⊖⊖. No data were available to address this question.

In patients with <u>established</u> RA with <u>moderate or high disease</u> activity, is it safer to use <u>TNFi therapy</u> <u>or</u> <u>oral tofacitinib</u> in the presence of previously treated solid organ cancer?

<u>Summary</u>: This PICO was not directly addressed by any studies.

<u>Quality of evidence across all critical outcomes</u>: Very low ⊕⊖⊖⊖. No data were available to address this question.

Section I: Safety in patients with serious infection risk

I.1: For patients with established RA with moderate or high disease activity and previous serious infection(s), we *conditionally* recommend treatment with combination DMARDs rather than TNFi.

Voting for this statement was based on the summary and evidence table below:

Summary: The safety of RA drug therapy in the presence of previous serious infections (I.1 and I.2) was addressed by eight observational studies (Table I) [90-97]. One large retrospective cohort study followed 12,933 RA patients hospitalized while receiving TNFi treatment and examined risk of infection during subsequent treatment [90]. Relative to patients who restarted their previous TNFi agent following hospitalized infections, patients who switched to a non-TNF biologic exhibited lower risk of subsequent hospitalized infections and those who switched to a different TNFi therapy had a greater risk of subsequent infections. Among the TNFi agents studied, infliximab was associated with the highest risk of infections, followed by adalimumab. Abatacept was associated with the lowest risk of subsequent infection among the therapies examined. Two studies examined the safety of non-TNF biologic therapy (both rituximab), revealing no recurrence of serious infections among 10 patients [91, 92]. In four cohort studies [93-95, 97] and one case series [96] examining infection recurrence among patients receiving TNFi therapy, two of 114 previously-infected patients experienced active tuberculosis. No evidence was available regarding infection risk among patients receiving oral tofacitinib.

Quality of evidence across all critical outcomes: Very low ⊕⊖⊖⊖

Table I: Use of Biologics in Patients with History of Serious Infections

Author, year	Study Type	Duration	Population Description	Treatment	Results
Yun, 2014 [90]	Retrospective observational cohort		Total: 12,933 RA patients hospitalized while receiving TNFi treatment (including etanercept, adalimumab, infliximab, certolizumab, golimumab)	Subsequent treatment (person-years of follow-up): Same TNFi (7067) Abatacept (333) Rituximab (133) Different TNFi (273)	Patients experienced 2,666 subsequent hospitalized infection events. *Adjusted hazard ratios by treatment-class*: Switched to a non-TNF biologic: HR: 0.86 (95%CI: 0.72 to 1.03) Switched to a different TNFi: HR: 1.10 (95%CI: 0.89 to 1.35) Restarted the same anti-TNF: 1.0 (ref) *Adjusted hazard ratios by drug therapy*: Abatacept 0.80 (0.64 to 0.99) (p=0.048) Rituximab 0.87 (0.63 to 1.20) Etanercept 0.83 (0.72 to 0.97) (p=0.013) Adalimumab 0.92 (0.79 to 1.09) Infliximab 1.0 (ref) RA Efficacy: N/A
Toussirot, 2010[91]	Retrospective study	N/A	TOTAL/PICO: 30 RA patients with a history of serious infections (21/30 had received prior TNFi therapy, and all 21 had experienced SI during TNFi treatment)	Rituximab (+/- DMARDs)	Infectious adverse event (AE): 6 patients experienced an infectious episode requiring admission after RTX therapy. Reactivation of prior serious infection: N/A RA Efficacy: N/A
Xanthouli, 2012[92]	Retrospective study	16 months (mean)	TOTAL/PICO: 32 RA patients with history of serious infections (All patients had prior TNFi therapy; 50% had discontinued due to serious infections as a result of TNFi therapy)	Rituximab (+/- DMARDs)	Infectious adverse event (AE): 4 patients experienced a serious infection during RTX treatment. Observed rate of 9/5 infections/100 patient years. Reactivation of prior serious infection: No relapse of TB in patients with TB history. Recommended prophylaxis had been received prior to treatment. RA Efficacy: Treatment with RTX was effective in 17/33 (51%) patients.
Denis, 2008[93]	Retrospective study	42.7 months (mean)	TOTAL: 21 patients who discontinued TNFi therapy due to TB as an adverse event. PICO: 14 patients with RA who discontinued TNFi therapy due to TB as an adverse event. 6 patients who recommenced TNFis after TB was resolved are	Infliximab (+/- DMARD)	Infectious adverse event (AE): 6 patients experienced an infectious episode requiring admission after RTX therapy. Reactivation of prior serious infection: N/A RA Efficacy: Subjective quality of life improved.

Author, year	Study Type	Duration	Population Description	Treatment	Results
			of particular interest (RA not specified).		
Aggarwal, 2009[94]	Retrospective study	24.6 months (mean)	TOTAL: 84 patients who had a positive PPD test and were at high risk for TB who were being treated with etanercept PICO: 58 patients with RA (69%) who were receiving treatment with ETN, had a positive PPD and were at high risk for TB	Etanercept	Infectious adverse event (AE): N/A Reactivation of prior serious infection: In spite of poor adherence to prophylactic regimen, 77% of patients had normal chest imaging results throughout the observation period. No patients experienced active TB. RA Efficacy: N/A
Jo, 2013[95]	Retrospective study	31.5 months (median)	TOTAL: 101 patients with rheumatic disorders and a history of TB (intestinal or other) receiving TNFis. PICO: 27 (26.7%) patients with RA with a history of non-intestinal TB receiving TNFis	TNFis (11 received LTBI treatment as well)	Infectious adverse event (AE): N/A Reactivation of prior serious infection: One case of TB developed during 297 patient years of follow up. Incidence rate of 336 per 100,000 patient years. Incidence rate was deemed acceptable. RA Efficacy: N/A
Cepeda, 2008[96]	Case series	28.1 months (mean)	TOTAL: 8 HIV positive patients with rheumatic diseases receiving treatment with TNFis. 2 patients had history of TB and received prophylaxis. PICO: 2 HIV positive patients with RA receiving treatment with TNFis.	TNFis (+/- various prophylactic measures)	Infectious adverse event (AE): N/A Reactivation of prior serious infection: No HIV-related adverse events occurred. One patient temporarily discontinued TNFi due to a substantial increase in viral load. Patients with TB history did not experience active TB during study period. RA Efficacy: N/A
Nobre, 2012[97]	Prospective observational cohort	3 years	TOTAL: 157 patients with rheumatic diseases (57.3% RA) being treated with IFX. PICO: 21 (13.4%) patients with LTBI (positive PPD skin test)	Infliximab (+/- DMARDs)	Infectious adverse event (AE): N/A Reactivation of prior serious infection: 3/157 patients developed active TB during the study period. Among the 21 with a prior positive PPD test, 1 patient developed active TB 11 months after isoniazid prophylaxis. RA Efficacy: N/A

I.2: For patients with established RA with moderate or high disease activity and previous serious infection(s), we *conditionally* recommend treatment with abatacept rather than TNFi.

Voting for I.2 was based on the evidence for I.1 (see table and summary above).

Section J: Live Vaccine—Immunization with Herpes Zoster Vaccine

J.1: In early or established RA patients aged 50 and over, we *conditionally* recommend giving the herpes zoster vaccine before the patient receives biologic therapy or tofacitinib for their RA.

Voting for J.1 was based on the summary and evidence tables below:

Summary: J.1 was addressed by two retrospective cohort study that included patients with a variety of immune-mediated diseases (63% and had RA) [98, 99]. One study of 463,541 Medicare beneficiaries (age 60+) examined associations between RA drug therapies and herpes zoster (HZ) incidence following HZ vaccination (Table J1) [98]. Patients receiving TNFi therapy were more likely than patients taking non-biologic DMARDs to develop HZ. An analysis of HZ incidence rate in the 42 days after vaccination demonstrated no cases of HZ among 633 patients exposed to biologics, including 551 patients exposed to TNFi therapy (Table J2). Thus, the study found that HZ vaccination was not associated with a short-term increase in HZ incidence, even among those exposed to biologic therapy. Another cohort study examining patients (age 50+) with immune-mediated diseases similarly found no increased risk of HZ in the 30 days following HZ vaccination; no HZ developed among 47 patients receiving immunosuppressive therapies [99].

Quality of evidence across all critical outcomes: Very low ⊕⊖⊖⊖

Table J1. Herpes zoster risk among patients receiving differing

DMARD type	Number of cases/Person-years	Adjusted hazard ratio (95% confidence interval)
Non-biologic DMARDs	2,390/177,209	1 [Reference]
TNFi	1,380/87,374	1.15 (1.08-1.23)
Non-TNF biologic	226/14,057	0.99 (0.86-1.13)
None	6,109/698,021	0.84 (0.80-0.88)

Table J2. Herpes zoster incidence within 42 days after vaccination vs. incidence among unvaccinated patients

Biologic therapy	Herpes zoster incidence among unvaccinated (95% CI) *Includes patients with any immune-mediated disorders, whether receiving biologic therapy or not*	Herpes zoster incidence among unvaccinated (95% CI) *Includes only those receiving biologic therapy*
Any biologic therapy	**11.6 (11.4 to 11.9)** cases per 1000 person-years	**0 to 4.7** cases per 1000 person-years
TNFi therapy		**0 to 5.4** cases per 1000 person-years

This PICO includes two retrospective cohort studies:	Zhang et al., 2012 [98]; Zhang et al., 2011 [98, 99]

J.2: In early RA patients who are currently receiving biologics, we *conditionally* recommend that live attenuated vaccines such as the herpes zoster (shingles) vaccine ***not* be used.**

The voting for J.2 was based on the evidence for J.1 (see table and summary above).

J.3: In established RA patients who are currently receiving biologics, we *conditionally* recommend that live attenuated vaccines such as the herpes zoster (shingles) vaccine ***not* be used.**

The voting for J.3 was based on the evidence for J.1 (see table and summary above).

J.4: In patients with early RA who are currently receiving biologics, we strongly recommend using appropriately indicated killed/inactivated vaccines.

The voting for J.4 was based on the evidence summary below:

The available evidence suggests that though MTX could possibly impair a patient's response to the pneumococcal vaccine, receiving the vaccine may be more beneficial, even in the context of MTX treatment, than harmful.

Summary: The effectiveness of pneumococcus vaccination in rheumatoid arthritis patients was examined in two reviews [100, 101], three randomized controlled trials (Kaine et al., 2007; Visvanathan et al., 2007; Mease et al., 2004) and three observational studies (Coulson et al., 2011; Kapetanovic et al., 2011; Kapetanovic et al., 2006; Elkayam et al., 2004)[102]. **This research indicated that the disease modifying agent methotrexate (MTX) could potentially reduce the efficacy of the pneumococcal vaccine in RA patients.** Six studies compared MTX mono-therapy with combination therapy including MTX and TNFi therapy (Kapetanovic et al., 2011; Kane et al., 2007; Visvanathan et al., 2007; Kapetanovic et al., 2006; Elkayam et al., 2004; Mease et al., 2004)[102]. The two reviews addressed the potential for a synergistic negative effect on serum pneumococcal antibody levels when adding TNFi agents to MTX treatment in RA patients receiving the pneumococcal vaccine [100, 101].

One review concluded that MTX use alone appeared result in an impaired immunological response to the pneumococcal vaccine in patients with established RA, as evidenced by below average antibody titers; however, the same effect was not noted for early RA patients [100]. Evidence regarding altered functioning of the immune response with the addition of TNFi therapy is inconsistent, but suggests that differences in effect may be related to the specific type of TNFi used. One RCT reported that patients taking adalimumab with concomitant MTX experienced a slightly more impaired immune response than those taking MTX alone, but the authors attributed this outcome to differences in patient characteristics at baseline (Kaine et al., 2007). An observational case-control study in 149 patients with RA noted that patients taking etanercept or infliximab with concomitant MTX showed a significantly more robust immune response than patients receiving MTX mono-therapy. The study found that ultimately the best immune response occurred when patients took TNFi therapy alone [102].

A second review reported similar findings regarding the tendency for RA patients receiving MTX to present with below average antibody titers after receiving the pneumococcal vaccine [101]. This review similarly found inconclusive evidence regarding the risk of further impairment associated with TNFi co-therapy. One study conducted a secondary analysis of the ASPIRE trial, in which psoriatic arthritis patients received either MTX and placebo or MTX and infliximab (Visvanathan et al., 2007). This analysis

demonstrated that immune responses were lower than expected across all treatment groups and reported no significant interaction between TNFi agents and MTX. Though the authors acknowledged MTX's probable role in impaired immune responses to the pneumococcal vaccine, their analyses did not detect a difference in vaccine response based on changes in MTX dosage throughout the study. In contrast, a 2004 observational study in 16 patients reported a more negative immune response in patients using TNFi agents, both alone and with concomitant MTX, than with other treatments (Elkayam, 2004).

A 2011 observational study compared the immune responses of established RA patients taking TNFi agents alone, MTX alone, or TNFi agents with concomitant MTX [102]. A subanalysis of RA patients only showed that MTX usage and older age were predictors of an impaired immune response to the pneumococcal vaccine. These results are consistent with a 2004 RCT of 205 psoriatic arthritis patients in which increased age, female sex, and MTX usage were the only significant predictors of a poor immune response. No significant interactions were noted between MTX usage and TNFi usage (Mease, 2004).

A 2011 observational study directly addressed MTX's relationship to immune response to the pneumococcal vaccine, rather than comparing it with TNFi agents or TNFi and MTX combination therapy [103]. **Over a period of ten years, infection rates were compared between vaccinated and unvaccinated RA patients taking MTX. The study noted significantly higher median antibody levels in vaccinated patients and concluded that it may be beneficial for RA patients to receive the pneumococcal vaccine, regardless of MTX use.**

Quality of evidence across all critical outcomes: Very low ⊕⊖⊖⊖

J.5: In patients with established RA who are currently receiving biologics, we strongly recommend using appropriately indicated killed/inactivated vaccines.

The voting for J.5 was based on the evidence for J.4 (see summary above).

PART 2: SUPPLEMENTARY PICO QUESTIONS

These questions were originally considered by the Voting Panel, but did not produce recommendations due to lack of clinical relevance or redundancy with other PICO questions.

Supplementary PICO Questions: Early Rheumatoid Arthritis (RA)

In patients with early RA with moderate or high disease activity, who are DMARD-naive, what is the impact of initiating treatment with a combination of triple-DMARD therapy and high-dose short-term GCs with an addition of an TNFi vs. a combination of triple-DMARD therapy and high-dose short-term GCs without a biologic on symptoms and AEs?

Summary: This PICO question is directly addressed by one double-blind RCT [104]. This trial randomized early RA patients to triple-DMARD therapy and glucocorticoid pulse therapy with or without additional TNFi therapy with infliximab. TNFi therapy (or placebo TNFi therapy) was only administered for the initial six months of the two-year trial. No statistically significant between-group differences were observed for any of the selected critical efficacy or safety outcomes.

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

TNFi therapy + short-term, high dose glucocorticoids + triple-DMARD therapy vs. short-term, high dose glucocorticoids + triple-DMARD therapy for patients with early RA with moderate/high disease activity who are DMARD-naive

Bibliography: *TNFi therapy +short-term, high dose glucocorticoids +triple-DMARD therapy vs. short-term, high dose glucocorticoids + triple-DMARD therapy in 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	
				Risk with Short-term, high dose glucocorticoids + triple-DMARD therapy	Risk difference with TNFi therapy + short-term, high dose glucocorticoids + triple-DMARD therapy (95% CI)
ACR remission response (RA disease activity)	99 (1 study) 2 years	⊕⊕⊕⊖ **MODERATE**[1] due to imprecision	**RR 1.24** (0.89 to 1.73)	**531 per 1000**	**127 more per 1000** (from 58 fewer to 387 more)
DAS-28 remission (RA disease activity) (DAS-28 score <2.6)	99 (1 study) 2 years	⊕⊕⊕⊖ **MODERATE**[1] due to imprecision	**RR 1** (0.83 to 1.21)	**816 per 1000**	**0 fewer per 1000** (from 139 fewer to 171 more)
Health Assessment Questionnaire (HAQ) (higher score indicates more severe	99 (1 study) 2 years	⊕⊕⊕⊖ **MODERATE**[1] due to imprecision			The mean Health Assessment Questionnaire (HAQ) in the intervention groups was **0.03 lower** (0.16 lower to 0.1 higher)

physical disability)					
Sharp radiographic progression score (higher score indicates more severe radiographic progression)	99 (1 study) 2 years	⊕⊕⊕⊖ **MODERATE**[1] due to imprecision			The mean Sharp radiographic progression score in the intervention groups was **0.8 lower** (3.3 lower to 1.7 higher)
Serious adverse events (SAEs)	99 (1 study) 2 years	⊕⊕⊕⊖ **MODERATE**[1] due to imprecision	**RR 0.74** (0.17 to 3.12)	**82 per 1000**	**21 fewer per 1000** (from 68 fewer to 173 more)
Gastrointestinal adverse events	99 (1 study) 2 years	⊕⊕⊕⊖ **MODERATE**[1] due to imprecision	**RR 0.91** (0.66 to 1.27)	**612 per 1000**	**55 fewer per 1000** (from 208 fewer to 165 more)
Hepatotoxicity (elevated liver enzymes)	99 (1 study) 2 years	⊕⊕⊕⊖ **MODERATE**[1] due to imprecision	**RR 0.74** (0.28 to 1.96)	**163 per 1000**	**42 fewer per 1000** (from 118 fewer to 157 more)

*The basis for the **assumed risk** (e.g., the median control group risk across studies) is provided in footnotes. The **corresponding risk** (and its 95% confidence interval) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI).

CI: Confidence interval; **RR:** Risk ratio;

GRADE Working Group grades of evidence
High quality: Further research is very unlikely to change our confidence in the estimate of effect.
Moderate quality: Further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate.
Low quality: Further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate.
Very low quality: We are very uncertain about the estimate.

[1] Wide confidence intervals around effect estimate due to small sample size (n=99) (Leirisalo-Repo et al., 2013).

This PICO includes one RCT:	Leirisalo-Repo et al., 2013 [104]

In patients with <u>early</u> RA with <u>moderate or high disease</u> activity, who have failed traditional DMARD therapy, what is the impact of combination DMARD therapy, TNFi therapy, or non-TNF biologic therapy with MTX vs. combination DMARD therapy, TNFi therapy, or non-TNF biologic therapy alone on symptoms and AEs?

The above PICO question was added after the literature search. It is based on the evidence tables and summaries for A.7.

In patients with early RA with moderate or high disease activity, who have failed traditional DMARD therapy, what is the impact of oral tofacitinib vs. non-TNF biologic on symptoms and AEs?

Summary: This PICO was not directly addressed by any studies.

Quality of evidence across all critical outcomes: Very low ⊕⊖⊖⊖. No data were available to address this question.

In patients with early RA with moderate or high disease activity, who have failed traditional DMARD therapy, what is the impact of oral tofacitinib + MTX vs. non-TNF biologic +MTX on symptoms and AEs?

Summary: This PICO was not directly addressed by any studies.
Quality of evidence across all critical outcomes: Very low ⊕⊖⊖⊖. No data were available to address this question.

In patients with early RA with moderate or high disease activity, who have failed traditional DMARD therapy, what is the impact of oral tofacitinib vs. combination triple DMARD therapy on symptoms and AEs?

Summary: This PICO was not directly addressed by any studies.
Quality of evidence across all critical outcomes: Very low ⊕⊖⊖⊖. No data were available to address this question.

In patients with early RA with moderate or high disease activity, who have failed traditional DMARD therapy, what is the impact of oral tofacitinib + MTX vs. combination triple DMARD therapy on symptoms and AEs?

Summary: This PICO was not directly addressed by any studies.

Quality of evidence across all critical outcomes: Very low ⊕⊖⊖⊖. No data were available to address this question.

In patients with early RA with moderate or high disease activity, what is the impact of adding a mono-or double DMARD therapy to an TNFi vs. the same TNFi therapy alone on symptoms and AEs?

Summary: This PICO question is directly addressed by two double-blind RCTs [30, 105]. These trials randomized early RA patients to TNFi therapy + MTX (with golimumab and adalimumab, respectively) or MTX therapy alone [30, 105]. TNFi + MTX therapy was significantly superior to MTX monotherapy for RA disease activity (as measured by ACR20 and DAS-28 remission responders) and physical disability (HAQ-DI); however, it was also associated with significantly more frequent serious infections. No statistically significant between-group difference was found for serious adverse events, malignancies, or hepatotoxicity, though these also trended toward more frequent in the TNFi +MTX group.

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

TNFi + mono/double DMARD therapy compared to TNFi therapy for patients with early RA with moderate/high disease activity

Bibliography: TNFi + mono or double DMARD therapy vs. TNFi therapy alone in patients with early RA with moderate/high disease activity

Outcomes	No of Participants (studies) Follow up	Quality of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects	
				Risk with TNFi therapy	Risk difference with TNFi + mono/double DMARD therapy (95% CI)
ACR20 response (RA disease activity)	860 (2 studies) 6-24 months	⊕⊕⊕⊕ **HIGH**	**RR 1.32** (1.12 to 1.55)	**499 per 1000**	**160 more per 1000** (from 60 more to 274 more)
ACR50 response (RA disease activity)	860 (2 studies) 6-24 months	⊕⊕⊕⊖ **MODERATE**[1] due to inconsistency, imprecision	**RR 1.36** (0.96 to 1.94)	**353 per 1000**	**127 more per 1000** (from 14 fewer to 332 more)
DAS-28 remission (RA disease activity) (DAS-28 score<2.6)	860 (2 studies) 6-24 months	⊕⊕⊕⊕ **HIGH**	**RR 1.63** (1.06 to 2.51)	**217 per 1000**	**137 more per 1000** (from 13 more to 328 more)
Health Assessment Questionnaire - Disability Index (higher score indicates more severe physical disability)	542 (1 study) 24 months	⊕⊕⊕⊕ **HIGH**[2]			The mean Health Assessment Questionnaire - Disability Index in the intervention groups was **0.2 lower** (0.33 to 0.07 lower)
Serious adverse events (SAEs)	316 (1 study) 6 months	⊕⊕⊕⊕ **HIGH**[3] imprecision	**RR 1.97** (0.69 to 5.65)	**32 per 1000**	**31 more per 1000** (from 10 fewer to 148 more)

Serious infections	858 (2 studies) 6-24 months	⊕⊕⊕⊕ **HIGH** imprecision	**RR 3.22** (1.19 to 8.72)	**12 per 1000**	**26 more per 1000** (from 2 more to 90 more)
Malignancies	858 (2 studies) 6 months	⊕⊕⊕⊕ **HIGH** imprecision	**RR 0.75** (0.17 to 3.34)	**9 per 1000**	**2 fewer per 1000** (from 8 fewer to 22 more)
Hepatotoxicity (ALT > 100% increased)	316 (1 study) 6 months	⊕⊕⊕⊕ **HIGH**[3] imprecision	**RR 1.69** (0.68 to 4.19)	**45 per 1000**	**31 more per 1000** (from 14 fewer to 142 more)

*The basis for the **assumed risk** (e.g., the median control group risk across studies) is provided in footnotes. The **corresponding risk** (and its 95% confidence interval) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI).

CI: Confidence interval; **RR:** Risk ratio;

GRADE Working Group grades of evidence
High quality: Further research is very unlikely to change our confidence in the estimate of effect.
Moderate quality: Further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate.
Low quality: Further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate.
Very low quality: We are very uncertain about the estimate.

[1] I-squared heterogeneity score=75% (Emery et al., 2009; Breedveld et al., 2006).
[2] Breedveld et al., 2006
[3] Emery et al., 2009

This PICO includes two RCTs:	Emery et al., 2009 [30]; Breedveld et al., 2006 [105]

Supplemental PICO Questions: Established Rheumatoid Arthritis (RA)

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

The voting for B.25 was based on the evidence table and summary for B.3.

In patients with established RA with only low disease activity, who are DMARD-naive, what is the impact of TNFi therapy vs. combination DMARD therapy on symptoms and AEs?

Summary: This PICO was indirectly addressed by three RCTs comparing TNFi therapy with traditional DMARD combination therapy [2, 17, 106]. Patients in the included trials had early RA with moderate/high disease activity rather than established RA with low disease activity. Moreover, a number of patients in the included trials had previously failed traditional DMARD therapy. No statistically significant between-group differences were found for DAS-28 score and Sharp score, though a greater proportion of ACR50 responders was found in the TNFi group than in those receiving combination DMARD therapy. Analyses of safety outcomes including serious adverse events (SAEs), serious infections, gastrointestinal adverse events, and malignancies also found no statistically significant between-group differences.

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

TNFi therapy vs. combination DMARD therapy for patients with established RA with low disease activity who are DMARD-naive

Bibliography: TNFi therapy vs. Combination DMARD therapy in Patients with Established RA and Low 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	
				Risk with Combination DMARD	Risk difference with TNFi (95% CI)
DAS-28 (RA disease activity)	544 (2 studies) 11-24 months	⊕⊕⊖⊖ **LOW**[1] due to indirectness			The mean DAS-28 (RA disease activity) in the intervention groups was **0.11 lower** (0.31 lower to 0.09 higher)
ACR50 response (RA disease activity)	944 (3 studies) 11-24 months	⊕⊕⊖⊖ **LOW**[1] due to indirectness, imprecision	**RR 1.23** (1.02 to 1.48)	**297 per 1000**	**68 more per 1000** (from 6 more to 143 more)
Sharp radiographic progression score (higher score indicates more severe disease progression)	754 (3 studies) 11-24 months	⊕⊕⊖⊖ **LOW**[1] due to indirectness, imprecision			The mean Sharp radiographic progression score in the intervention groups was **0.33 lower** (0.95 lower to 0.3 higher)
Serious adverse events (SAEs)	1075 (3 studies) 11-24 months	⊕⊕⊖⊖ **LOW**[1] due to indirectness, imprecision	**RR 1.03** (0.74 to 1.44)	**103 per 1000**	**3 more per 1000** (from 27 fewer to 45 more)
Serious infections	1075 (3 studies) 11-24 months	⊕⊕⊖⊖ **LOW**[1] due to indirectness, imprecision	**RR 1.66** (0.73 to 3.78)	**17 per 1000**	**11 more per 1000** (from 4 fewer to 46 more)

Gastrointestinal adverse events	1075 (3 studies) 11-24 months	⊕⊕⊖⊖ **LOW**[1] due to indirectness, imprecision	**RR 0.35** (0.11 to 1.07)	**184 per 1000**	**120 fewer per 1000** (from 164 fewer to 13 more)
Malignancies	376 (1 study) 11-24 months	⊕⊕⊖⊖ **LOW**[1] due to indirectness	**RR 5.97** (0.33 to 107.16)	**0 per 1000**	**-**

*The basis for the **assumed risk** (e.g., the median control group risk across studies) is provided in footnotes. The **corresponding risk** (and its 95% confidence interval) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI).

CI: Confidence interval; **RR:** Risk ratio; **RA:** rheumatoid arthritis

GRADE Working Group grades of evidence
High quality: Further research is very unlikely to change our confidence in the estimate of effect.
Moderate quality: Further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate.
Low quality: Further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate.
Very low quality: We are very uncertain about the estimate.

[1] All trials analyzed for this PICO are indirect evidence: the three included trials examine early RA patients with moderate/high disease activity, many of whom have failed DMARD therapy (O'Dell et al., 2013; Moreland et al., 2012; van Vollenhoven et al., 2012). The PICO addresses patients with ESTABLISHED RA and LOW disease activity who HAVE NOT FAILED TRADITIONAL DMARDS.

This PICO includes three RCTs:	O'Dell et al., 2013 [106]; Moreland et al., 2012 [2]; van Vollenhoven et al., 2012 [17]

In patients with <u>established</u> RA with <u>moderate or high disease</u> activity, who have failed traditional DMARD therapy, what is the impact of combination DMARDs, TNFi therapy, non-TNF biologic therapy, or tofacitinib with MTX vs. combination DMARDs, TNFi therapy, non-TNF biologic therapy, or tofacitinib without MTX on symptoms and AEs?

The above PICO question was added after the literature search. It is based on the evidence tables and summaries for B.5.

Supplemental PICO Questions: Safety in high-risk patients

In patients with established RA with moderate or high disease activity, is it safer to use TNFi therapy or combination DMARD therapy in the presence of acute hepatitis B infection?

Quality of evidence across all critical outcomes: Very low ⊕⊖⊖⊖ (Evidence for this PICO is indirect: addresses chronic hepatitis B)

In patients with established RA with moderate or high disease activity, is it safer to use TNFi therapy or non-TNF biologic therapy in the presence of acute hepatitis B infection?

Quality of evidence across all critical outcomes: Very low ⊕⊖⊖⊖ (Evidence for this PICO is indirect: addresses chronic hepatitis B)

In patients with established RA with moderate or high disease activity, is it safer to use TNFi therapy or oral tofacitinib in the presence of acute hepatitis B infection?

Quality of evidence across all critical outcomes: Very low ⊕⊖⊖⊖ (Evidence for this PICO is indirect: addresses chronic hepatitis B)

In patients with established RA with moderate or high disease activity, is it safer to use TNFi therapy or combination DMARD therapy in the presence of chronic hepatitis B infection?

Quality of evidence across all critical outcomes: Very low ⊕⊖⊖⊖

In patients with established RA with moderate or high disease activity, is it safer to use TNFi therapy or non-TNF biologic therapy in the presence of chronic hepatitis B infection?

Quality of evidence across all critical outcomes: Very low ⊕⊖⊖⊖

In patients with established RA with moderate or high disease activity, is it safer to use TNFi therapy or oral tofacitinib in the presence of chronic hepatitis B infection?

Quality of evidence across all critical outcomes: Very low ⊕⊖⊖⊖

In patients with established RA with moderate or high disease activity, is it safer to use TNFi therapy or combination DMARD therapy in the presence of hepatitis C with high viral load?

Quality of evidence across all critical outcomes: Very low ⊕⊖⊖⊖

In patients with established RA with moderate or high disease activity in the presence of hepatitis C infection (with high or low viral load), who are not receiving effective antiviral treatment or do not currently require antiviral treatment, is it safer to treat them with traditional DMARD therapy or with TNFi therapy?

The above PICO question was added after the literature search. It is based on the evidence for D.1.

In patients with established RA with moderate or high disease activity, is it safer to use TNFi therapy or non-TNF biologic therapy in the presence of hepatitis C with high viral load?

Quality of evidence across all critical outcomes: Very low ⊕⊖⊖⊖

In patients with established RA with moderate or high disease activity, is it safer to use TNFi therapy or oral tofacitinib in the presence of hepatitis C with high viral load?

Quality of evidence across all critical outcomes: Very low ⊕⊖⊖⊖

In patients with established RA with moderate or high disease activity, is it safer to use TNFi therapy or combination DMARD therapy in the presence of hepatitis C with low or undetectable viral load?

Quality of evidence across all critical outcomes: Very low ⊕⊖⊖⊖

In patients with established RA with moderate or high disease activity, is it safer to use TNFi therapy or non-TNF biologic therapy in the presence of hepatitis C with low or undetectable viral load?

Quality of evidence across all critical outcomes: Very low ⊕⊖⊖⊖

In patients with established RA with moderate or high disease activity, is it safer to use TNFi therapy or oral tofacitinib in the presence of hepatitis C with low or undetectable viral load?

Quality of evidence across all critical outcomes: Very low ⊕⊖⊖⊖

In patients with established RA with moderate or high disease activity and evidence of chronic hepatitis C infection, who are receiving effective antiviral treatment, is it safer to treat them just as the patients without hepatitis C or to alter therapy?

The above PICO question was added after the literature search. It is based on the evidence for E.1 and E.2.

In patients with established RA with moderate or high disease activity, is it safer to use TNFi therapy or oral tofacitinib in the presence of previously treated or untreated melanoma skin cancer?

Summary: This PICO was not directly addressed by any studies.

Quality of evidence across all critical outcomes: Very low ⊕⊖⊖⊖. No data were available to address this question. Recommendations were formulated based on the expertise of the voting panel.

In patients with established RA with moderate or high disease activity and a history of previously treated or untreated melanoma skin cancer, is it safer to use traditional DMARD therapy or biologics (TNFi therapy or non-TNF biologic therapy)?

The above PICO question was added after the literature search. It is based on the evidence for F.1.

In patients with established RA with moderate or high disease activity, is it safer to use TNFi therapy or oral tofacitinib in the presence of previously treated or untreated non-melanoma skin cancer?

Summary: This PICO was not directly addressed by any studies.

Quality of evidence across all critical outcomes: Very low ⊕⊖⊖⊖. No data were available to address this question. Recommendations were formulated based on the expertise of the voting panel.

In patients with established RA with moderate or high disease activity and a history of previously treated or untreated non-melanoma skin cancer, is it safer to use traditional DMARD therapy or biologics (TNFi therapy or non-TNF biologic therapy)?

The above PICO question was added after the literature search. It is based on the evidence for F.3.

In patients with established RA with moderate or high disease activity, is it safer to use TNFi therapy or rituximab therapy in the presence of previously treated lymphoproliferative disorder?

The above PICO question was added after the literature search. It is based on the evidence for G.1, as well as on the expertise of the voting panel.

In patients with established RA with moderate or high disease activity, is it safer to use TNFi therapy or abatacept therapy in the presence of previously treated lymphoproliferative disorder?

The above PICO question was added after the literature search. It is based on the evidence for G.1, as well as on the expertise of the voting panel.

In patients with established RA with moderate or high disease activity, is it safer to use TNFi therapy or tocilizumab therapy in the presence of previously treated lymphoproliferative disorder?

The above PICO question was added after the literature search. It is based on the evidence for G.1, as well as on the expertise of the voting panel.

In patients with established RA with moderate or high disease activity, is it safer to use TNFi therapy or oral tofacitinib in the presence of previously treated lymphoproliferative disorder?

Summary: This PICO was not directly addressed by any studies.

Quality of evidence across all critical outcomes: Very low ⊕⊖⊖⊖. No data were available to address this question.

In patients with established RA with moderate or high disease activity and a history of previously treated solid organ cancer, is it safer to treat them just as the patients without a history of solid organ cancer or to alter therapy?

The above PICO question was added after the literature search. It is based on the evidence for H.1.

In patients with established RA with moderate or high disease activity, is it safer to use TNFi therapy or combination DMARD therapy in the presence of previous serious infections?

Voting for this PICO question was based on the evidence for I.1.

In patients with established RA with moderate or high disease activity, is it safer to use TNFi therapy or non-TNF biologic therapy in the presence of previous serious infections?

Voting for this PICO question was based on the evidence for I.1.

In patients with established RA with moderate or high disease activity, is it safer to use TNFi therapy or abatacept therapy in the presence of previous serious infections?

The above PICO question was added after the literature search. Voting for this PICO question was based on the evidence for I.1.

In patients with established RA with moderate or high disease activity, is it safer to use TNFi therapy or rituximab therapy in the presence of previous serious infections?

The above PICO question was added after the literature search. Voting for this PICO question was based on the evidence for I.1.

In patients with established RA with moderate or high disease activity, is it safer to use TNFi therapy or tocilizumab therapy in the presence of previous serious infections?

The above PICO question was added after the literature search. Voting for this PICO question was based on the evidence for I.1.

In patients with established RA with moderate or high disease activity, is it safer to use TNFi therapy or oral tofacitinib in the presence of previous serious infections?

Voting for this PICO question was based on the evidence for I.1.

Supplemental PICO Questions: Vaccination

In patients with <u>early</u> RA currently on biologics, is it safe to give live attenuated vaccines such as herpes zoster (shingles) vaccine?

Voting for this PICO question was based on the evidence for J.1

In patients with <u>established</u> RA currently on biologics, is it safe to give live attenuated vaccines such as herpes zoster (shingles) vaccine?

Voting for this PICO question was based on the evidence for J.1

In patients aged 50 and over, should the herpes zoster vaccine be given *before* a patient receives biologic therapy for their RA?

Voting for this PICO question was based on the evidence for J.1

In patients with <u>early</u> RA currently receiving MTX, is it safe to give killed or inactivated vaccines such as the pneumococcal vaccine?

Voting for this PICO question was based on the evidence for J.4

In patients with <u>established</u> RA currently receiving MTX, is it safe to give killed or inactivated vaccines such as the pneumococcal vaccine?

Voting for this PICO question was based on the evidence for J.4.

Supplemental PICO Questions: Tapering RA treatments in patients with low disease activity or disease remission

In patients with early 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 not directly addressed by any studies.

Quality of evidence across all critical outcomes: Very low ⊕⊖⊖⊖. No data were available to address this question.

In patients with early RA in disease remission, what is the impact of tapering traditional DMARD therapy vs. continuing traditional DMARDs on symptoms and AEs?

Summary: This PICO was not directly addressed by any studies.

Quality of evidence across all critical outcomes: Very low ⊕⊖⊖⊖. No data were available to address this question.

Supplemental PICO Questions: Glucocorticoids

In patients with early RA with only low disease activity, who are NOT on background DMARDs, what is the impact of short-term high-dose glucocorticoid therapy vs. traditional DMARDs without glucocorticoids on symptoms and AEs?

Summary: This PICO was not directly addressed by any studies.

Quality of evidence across all critical outcomes: Very low ⊕⊖⊖⊖. No data were available to address this question.

In patients with early RA with moderate or high disease activity, who are NOT on background DMARDs, what is the impact of long-term, low dose glucocorticoid therapy vs. no DMARD/biologic treatment (i.e., placebo) on symptoms and AEs?

Summary: This PICO was directly addressed by three double-blind RCTs (published in four articles) [107-110]. Analysis of physical disability (measured by HAQ-DI) at two-year follow-up in two trials (n=206) demonstrated a statistically non-significant trend in favor of GC therapy over placebo [108, 110]. A significant benefit of GCs on radiographic disease progression was found at 2-3 year follow-up in three trials [108-110]. No statistically significant between-group differences were found for bone mineral content in the femoral neck or lumbar spine, or for cumulative incidence of fractures [107, 108].Two trials mentioned overall adverse events, noting that AEs were in keeping with recognized patterns [108, 110].

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

Long-term, low dose glucocorticoid therapy compared to no DMARD/biologic treatment (i.e., placebo) for patients with early RA with moderate/high disease activity

Bibliography: Long-term, low dose glucocorticoid therapy vs. no DMARD/biologic treatment (i.e., placebo) in patients with early RA with moderate/high disease activity.

Outcomes	No of Participants (studies) Follow up	Quality of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects	
				Risk with No DMARD/biologic treatment (i.e., placebo)	Risk difference with Long-term, low dose glucocorticoid therapy (95% CI)
Health Assessment Questionnaire-Disability Index (HAQ-DI) (higher score indicates more severe physical disability)	206 (2 studies) 2 years	⊕⊕⊕⊖ **MODERATE**[1] due to imprecision			The mean health assessment questionnaire-disability index (HAQ-DI) in the intervention groups was **0.25 lower** (0.54 lower to 0.03 higher)
Larsen radiographic progression score (higher score indicates more severe disease progression)	302 (3 studies) 2-3 years	⊕⊕⊕⊖ **MODERATE**[2] due to inconsistency, imprecision			The mean Larsen radiographic progression score in the intervention groups was **3.99 lower** (7.92 to 0.06 lower)
Bone mineral density in femoral neck	65 (1 study) 2 years	⊕⊕⊖⊖ **LOW**[3] due to imprecision			The mean bone mineral content (BMC) in femoral neck in the intervention groups was **0.1 higher** (1.87 lower to 2.07 higher)
Bone mineral density in lumbar spine	65 (1 study) 2 years	⊕⊕⊖⊖ **LOW**[3] due to imprecision			The mean bone mineral content (BMC) in lumbar spine in the intervention groups was **4 lower** (11.07 lower to 3.07 higher)
Cumulative incidence of fracture	81 (1 study) 2 years	⊕⊕⊖⊖ **LOW**[3] due to imprecision	**RR 1.79** (0.57 to 5.66)	**198 per 1000**	**77 more per 1000** (from 42 fewer to 455 more)

Serious adverse events	70 (1 study) 2 years	⊕⊕⊖⊖ **LOW**[4] due to imprecision	**RR 0.79** (0.12 to 5.33)	**65 per 1000**	**14 fewer per 1000** (from 57 fewer to 279 more)

*The basis for the **assumed risk** (e.g., the median control group risk across studies) is provided in footnotes. The **corresponding risk** (and its 95% confidence interval) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI).

CI: Confidence interval; **RR:** Risk ratio;

GRADE Working Group grades of evidence
High quality: Further research is very unlikely to change our confidence in the estimate of effect.
Moderate quality: Further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate.
Low quality: Further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate.
Very low quality: We are very uncertain about the estimate.

[1] Wide confidence intervals around effect estimate due to small sample size (van Everdingen et al., 2002; Kirwan 1995).
[2] Considerable inconsistency between trials: I-squared heterogeneity score=100% (van Everdingen et al., 2002; Hickling et al., 1998; Kirwan 1995).
[3] Wide confidence intervals around effect estimate due to small sample size (van Everdingen et al., 2003; van Everdingen et al., 2002).
[4] Wide confidence intervals around effect estimate due to small sample size (Kirwan 1995).

This PICO was supported by four RCTs:	van Everdingen et al., 2003 [107]; van Everdingen et al., 2002 [108]; Hickling et al., 1998 [109]; Kirwan 1995 [110]

In patients with <u>early</u> RA with <u>moderate or high disease</u> activity, what is the impact of <u>short-term high-dose glucocorticoid therapy</u> vs. <u>traditional DMARDs without glucocorticoids</u> on symptoms and AEs?

<u>Summary</u>: This PICO was not directly addressed by any studies.

<u>Quality of evidence across all critical outcomes</u>: Very low ⊕⊖⊖⊖. No data were available to address this question.

In patients with early RA with moderate or high disease activity, who are on TNFi or non-TNF biologic therapy, what is the impact of adding low-dose glucocorticoid therapy to biologic therapy vs. biologic therapy without glucocorticoids on symptoms and AEs?

The above PICO question was added after the literature search. Voting for this PICO was based on the evidence for A.12.

In patients with established RA with moderate or high disease activity, what is the impact of adding low-dose glucocorticoid therapy to TNFi or non-TNF biologic therapy vs. TNFi or non-TNF biologic therapy without glucocorticoids on symptoms and AEs?

The above PICO question was added after the literature search. Voting for this PICO was based on the evidence for A.12.

In patients with established RA with only low disease activity, what is the impact of adding short-term high-dose glucocorticoid therapy to traditional DMARDs vs. traditional DMARDs without glucocorticoids on symptoms and AEs?

Summary: This PICO was indirectly addressed by two RCTs [23, 25]. While this PICO examines those with early RA experiencing acute disease flare, the closest available evidence was gathered from RCTs in patients with established RA and moderate/high disease activity. The trials compared traditional DMARD therapy + short-term, high dose glucocorticoids with traditional DMARD therapy alone. No statistically significant between-group differences were found for any of the critical efficacy or safety outcomes analyzed.

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

Short-term, high dose glucocorticoids + traditional DMARDs vs. traditional DMARDs alone for patients with established RA with low disease activity

Bibliography: Short-term, high-dose glucocorticoids + DMARDs vs. DMARDs alone 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	
				Risk with Traditional DMARDs alone	Risk difference with Short-term, high dose glucocorticoids +traditional DMARDs (95% CI)
DAS-28 (RA disease activity) (higher score indicates more severe disease activity)	91 (1 study) 2 years	⊕⊕⊖⊖ **LOW**[1,2] due to indirectness, imprecision			The mean DAS-28 (RA disease activity) in the intervention groups was **0.24 lower** (0.97 lower to 0.49 higher)
Health Assessment Questionnaire (HAQ) (higher score indicates more severe physical disability)	120 (2 studies) 6-24 months	⊕⊕⊖⊖ **LOW**[3,4] due to indirectness, imprecision			The mean health assessment questionnaire (HAQ) in the intervention groups was **0.1 higher** (0.22 lower to 0.43 higher)
Larsen radiographic progression score (scored 0-200; higher score indicates more severe disease progression)	91 (1 study) 2 years	⊕⊕⊖⊖ **LOW**[1,2] due to indirectness, imprecision			The mean Larsen radiographic progression score in the intervention groups was **4.76 higher** (13.4 lower to 22.92 higher)
Serious adverse events (SAEs)	91 (1 study) 2 years	⊕⊕⊖⊖ **LOW**[1,2] due to indirectness, imprecision	**RR 1.79** (0.35 to 9.3)	**47 per 1000**	**37 more per 1000** (from 30 fewer to 386 more)

*The basis for the **assumed risk** (e.g., the median control group risk across studies) is provided in footnotes. The **corresponding risk** (and its 95% confidence interval) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI).

CI: Confidence interval;

GRADE Working Group grades of evidence
High quality: Further research is very unlikely to change our confidence in the estimate of effect.
Moderate quality: Further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate.
Low quality: Further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate.
Very low quality: We are very uncertain about the estimate.

[1] Indirect evidence: this PICO addresses patients with established RA with low disease activity. The evidence for this outcome is drawn from an RCT in patients with established RA with moderate/high disease activity (Choy et al., 2005).
[2] Wide confidence intervals around effect estimate due to small sample size (Choy et al., 2005).
[3] Indirect evidence: this PICO addresses patients with established RA with low disease activity. The evidence for this outcome is drawn from two RCTs in patients with established RA with moderate/high disease activity (Choy et al., 2005; Ciconelli et al., 1996).
[4] Wide confidence intervals around effect estimate due to small sample size (Choy et al., 2005; Ciconelli et al., 2005).

This PICO includes two RCTs:	Choy et al., 2005 [23]; Ciconelli et al., 1996 [25]

In patients with established RA with moderate or high disease activity, what is the impact of long-term low-dose glucocorticoid therapy vs. no DMARD/biologic treatment (placebo) on symptoms and AEs?

Summary: This PICO was directly addressed by two small placebo-controlled, double-blind RCTs [111, 112]. One trial (n=34) assessed the efficacy of 5 mg/d oral prednisone versus matching placebo over the course of 24 weeks [111]. This trial demonstrated no statistically significant differences in joint pain, tenderness, or swelling between GC and placebo groups at 12 or 24-week follow-up. Significant improvement from baseline in all three parameters was nevertheless observed in the group receiving prednisone only, though pain levels nearly returned to baseline values by week 24. A second small trial (n=49) examined the safety and efficacy of administration of 3 mg/day or 5 mg/day of oral prednisolone vs. matching placebo over the course of a maximum trial period of 3 years (41/49 patients completed at least 2 years) [112]. At one year follow-up, participants in the 5 mg/d prednisolone group demonstrated statistically significantly superior improvement vs. placebo in physical function (timed walk) and joint tenderness. Adverse events were evenly distributed between groups, with mild dyspepsia occurring in a similar proportion of patients in each treatment group. Osteoporotic vertebral collapse occurred in two patients, one in the placebo group and one in the 5mg prednisolone group. Both trials were consistent in their conclusions that low dose glucocorticoids are modestly more efficacious than placebo, and are safe for long term use in RA patients.

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

This PICO was supported by two RCTs:	Harris et al., 1983 [111]; Chamberlain et al., 1976 [112]

In patients with established RA with moderate or high disease activity, what is the impact of adding short-term, high dose glucocorticoid therapy to traditional DMARDs vs. traditional DMARDs without glucocorticoids on symptoms and AEs?

Summary: This PICO question is directly addressed by two small, double-blind RCTs [24, 25]. One two-week trial (n=21) examined the effects of addition of prednisolone therapy to usual DMARD therapy for two weeks. The trial found a statistically significant benefit of GC addition for reducing RA disease activity (as measured by DAS-28 score and ACR20 response) [24]. A second RCT (n=29) examined the effect of adding monthly methylprednisolone treatment to sulfasalazine therapy vs. sulfasalazine alone. At 6-month follow-up, this trial found no significant benefit of GC addition over DMARDs alone on physical disability (measured by Health Assessment Questionnaire) [25]. This trial reported that treatment-related adverse events were rare and of mild severity.

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

Short-term, high dose glucocorticoids + traditional DMARD therapy compared to traditional DMARD therapy alone for patients with established RA with moderate/high disease activity

Bibliography: Short-term, high dose glucocorticoids + traditional DMARD therapy vs. traditional DMARD therapy alone in patients with established RA with moderate/high disease activity.

Outcomes	No of Participants (studies) Follow up	Quality of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects	
				Risk with Traditional DMARD therapy alone	Risk difference with Short-term, high dose glucocorticoids + traditional DMARD therapy (95% CI)
DAS-28 (RA disease activity) (higher score indicates more severe disease activity)	21 (1 study) 2 weeks	⊕⊕⊖⊖ **LOW**[1] due to imprecision			The mean DAS-28 (RA disease activity) in the intervention groups was **1.57 lower** (2.75 to 0.39 lower)
ACR20 response (RA disease activity)	21 (1 study) 2 weeks	⊕⊕⊖⊖ **LOW**[1] due to imprecision	**RR 16.36** (1.05 to 254.26)	**0 per 1000**	**-**
Health Assessment Questionnaire (HAQ) (higher score indicates more severe physical disability)	29 (1 study) 6 months	⊕⊕⊖⊖ **LOW**[2] due to imprecision			The mean health assessment questionnaire (HAQ) in the intervention groups was **0.03 higher** (0.35 lower to 0.41 higher)

*The basis for the **assumed risk** (e.g., the median control group risk across studies) is provided in footnotes. The **corresponding risk** (and its 95% confidence interval) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI).

CI: Confidence interval; **RR:** Risk ratio;

GRADE Working Group grades of evidence
High quality: Further research is very unlikely to change our confidence in the estimate of effect.

Moderate quality: Further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate.
Low quality: Further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate.
Very low quality: We are very uncertain about the estimate.

[1] Wide confidence intervals around effect estimate due to very small sample size (n=21) (Gerlag et al., 2004).
[2] Wide confidence intervals around effect estimate due to very small sample size (n=29) (Ciconelli et al., 1996).

This PICO was supported by two RCTs:	Gerlag et al., 2004 [24]; Ciconelli et al., 1996 [25]

In patients with established RA with moderate or high disease activity with an acute disease flare (RA flare), what is the impact of adding short-term glucocorticoid therapy to traditional DMARDs, TNFi therapy, or non-TNF biologic therapy vs. traditional DMARDs, TNFi therapy, or non-TNF biologic therapy without glucocorticoids on symptoms and AEs?

The above PICO question was added after the literature search. Voting for this PICO was based on the evidence for B.28.

Bibliography

1. Verstappen SM, Jacobs JW, van der Veen MJ, Heurkens AH, Schenk Y, ter Borg EJ, Blaauw AA, Bijlsma JW: **Intensive treatment with methotrexate in early rheumatoid arthritis: aiming for remission. Computer Assisted Management in Early Rheumatoid Arthritis (CAMERA, an open-label strategy trial)**. *Ann Rheum Dis* 2007, **66**(11):1443-1449.
2. Moreland LW, O'Dell JR, Paulus HE, Curtis JR, Bathon JM, St Clair EW, Bridges SL, Jr., Zhang J, McVie T, Howard G *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):2824-2835.
3. Capell HA, Madhok R, Porter DR, Munro RA, McInnes IB, Hunter JA, Steven M, Zoma A, Morrison E, Sambrook M *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):235-241.
4. Kremer JM, Genovese MC, Cannon GW, Caldwell JR, Cush JJ, Furst DE, Luggen ME, Keystone E, Weisman MH, Bensen WM *et al*: **Concomitant leflunomide therapy in patients with active rheumatoid arthritis despite stable doses of methotrexate. A randomized, double-blind, placebo-controlled trial**. *Ann Intern Med* 2002, **137**(9):726-733.
5. Dougados M, Combe B, Cantagrel A, Goupille P, Olive P, Schattenkirchner M, Meusser S, Paimela L, Rau R, Zeidler H *et al*: **Combination therapy in early rheumatoid arthritis: a randomised, controlled, double blind 52 week clinical trial of sulphasalazine and methotrexate compared with the single components**. *Ann Rheum Dis* 1999, **58**(4):220-225.
6. Haagsma CJ, van Riel PL, de Jong AJ, van de Putte LB: **Combination of sulphasalazine and methotrexate versus the single components in early rheumatoid arthritis: a randomized, controlled, double-blind, 52 week clinical trial**. *British journal of rheumatology* 1997, **36**(10):1082-1088.
7. de Jong PH, Hazes JM, Barendregt PJ, Huisman M, van Zeben D, van der Lubbe PA, Gerards AH, de Jager MH, de Sonnaville PB, Grillet BA *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):72-78.
8. Saunders SA, Capell HA, Stirling A, Vallance R, Kincaid W, McMahon AD, Porter DR: **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):1310-1317.
9. Mottonen T, Hannonen P, Leirisalo-Repo M, Nissila M, Kautiainen H, Korpela M, Laasonen L, Julkunen H, Luukkainen R, Vuori K *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):1568-1573.
10. Bakker MF, Jacobs JW, Welsing PM, Verstappen SM, Tekstra J, Ton E, Geurts MA, van der Werf JH, van Albada-Kuipers GA, Jahangier-de Veen ZN *et al*: **Low-dose prednisone inclusion in a methotrexate-based, tight control strategy for early rheumatoid arthritis: a randomized trial**. *Ann Intern Med* 2012, **156**(5):329-339.

11. Montecucco C, Todoerti M, Sakellariou G, Scire CA, Caporali R: **Low-dose oral prednisone improves clinical and ultrasonographic remission rates in early rheumatoid arthritis: results of a 12-month open-label randomised study**. *Arthritis research & therapy* 2012, **14**(3):R112.
12. Todoerti M, Scire CA, Boffini N, Bugatti S, Montecucco C, Caporali R: **Early disease control by low-dose prednisone comedication may affect the quality of remission in patients with early rheumatoid arthritis**. *Annals of the New York Academy of Sciences* 2010, **1193**:139-145.
13. Choy EH, Smith CM, Farewell V, Walker D, Hassell A, Chau L, Scott DL: **Factorial randomised controlled trial of glucocorticoids and combination disease modifying drugs in early rheumatoid arthritis**. *Ann Rheum Dis* 2008, **67**(5):656-663.
14. Svensson B, Boonen A, Albertsson K, van der Heijde D, Keller C, Hafstrom I: **Low-dose prednisolone in addition to the initial disease-modifying antirheumatic drug in patients with early active rheumatoid arthritis reduces joint destruction and increases the remission rate: a two-year randomized trial**. *Arthritis Rheum* 2005, **52**(11):3360-3370.
15. Wassenberg S, Rau R, Steinfeld P, Zeidler H: **Very low-dose prednisolone in early rheumatoid arthritis retards radiographic progression over two years: a multicenter, double-blind, placebo-controlled trial**. *Arthritis Rheum* 2005, **52**(11):3371-3380.
16. Capell HA, Madhok R, Hunter JA, Porter D, Morrison E, Larkin J, Thomson EA, Hampson R, Poon FW: **Lack of radiological and clinical benefit over two years of low dose prednisolone for rheumatoid arthritis: results of a randomised controlled trial**. *Ann Rheum Dis* 2004, **63**(7):797-803.
17. van Vollenhoven RF, Geborek P, Forslind K, Albertsson K, Ernestam S, Petersson IF, Chatzidionysiou K, Bratt J: **Conventional combination treatment versus biological treatment in methotrexate-refractory early rheumatoid arthritis: 2 year follow-up of the randomised, non-blinded, parallel-group Swefot trial**. *Lancet* 2012, **379**(9827):1712-1720.
18. Kume K, Amano K, Yamada S, Hatta K, Ohta H, Kuwaba N: **Tocilizumab monotherapy reduces arterial stiffness as effectively as etanercept or adalimumab monotherapy in rheumatoid arthritis: an open-label randomized controlled trial**. *J Rheumatol* 2011, **38**(10):2169-2171.
19. Weinblatt ME, Schiff M, Valente R, van der Heijde D, Citera G, Zhao C, Maldonado M, Fleischmann R: **Head-to-head comparison of subcutaneous abatacept versus adalimumab for rheumatoid arthritis: findings of a phase IIIb, multinational, prospective, randomized study**. *Arthritis Rheum* 2013, **65**(1):28-38.
20. Fleischmann R, Cutolo M, Genovese MC, Lee EB, Kanik KS, Sadis S, Connell CA, Gruben D, Krishnaswami S, Wallenstein G *et al*: **Phase IIb dose-ranging study of the oral JAK inhibitor tofacitinib (CP-690,550) or adalimumab monotherapy versus placebo in patients with active rheumatoid arthritis with an inadequate response to disease-modifying antirheumatic drugs**. *Arthritis and rheumatism* 2012, **64**(3):617-629.
21. van Vollenhoven RF, Fleischmann R, Cohen S, Lee EB, Garcia Meijide JA, Wagner S, Forejtova S, Zwillich SH, Gruben D, Koncz T *et al*: **Tofacitinib or adalimumab versus placebo in rheumatoid arthritis**. *The New England journal of medicine* 2012, **367**(6):508-519.
22. Durez P, Malghem J, Nzeusseu Toukap A, Depresseux G, Lauwerys BR, Westhovens R, Luyten FP, Corluy L, Houssiau FA, Verschueren P: **Treatment of early rheumatoid arthritis: a randomized magnetic resonance imaging study comparing the effects of methotrexate**

alone, methotrexate in combination with infliximab, and methotrexate in combination with intravenous pulse methylprednisolone. *Arthritis Rheum* 2007, **56**(12):3919-3927.

23. Choy EH, Kingsley GH, Khoshaba B, Pipitone N, Scott DL: **A two year randomised controlled trial of intramuscular depot steroids in patients with established rheumatoid arthritis who have shown an incomplete response to disease modifying antirheumatic drugs**. *Ann Rheum Dis* 2005, **64**(9):1288-1293.
24. Gerlag DM, Haringman JJ, Smeets TJ, Zwinderman AH, Kraan MC, Laud PJ, Morgan S, Nash AF, Tak PP: **Effects of oral prednisolone on biomarkers in synovial tissue and clinical improvement in rheumatoid arthritis**. *Arthritis Rheum* 2004, **50**(12):3783-3791.
25. Ciconelli RM, Ferraz MB, Visioni RA, Oliveira LM, Atra E: **A randomized double-blind controlled trial of sulphasalazine combined with pulses of methylprednisolone or placebo in the treatment of rheumatoid arthritis**. *British journal of rheumatology* 1996, **35**(2):150-154.
26. Fransen J, Moens HB, Speyer I, van Riel PL: **Effectiveness of systematic monitoring of rheumatoid arthritis disease activity in daily practice: a multicentre, cluster randomised controlled trial**. *Ann Rheum Dis* 2005, **64**(9):1294-1298.
27. Symmons D, Tricker K, Roberts C, Davies L, Dawes P, Scott DL: **The British Rheumatoid Outcome Study Group (BROSG) randomised controlled trial to compare the effectiveness and cost-effectiveness of aggressive versus symptomatic therapy in established rheumatoid arthritis**. *Health technology assessment (Winchester, England)* 2005, **9**(34):iii-iv, ix-x, 1-78.
28. Grigor C, Capell H, Stirling A, McMahon AD, Lock P, Vallance R, Kincaid W, Porter D: **Effect of a treatment strategy of tight control for rheumatoid arthritis (the TICORA study): a single-blind randomised controlled trial**. *Lancet* 2004, **364**(9430):263-269.
29. Ostergaard M, Emery P, Conaghan PG, Fleischmann R, Hsia EC, Xu W, Rahman MU: **Significant improvement in synovitis, osteitis, and bone erosion following golimumab and methotrexate combination therapy as compared with methotrexate alone: a magnetic resonance imaging study of 318 methotrexate-naive rheumatoid arthritis patients**. *Arthritis Rheum* 2011, **63**(12):3712-3722.
30. Emery P, Fleischmann RM, Moreland LW, Hsia EC, Strusberg I, Durez P, Nash P, Amante EJ, Churchill M, Park W *et al*: **Golimumab, a human anti-tumor necrosis factor alpha monoclonal antibody, injected subcutaneously every four weeks in methotrexate-naïve patients with active rheumatoid arthritis: twenty-four-week results of a phase III, multicenter, randomized, double-blind, placebo-controlled study of golimumab before methotrexate as first-line therapy for early-onset rheumatoid arthritis**. *Arthritis Rheum* 2009, **60**(8):2272-2283.
31. Lee EB, Fleischmann R, Hall S, Wilkinson B, Bradley JD, Gruben D, Koncz T, Krishnaswami S, Wallenstein GV, Zang C *et al*: **Tofacitinib versus methotrexate in rheumatoid arthritis**. *The New England journal of medicine* 2014, **370**(25):2377-2386.
32. Gabay C, Emery P, van Vollenhoven R, Dikranian A, Alten R, Pavelka K, Klearman M, Musselman D, Agarwal S, Green J *et al*: **Tocilizumab monotherapy versus adalimumab monotherapy for treatment of rheumatoid arthritis (ADACTA): a randomised, double-blind, controlled phase 4 trial**. *Lancet* 2013, **381**(9877):1541-1550.
33. Schiff M, Keiserman M, Codding C, Songcharoen S, Berman A, Nayiager S, Saldate C, Li T, Aranda R, Becker JC *et al*: **Efficacy and safety of abatacept or infliximab vs placebo in ATTEST: a phase III, multi-centre, randomised, double-blind, placebo-controlled study in patients with rheumatoid arthritis and an inadequate response to methotrexate**. *Ann Rheum Dis* 2008, **67**(8):1096-1103.

34. Schiff M, Weinblatt ME, Valente R, van der Heijde D, Citera G, Elegbe A, Maldonado M, Fleischmann R: **Head-to-head comparison of subcutaneous abatacept versus adalimumab for rheumatoid arthritis: two-year efficacy and safety findings from AMPLE trial**. *Ann Rheum Dis* 2014, **73**(1):86-94.
35. O'Dell JR, Mikuls TR, Taylor TH, Ahluwalia V, Brophy M, Warren SR, Lew RA, Cannella AC, Kunkel G, Phibbs CS *et al*: **Therapies for active rheumatoid arthritis after methotrexate failure**. *N Engl J Med* 2013, **369**(4):307-318.
36. Burmester GR, Blanco R, Charles-Schoeman C, Wollenhaupt J, Zerbini C, Benda B, Gruben D, Wallenstein G, Krishnaswami S, Zwillich SH *et al*: **Tofacitinib (CP-690,550) in combination with methotrexate in patients with active rheumatoid arthritis with an inadequate response to tumour necrosis factor inhibitors: a randomised phase 3 trial**. *Lancet* 2013, **381**(9865):451-460.
37. Kremer J, Li ZG, Hall S, Fleischmann R, Genovese M, Martin-Mola E, Isaacs JD, Gruben D, Wallenstein G, Krishnaswami S *et al*: **Tofacitinib in combination with nonbiologic disease-modifying antirheumatic drugs in patients with active rheumatoid arthritis: a randomized trial**. *Ann Intern Med* 2013, **159**(4):253-261.
38. van der Heijde D, Tanaka Y, Fleischmann R, Keystone E, Kremer J, Zerbini C, Cardiel MH, Cohen S, Nash P, Song YW *et al*: **Tofacitinib (CP-690,550) in patients with rheumatoid arthritis receiving methotrexate: twelve-month data from a twenty-four-month phase III randomized radiographic study**. *Arthritis Rheum* 2013, **65**(3):559-570.
39. Fleischmann R, Kremer J, Cush J, Schulze-Koops H, Connell CA, Bradley JD, Gruben D, Wallenstein GV, Zwillich SH, Kanik KS: **Placebo-controlled trial of tofacitinib monotherapy in rheumatoid arthritis**. *N Engl J Med* 2012, **367**(6):495-507.
40. Tanaka Y, Suzuki M, Nakamura H, Toyoizumi S, Zwillich SH: **Phase II study of tofacitinib (CP-690,550) combined with methotrexate in patients with rheumatoid arthritis and an inadequate response to methotrexate**. *Arthritis Care Res (Hoboken)* 2011, **63**(8):1150-1158.
41. Kremer JM, Cohen S, Wilkinson BE, Connell CA, French JL, Gomez-Reino J, Gruben D, Kanik KS, Krishnaswami S, Pascual-Ramos V *et al*: **A phase IIb dose-ranging study of the oral JAK inhibitor tofacitinib (CP-690,550) versus placebo in combination with background methotrexate in patients with active rheumatoid arthritis and an inadequate response to methotrexate alone**. *Arthritis Rheum* 2012, **64**(4):970-981.
42. Kameda H, Ueki Y, Saito K, Nagaoka S, Hidaka T, Atsumi T, Tsukano M, Kasama T, Shiozawa S, Tanaka Y *et al*: **Etanercept (ETN) with methotrexate (MTX) is better than ETN monotherapy in patients with active rheumatoid arthritis despite MTX therapy: a randomized trial**. *Modern rheumatology / the Japan Rheumatism Association* 2010, **20**(6):531-538.
43. Kremer J, Ritchlin C, Mendelsohn A, Baker D, Kim L, Xu Z, Han J, Taylor P: **Golimumab, a new human anti-tumor necrosis factor alpha antibody, administered intravenously in patients with active rheumatoid arthritis: Forty-eight-week efficacy and safety results of a phase III randomized, double-blind, placebo-controlled study**. *Arthritis Rheum* 2010, **62**(4):917-928.
44. Keystone EC, Genovese MC, Klareskog L, Hsia EC, Hall ST, Miranda PC, Pazdur J, Bae SC, Palmer W, Zrubek J *et al*: **Golimumab, a human antibody to tumour necrosis factor {alpha} given by monthly subcutaneous injections, in active rheumatoid arthritis despite methotrexate therapy: the GO-FORWARD Study**. *Ann Rheum Dis* 2009, **68**(6):789-796.
45. Combe B, Codreanu C, Fiocco U, Gaubitz M, Geusens PP, Kvien TK, Pavelka K, Sambrook PN, Smolen JS, Wajdula J *et al*: **Etanercept and sulfasalazine, alone and combined, in patients with active rheumatoid arthritis despite receiving sulfasalazine: a double-blind comparison**. *Ann Rheum Dis* 2006, **65**(10):1357-1362.

46. van Riel PL, Taggart AJ, Sany J, Gaubitz M, Nab HW, Pedersen R, Freundlich B, MacPeek D: **Efficacy and safety of combination etanercept and methotrexate versus etanercept alone in patients with rheumatoid arthritis with an inadequate response to methotrexate: the ADORE study**. *Ann Rheum Dis* 2006, **65**(11):1478-1483.
47. Klareskog L, van der Heijde D, de Jager JP, Gough A, Kalden J, Malaise M, Martin Mola E, Pavelka K, Sany J, Settas L *et al*: **Therapeutic effect of the combination of etanercept and methotrexate compared with each treatment alone in patients with rheumatoid arthritis: double-blind randomised controlled trial**. *Lancet* 2004, **363**(9410):675-681.
48. Johnston SS, Turpcu A, Shi N, Fowler R, Chu BC, Alexander K: **Risk of infections in rheumatoid arthritis patients switching from anti-TNF agents to rituximab, abatacept, or another anti-TNF agent, a retrospective administrative claims analysis**. *Semin Arthritis Rheum* 2013, **43**(1):39-47.
49. Finckh A, Ciurea A, Brulhart L, Moller B, Walker UA, Courvoisier D, Kyburz D, Dudler J, Gabay C: **Which subgroup of patients with rheumatoid arthritis benefits from switching to rituximab versus alternative anti-tumour necrosis factor (TNF) agents after previous failure of an anti-TNF agent?** *Ann Rheum Dis* 2010, **69**(2):387-393.
50. Gomez-Reino JJ, Maneiro JR, Ruiz J, Rosello R, Sanmarti R, Romero AB: **Comparative effectiveness of switching to alternative tumour necrosis factor (TNF) antagonists versus switching to rituximab in patients with rheumatoid arthritis who failed previous TNF antagonists: the MIRAR Study**. *Ann Rheum Dis* 2012, **71**(11):1861-1864.
51. Chatzidionysiou K, van Vollenhoven RF: **Rituximab versus anti-TNF in patients who previously failed one TNF inhibitor in an observational cohort**. *Scand J Rheumatol* 2013, **42**(3):190-195.
52. Kekow J, Mueller-Ladner U, Schulze-Koops H: **Rituximab is more effective than second anti-TNF therapy in rheumatoid arthritis patients and previous TNFalpha blocker failure**. *Biologics : targets & therapy* 2012, **6**:191-199.
53. Soliman MM, Hyrich KL, Lunt M, Watson KD, Symmons DP, Ashcroft DM: **Rituximab or a second anti-tumor necrosis factor therapy for rheumatoid arthritis patients who have failed their first anti-tumor necrosis factor therapy? Comparative analysis from the British Society for Rheumatology Biologics Register**. *Arthritis Care Res (Hoboken)* 2012, **64**(8):1108-1115.
54. Emery P, Gottenberg JE, Rubbert-Roth A, Sarzi-Puttini P, Choquette D, Martinez Taboada VM, Barile-Fabris L, Moots RJ, Ostor A, Andrianakos A *et al*: **Rituximab versus an alternative TNF inhibitor in patients with rheumatoid arthritis who failed to respond to a single previous TNF inhibitor: SWITCH-RA, a global, observational, comparative effectiveness study**. *Ann Rheum Dis* 2014.
55. Harrold LR, Reed GW, Kremer JM, Curtis JR, Solomon DH, Hochberg MC, Greenberg JD: **The comparative effectiveness of abatacept versus anti-tumour necrosis factor switching for rheumatoid arthritis patients previously treated with an anti-tumour necrosis factor**. *Annals of the rheumatic diseases* 2014.
56. Wakabayashi H, Hasegawa M, Nishioka Y, Sudo A, Nishioka K: **Which subgroup of rheumatoid arthritis patients benefits from switching to tocilizumab versus etanercept after previous infliximab failure? A retrospective study**. *Modern rheumatology / the Japan Rheumatism Association* 2012, **22**(1):116-121.
57. Finckh A, Ciurea A, Brulhart L, Kyburz D, Moller B, Dehler S, Revaz S, Dudler J, Gabay C: **B cell depletion may be more effective than switching to an alternative anti-tumor necrosis factor agent in rheumatoid arthritis patients with inadequate response to anti-tumor necrosis factor agents**. *Arthritis Rheum* 2007, **56**(5):1417-1423.

58. Buttgereit F, Mehta D, Kirwan J, Szechinski J, Boers M, Alten RE, Supronik J, Szombati I, Romer U, Witte S *et al*: **Low-dose prednisone chronotherapy for rheumatoid arthritis: a randomised clinical trial (CAPRA-2)**. *Ann Rheum Dis* 2013, **72**(2):204-210.
59. Hansen M, Podenphant J, Florescu A, Stoltenberg M, Borch A, Kluger E, Sorensen SF, Hansen TM: **A randomised trial of differentiated prednisolone treatment in active rheumatoid arthritis. Clinical benefits and skeletal side effects**. *Ann Rheum Dis* 1999, **58**(11):713-718.
60. ten Wolde S, Breedveld FC, Hermans J, Vandenbroucke JP, van de Laar MA, Markusse HM, Janssen M, van den Brink HR, Dijkmans BA: **Randomised placebo-controlled study of stopping second-line drugs in rheumatoid arthritis**. *Lancet* 1996, **347**(8998):347-352.
61. Smolen JS, Emery P, Fleischmann R, van Vollenhoven RF, Pavelka K, Durez P, Guerette B, Kupper H, Redden L, Arora V *et al*: **Adjustment of therapy in rheumatoid arthritis on the basis of achievement of stable low disease activity with adalimumab plus methotrexate or methotrexate alone: the randomised controlled OPTIMA trial**. *Lancet* 2014, **383**(9914):321-332.
62. Smolen JS, Nash P, Durez P, Hall S, Ilivanova E, Irazoque-Palazuelos F, Miranda P, Park MC, Pavelka K, Pedersen R *et al*: **Maintenance, reduction, or withdrawal of etanercept after treatment with etanercept and methotrexate in patients with moderate rheumatoid arthritis (PRESERVE): a randomised controlled trial**. *Lancet* 2013, **381**(9870):918-929.
63. Mann DL, McMurray JJ, Packer M, Swedberg K, Borer JS, Colucci WS, Djian J, Drexler H, Feldman A, Kober L *et al*: **Targeted anticytokine therapy in patients with chronic heart failure: results of the Randomized Etanercept Worldwide Evaluation (RENEWAL)**. *Circulation* 2004, **109**(13):1594-1602.
64. Chung ES, Packer M, Lo KH, Fasanmade AA, Willerson JT: **Randomized, double-blind, placebo-controlled, pilot trial of infliximab, a chimeric monoclonal antibody to tumor necrosis factor-alpha, in patients with moderate-to-severe heart failure: results of the anti-TNF Therapy Against Congestive Heart Failure (ATTACH) trial**. *Circulation* 2003, **107**(25):3133-3140.
65. Lok AS, McMahon BJ: **Chronic hepatitis B**. *Hepatology* 2007, **45**(2):507-539.
66. Lok AS, McMahon BJ: **Chronic hepatitis B: update 2009**. *Hepatology* 2009, **50**(3):661-662.
67. Thong BY, Koh ET, Chng HH, Chow WC: **Outcomes of chronic hepatitis B infection in Oriental patients with rheumatic diseases**. *Annals of the Academy of Medicine, Singapore* 2007, **36**(2):100-105.
68. Lan JL, Chen YM, Hsieh TY, Chen YH, Hsieh CW, Chen DY, Yang SS: **Kinetics of viral loads and risk of hepatitis B virus reactivation in hepatitis B core antibody-positive rheumatoid arthritis patients undergoing anti-tumour necrosis factor alpha therapy**. *Ann Rheum Dis* 2011, **70**(10):1719-1725.
69. Kim PS, Ho GY, Prete PE, Furst DE: **Safety and efficacy of abatacept in eight rheumatoid arthritis patients with chronic hepatitis B**. *Arthritis Care Res (Hoboken)* 2012, **64**(8):1265-1268.
70. Tamori A, Koike T, Goto H, Wakitani S, Tada M, Morikawa H, Enomoto M, Inaba M, Nakatani T, Hino M *et al*: **Prospective study of reactivation of hepatitis B virus in patients with rheumatoid arthritis who received immunosuppressive therapy: evaluation of both HBsAg-positive and HBsAg-negative cohorts**. *Journal of gastroenterology* 2011, **46**(4):556-564.
71. Roux CH, Brocq O, Breuil V, Albert C, Euller-Ziegler L: **Safety of anti-TNF-alpha therapy in rheumatoid arthritis and spondylarthropathies with concurrent B or C chronic hepatitis**. *Rheumatology (Oxford)* 2006, **45**(10):1294-1297.

72. Li S, Kaur PP, Chan V, Berney S: **Use of tumor necrosis factor-alpha (TNF-alpha) antagonists infliximab, etanercept, and adalimumab in patients with concurrent rheumatoid arthritis and hepatitis B or hepatitis C: a retrospective record review of 11 patients**. *Clin Rheumatol* 2009, **28**(7):787-791.
73. Pompili M, Biolato M, Miele L, Grieco A: **Tumor necrosis factor-alpha inhibitors and chronic hepatitis C: a comprehensive literature review**. *World journal of gastroenterology : WJG* 2013, **19**(44):7867-7873.
74. Zein NN: **Etanercept as an adjuvant to interferon and ribavirin in treatment-naive patients with chronic hepatitis C virus infection: a phase 2 randomized, double-blind, placebo-controlled study**. *Journal of hepatology* 2005, **42**(3):315-322.
75. Lin MV, Blonski W, Buchner AM, Reddy KR, Lichtenstein GR: **The influence of anti-TNF therapy on the course of chronic hepatitis C virus infection in patients with inflammatory bowel disease**. *Digestive diseases and sciences* 2013, **58**(4):1149-1156.
76. Marotte H, Fontanges E, Bailly F, Zoulim F, Trepo C, Miossec P: **Etanercept treatment for three months is safe in patients with rheumatological manifestations associated with hepatitis C virus**. *Rheumatology (Oxford)* 2007, **46**(1):97-99.
77. Terrier B, Saadoun D, Sene D, Sellam J, Perard L, Coppere B, Karras A, Blanc F, Buchler M, Plaisier E *et al*: **Efficacy and tolerability of rituximab with or without PEGylated interferon alfa-2b plus ribavirin in severe hepatitis C virus-related vasculitis: a long-term followup study of thirty-two patients**. *Arthritis Rheum* 2009, **60**(8):2531-2540.
78. Frankel AJ, Van Voorhees AS, Hsu S, Korman NJ, Lebwohl MG, Bebo BF, Jr., Gottlieb AB: **Treatment of psoriasis in patients with hepatitis C: from the Medical Board of the National Psoriasis Foundation**. *Journal of the American Academy of Dermatology* 2009, **61**(6):1044-1055.
79. Iannone F, La Montagna G, Bagnato G, Gremese E, Giardina A, Lapadula G: **Safety of etanercept and methotrexate in patients with rheumatoid arthritis and hepatitis C virus infection: a multicenter randomized clinical trial**. *J Rheumatol* 2014, **41**(2):286-292.
80. Ferri C, Ferraccioli G, Ferrari D, Galeazzi M, Lapadula G, Montecucco C, Triolo G, Valentini G, Valesini G: **Safety of anti-tumor necrosis factor-alpha therapy in patients with rheumatoid arthritis and chronic hepatitis C virus infection**. *J Rheumatol* 2008, **35**(10):1944-1949.
81. Peterson JR, Hsu FC, Simkin PA, Wener MH: **Effect of tumour necrosis factor alpha antagonists on serum transaminases and viraemia in patients with rheumatoid arthritis and chronic hepatitis C infection**. *Ann Rheum Dis* 2003, **62**(11):1078-1082.
82. Parke FA, Reveille JD: **Anti-tumor necrosis factor agents for rheumatoid arthritis in the setting of chronic hepatitis C infection**. *Arthritis Rheum* 2004, **51**(5):800-804.
83. Cavazzana I, Ceribelli A, Cattaneo R, Franceschini F: **Treatment with etanercept in six patients with chronic hepatitis C infection and systemic autoimmune diseases**. *Autoimmunity reviews* 2008, **8**(2):104-106.
84. Cansu DU, Kalifoglu T, Korkmaz C: **Short-term course of chronic hepatitis B and C under treatment with etanercept associated with different disease modifying antirheumatic drugs without antiviral prophylaxis**. *J Rheumatol* 2008, **35**(3):421-424.
85. Raaschou P, Simard JF, Holmqvist M, Askling J: **Rheumatoid arthritis, anti-tumour necrosis factor therapy, and risk of malignant melanoma: nationwide population based prospective cohort study from Sweden**. *Bmj* 2013, **346**:f1939.
86. Dixon WG, Watson KD, Lunt M, Mercer LK, Hyrich KL, Symmons DP: **Influence of anti-tumor necrosis factor therapy on cancer incidence in patients with rheumatoid arthritis who have had a prior malignancy: results from the British Society for Rheumatology Biologics Register**. *Arthritis Care Res (Hoboken)* 2010, **62**(6):755-763.

87. Chakravarty EF, Michaud K, Wolfe F: **Skin cancer, rheumatoid arthritis, and tumor necrosis factor inhibitors**. *J Rheumatol* 2005, **32**(11):2130-2135.
88. Kameda T, Dobashi H, Miyatake N, Inoo M, Onishi I, Kurata N, Mitsunaka H, Kawakami K, Fukumoto T, Susaki K *et al*: **Association of higher methotrexate dose with lymphoproliferative disease onset in rheumatoid arthritis patients**. *Arthritis Care Res (Hoboken)* 2014, **66**(9):1302-1309.
89. Raaschou P, Frisell T, Askling J: **TNF inhibitor therapy and risk of breast cancer recurrence in patients with rheumatoid arthritis: a nationwide cohort study**. *Ann Rheum Dis* 2014.
90. Yun H, Xie F, Delzell E, Chen L, Levitan EB, Lewis JD, Saag KG, Beukelman T, Winthrop K, Baddley JW *et al*: **Risk of hospitalised infection in rheumatoid arthritis patients receiving biologics following a previous infection while on treatment with anti-TNF therapy**. *Ann Rheum Dis* 2015, **74**(6):1065-1071.
91. Toussirot E, Pertuiset E, Sordet C, Auge B, Wendling D, Pallot-Prades B, Collet P, Lohse A, Balblanc JC: **Safety of rituximab in rheumatoid arthritis patients with a history of severe or recurrent bacterial infection: observational study of 30 cases in everyday practice**. *Joint, bone, spine : revue du rhumatisme* 2010, **77**(2):142-145.
92. Xanthouli P, Sailer S, Fiehn C: **Rituximab (RTX) as an Alternative to TNF-Alpha Antagonists in Patients with Rheumatoid Arthritis and High Risk of Severe Infections: A Systematic Analysis of the Experience in One Center**. *Open Rheumatol J* 2012, **6**:286-289.
93. Denis B, Lefort A, Flipo RM, Tubach F, Lemann M, Ravaud P, Salmon D, Mariette X, Lortholary O: **Long-term follow-up of patients with tuberculosis as a complication of tumour necrosis factor (TNF)-alpha antagonist therapy: safe re-initiation of TNF-alpha blockers after appropriate anti-tuberculous treatment**. *Clinical microbiology and infection : the official publication of the European Society of Clinical Microbiology and Infectious Diseases* 2008, **14**(2):183-186.
94. Aggarwal R, Manadan AM, Poliyedath A, Sequeira W, Block JA: **Safety of etanercept in patients at high risk for mycobacterial tuberculosis infections**. *J Rheumatol* 2009, **36**(5):914-917.
95. Jo KW, Hong Y, Jung YJ, Yoo B, Lee CK, Kim YG, Yang SK, Byeon JS, Kim KJ, Ye BD *et al*: **Incidence of tuberculosis among anti-tumor necrosis factor users in patients with a previous history of tuberculosis**. *Respiratory medicine* 2013, **107**(11):1797-1802.
96. Cepeda EJ, Williams FM, Ishimori ML, Weisman MH, Reveille JD: **The use of anti-tumour necrosis factor therapy in HIV-positive individuals with rheumatic disease**. *Ann Rheum Dis* 2008, **67**(5):710-712.
97. Nobre CA, Callado MR, Lima JR, Gomes KW, Martiniano GV, Vieira WP: **Tuberculosis infection in rheumatic patients with infliximab therapy: experience with 157 patients**. *Rheumatol Int* 2012, **32**(9):2769-2775.
98. Zhang J, Xie F, Delzell E, Chen L, Winthrop KL, Lewis JD, Saag KG, Baddley JW, Curtis JR: **Association between vaccination for herpes zoster and risk of herpes zoster infection among older patients with selected immune-mediated diseases**. *Jama* 2012, **308**(1):43-49.
99. Zhang J, Delzell E, Xie F, Baddley JW, Spettell C, McMahan RM, Fernandes J, Chen L, Winthrop K, Curtis JR: **The use, safety, and effectiveness of herpes zoster vaccination in individuals with inflammatory and autoimmune diseases: a longitudinal observational study**. *Arthritis research & therapy* 2011, **13**(5):R174.
100. Brezinschek HP, Hofstaetter T, Leeb BF, Haindl P, Graninger WB: **Immunization of patients with rheumatoid arthritis with antitumor necrosis factor alpha therapy and methotrexate**. *Current opinion in rheumatology* 2008, **20**(3):295-299.

101. Gluck T, Muller-Ladner U: **Vaccination in patients with chronic rheumatic or autoimmune diseases**. *Clinical infectious diseases : an official publication of the Infectious Diseases Society of America* 2008, **46**(9):1459-1465.
102. Kapetanovic MC, Roseman C, Jonsson G, Truedsson L, Saxne T, Geborek P: **Antibody response is reduced following vaccination with 7-valent conjugate pneumococcal vaccine in adult methotrexate-treated patients with established arthritis, but not those treated with tumor necrosis factor inhibitors**. *Arthritis Rheum* 2011, **63**(12):3723-3732.
103. Coulson E, Saravanan V, Hamilton J, So KL, Morgan L, Heycock C, Rynne M, Kelly C: **Pneumococcal antibody levels after pneumovax in patients with rheumatoid arthritis on methotrexate**. *Ann Rheum Dis* 2011, **70**(7):1289-1291.
104. Leirisalo-Repo M, Kautiainen H, Laasonen L, Korpela M, Kauppi MJ, Kaipiainen-Seppanen O, Luosujarvi R, Luukkainen R, Karjalainen A, Blafield H *et al*: **Infliximab for 6 months added on combination therapy in early rheumatoid arthritis: 2-year results from an investigator-initiated, randomised, double-blind, placebo-controlled study (the NEO-RACo Study)**. *Ann Rheum Dis* 2013, **72**(6):851-857.
105. Breedveld FC, Weisman MH, Kavanaugh AF, Cohen SB, Pavelka K, van Vollenhoven R, Sharp J, Perez JL, Spencer-Green GT: **The PREMIER study: A multicenter, randomized, double-blind clinical trial of combination therapy with adalimumab plus methotrexate versus methotrexate alone or adalimumab alone in patients with early, aggressive rheumatoid arthritis who had not had previous methotrexate treatment**. *Arthritis Rheum* 2006, **54**(1):26-37.
106. O'Dell JR, Curtis JR, Mikuls TR, Cofield SS, Bridges SL, Jr., Ranganath VK, Moreland LW: **Validation of the methotrexate-first strategy in patients with early, poor-prognosis rheumatoid arthritis: results from a two-year randomized, double-blind trial**. *Arthritis Rheum* 2013, **65**(8):1985-1994.
107. van Everdingen AA, Siewertsz van Reesema DR, Jacobs JW, Bijlsma JW: **Low-dose glucocorticoids in early rheumatoid arthritis: discordant effects on bone mineral density and fractures?** *Clinical and experimental rheumatology* 2003, **21**(2):155-160.
108. van Everdingen AA, Jacobs JW, Siewertsz Van Reesema DR, Bijlsma JW: **Low-dose prednisone therapy for patients with early active rheumatoid arthritis: clinical efficacy, disease-modifying properties, and side effects: a randomized, double-blind, placebo-controlled clinical trial**. *Ann Intern Med* 2002, **136**(1):1-12.
109. Hickling P, Jacoby RK, Kirwan JR: **Joint destruction after glucocorticoids are withdrawn in early rheumatoid arthritis. Arthritis and Rheumatism Council Low Dose Glucocorticoid Study Group**. *British journal of rheumatology* 1998, **37**(9):930-936.
110. Kirwan JR: **The effect of glucocorticoids on joint destruction in rheumatoid arthritis. The Arthritis and Rheumatism Council Low-Dose Glucocorticoid Study Group**. *N Engl J Med* 1995, **333**(3):142-146.
111. Harris ED, Jr., Emkey RD, Nichols JE, Newberg A: **Low dose prednisone therapy in rheumatoid arthritis: a double blind study**. *J Rheumatol* 1983, **10**(5):713-721.
112. Chamberlain MA, Keenan J: **The effect of low doses of prednisolone compared with placebo on function and on the hypothalamic pituitary adrenal axis in patients with rheumatoid arthritis**. *Rheumatology and rehabilitation* 1976, **15**(1):17-23.