National Essential Medicine List
Tertiary Level Medication Review Process
Component: ANTINEOPLASTIC AND IMMUNOMODULATING AGENTS

MEDICINE MOTIVATION:

1. **Executive Summary**

Date: July 2018
Medicine (INN): Rituximab
Medicine (ATC): L01XC02
Indication (ICD10 code): M06.9
Patient population: Rheumatoid Arthritis patients refractory to synthetic DMARDs
Prevalence of condition: 1% of population – estimated to be similar to that seen in developed countries. [1, 2, 3]
Level of Care: Tertiary
Prescriber Level: Specialist
Current standard of Care: Synthetic disease-modifying antirheumatic drugs (sDMARDs)
Efficacy estimates: (preferably NNT): ACR50 at 24 weeks NNT = 6 (95% CI 4 - 9)
Clinical remission (DAS28) at 52 weeks: NNT = 7 (95% CI 4 -13) [4]
Reviewer name(s): Prof Reuter, Dr Makiwane

2. **Name of author(s)/motivator(s):** Prof Reuter, Dr Makiwane

3. **Author affiliation and conflict of interest details**

Prof Reuter	• Served on Advisory Boards for last 4 years. • Division of Clinical Pharmacology. • Involved in Clinical Trials - Rheumatology. • Speaker at academic meeting. • Donation for bursaries	Fees to attend Advisory Board meetings - only in field of rheumatology. Received funding for the Postgraduate diploma in Medicine Development and bursaries No direct financial compensation. Abbvie Sandoz	Potentially significant.
Dr Makiwane	No conflicts declared		

4. **Introduction/ Background**

Rituximab is a selective, B-cell depleting, biologic agent for treating refractory rheumatoid arthritis (RA). Rituximab is a chimeric monoclonal antibody targeted against CD 20 for patients who fail to respond to conventional synthetic disease modifying anti-rheumatism drugs (DMARDs) and/or other biologics. There is evidence to suggest that rituximab is effective and well tolerated when used in combination with methotrexate for RA.

Rheumatoid arthritis (RA) is an inflammatory disease, which largely affects synovial joints, typically affects the small joints of the hands and the feet, and usually both sides equally and symmetrically, although any synovial joint can be affected. It is a systemic disease and so can affect the whole body, including the heart, lungs and eyes.

Disease modification is the mainstay of RA treatment and constitutes an amalgam of characteristics: relief of signs and symptoms; normalisation—or at least important improvement—of impairment in physical function, quality of life and social and work capacity; and—as the foremost distinguishing characteristic of DMARDs compared with symptomatic agents—inhibition of structural damage to cartilage and bone.

A combination of DMARDs (including methotrexate and at least one other DMARD, plus short-term glucocorticoids) as first-line treatment should be used as soon as possible, ideally within 3 months of the onset of persistent symptoms.

Rituximab is licensed and well established for patients with non-Hodgkin's lymphoma. Rituximab has also been approved by the US Food and Drug Administration (FDA) and by the European Medicines Agency (EMA) in Europe for the treatment of patients with RA who have had an inadequate response or were intolerant to tumour necrosis factor (TNF) inhibitors. In these patients, according to the licence, rituximab is given intravenously as two 1 g infusions (with intravenous glucocorticoid premedication, separated by 2 weeks, with concomitant methotrexate.

The efficacy and durability of monotherapy is less than that of combination treatment with methotrexate (category IB). Subsequent studies on rituximab in combination with methotrexate have proved to be successful in markedly reducing inflammatory activity and increasing functional ability and quality of life (category IA). In responding patients, the duration of the response to a single course of rituximab usually lasts more than 6 months (category IB).

5. Purpose/Objective i.e. PICO question

-P *(patient/population): Adult Rheumatoid Arthritis patient's refractory to synthetic DMARD therapy.*
-I *(intervention): Rituxumab*
-C *(comparator): Synthetic DMARD therapy, other biologicals*
-O *(outcome):*

- *Improvement criteria – ACR50*
- *Disease remission (DAS28)*
- *Functional status (*Health Assessment Questionnaire (HAQ))
- *Radiographic progression*
- *Health related quality of life (*Short-Form Health Survey (SF-36))
- *Withdrawal due to adverse events*
- *Serious adverse events*

6. Methods:

Evidence synthesis

Author, date	***Type of study***	**n**	**Comparators**	**Major outcomes** (see annexures – forest plots)	**Effect sizes vs MTX monotherapy**
Lopez-Olivo et.al. 2015[4]	Systematic Review	2720	• MTX monoRx (And Other DMARDS, Placebo)	1. Improvement criteria. Measured by the ACR 50 response which represent a 50% improvement in tender and swollen joint counts plus a 50% improvement in three of the five core components	**ACR 50** At 24 weeks: RR (95% CI) = 3.25 (2.31 – 4.58) At 48-56 weeks: RR(95% CI) = 2.24 (1.26 – 3.95) At 104 weeks: 1.49 (1.25 – 1.77)

				2. Disease remission. Measured by Disease Activity Scores (DAS) < 2.6	**Clinical Remission (DAS28<2.6)** At 24 weeks: RR (95%) = 0.08 (0.06 – 0.11) At 48-52 weeks: RR (95%) = 0.11 (0.02 – 0.20) At 104 weeks: RR (95% CI) = 0.19 (0.12 – 0.26)
				3. Functional status. Measured by the Health Assessment Questionnaire (HAQ)	**HAQ-DI MCID = -0.22** At 24 weeks: RR (95% CI) = 1.61 (1.22 – 2.12) At 48-52 weeks: RR (95% CI) = 1.57 (0.71-3.44) At 104 weeks: RR (95% CI) = 1.39 (1.25 – 1.55)
				4. Radiographic progression for studies with a minimum of six months duration	**No radiographic progression** At 24 weeks: RR (95% CI) = 1.18 (1.03 – 1.35) At 52-56 weeks: RR (95% CI) = 1.25 (1.11 – 1.40) At 104 weeks: RR (95% CI) = 1.50 (1.30 – 1.73)
				5. Health-related quality of life. Measured by the Medical Outcomes Study Short-Form Health Survey (SF-36)	**SF-36 PCS (= or > MCID of 5 of 5.42)** At 24 weeks: RR (95% CI) = 2.32 (1.41 – 3.84) At 52 weeks: RR (95% CI) = 1.21 (1.07 – 1.36) Total of above: RR (95% CI) = 1.96 (1.14 – 3.36)
				6. Withdrawals due to adverse events	**Withdrawals due to adverse effects:** At 24 weeks: RR (95% CI) = 2.72 (1.04 – 7.13) At 48 – 52 weeks: RR (95% CI): 1.00 (0.44 – 2.29) At 104 weeks: RR (95% CI) = 0.56 (0.25 – 1.25)
				7. Serious adverse events	**Serious adverse events:** At 24 weeks: RR (95% CI) = 1.01 (0.69 – 1.49) At 48 – 56 weeks: RR (95% CI) = 0.94 (0.57 – 1.53) At 104 weeks: RR (95% CI) = 0.78 (0.51 – 1.19)

Clinical efficacy
Rituximab was efficacious in clinical trials of patients with RA, including those who are methotrexate naïve, those with an incomplete response to methotrexate, and those with an incomplete response to tumor necrosis factor inhibitors.

Safety
Consequences of B-cell depletion, namely low baseline IgG levels and the observation of subsequent greater infection risk and hepatitis B reactivation.

Patients considered for treatment generally should thus have active disease defined as at least moderate disease activity by composite scores, such as by the 28-joint disease activity score (DAS28, >3.2), the simplified disease activity index (SDAI, >11), the clinical disease activity index (CDAI, >10) or similar measures.

Dose
Two treatment regimens have been tested in patients with RA, namely two cycles of 1000 mg (separated by two weeks) or two cycles of 500 mg (separated by two weeks) at 6-monthly intervals, respectively, and these have been demonstrated to be equally effective in controlling disease activity.

Author, date	***Type of study***	**n**	**Primary endpoint**	**Effect sizes vs MTX monotherapy**
Mirror Trial, 2010 [5]	*Phase III – Randomised study*	123 – 2 x 500mg (repeated after 24 weeks) 128 - 2 x 500mg then 2 x 1000mg (24 weeks apart) 127 – 2 x 1000mg (repeated after 24 weeks 24 weeks apart)	Proportion of patients achieving ACR20 at week 48	At week 48 responses were not statistically significantly different between dosing regimens.

Evidence quality: All controlled trials comparing treatment with rituximab as monotherapy or in combination with any disease modifying anti-rheumatic drug (DMARD) (traditional or biologic) versus placebo or other DMARD (synthetic or biologic) in adult patients with active RA.

The level of evidence for Cochrane review[Error! Bookmark not defined.] ranged from low to high, but was rated as moderate for most outcomes.

Outcome measures
Composite indices whose comparative construct, content, and discriminant validity – the DAS28, the SDAI, and the CDAI – is well documented and widely accepted, were used to assess outcomes.[6] All of these indices include a patient self-reported measure and are simple enough to employ unrestrictedly in clinical studies and in routine practice. They allow the integration of various aspects of the disease into a single numerical value.

ACR50: based on American College of Rheumatology criteria—of at least a 50% improvement in the number of tender and swollen joints, and a 50% improvement in at least 3 of the following: the patient's global assessment of disease status; the patient's assessment of pain; the patient's assessment of function—measured using the Stanford Health Assessment Questionnaire—the physician's global assessment of disease status; serum C-reactive protein levels. ACR50 should be done by an independent blinded joint assessor.

Although there is a degree of subjectivity, this is a robust outcome used by most studies in the field of Rheumatoid Arthritis.

DAS 28: system developed and validated by the EULAR (European League Against Rheumatism) to measure the progress and improvement of Rheumatoid Arthritis. "28" describes the number of different joints including in the measurement:

- proximal interphalangeal joints (10 joints)
- metacarpophalangeal joints (10)
- wrists (2)
- elbows (2)
- shoulders (2)
- knees (2)

When looking at these joints, both the number of joints with tenderness upon touching and swelling are counted. In addition, the erythrocyte sedimentation rate is measured. In addition, the patient makes a subjective assessment of disease activity during the preceding 7 days on a scale between 0 and 100, where 0 is "no activity" and 100 is "highest activity possible".

7. **Alternative agents:** *Synthetic DMARDs, and TNF-inhibitors*

8. **Costs**

Medicine Prices *(National Contract prices, March 2018)*

Medicine	Ave Dose	Frequency	Tabs	Cost per pack	Ave Cost per annum	Ave Cost per month
Methotrexate	25mg	Weekly	2.5mg	R 87.87	R 421.78	R 35.15
Sulphasalazine	1g	12 hourly	500mg	R 236.45	R 3,177.89	R 264.82
Chloroquine	200mg	5 x weekly	200mg	R 66.79	R 60.30	R 13.36
Leflunomide	20mg	Daily	20mg	R 333.65	R 3,736.88	R 311.41
Rituximab	500mg	2-weekly every 6 months	500mg/50ml	R 7,950.01	R 33,488.04	R 2,790.67

Based on estimates from Rheumatologists, it was estimated that approximately 10 000 patients would require triple therapy for rheumatoid arthritis. Of these, it was estimated that approximately 5% would have intolerance to methotrexate or sulphasalazine, and require treatment with leflunomide (n = 500); and 10% would become refractory to synthetic DMARDs and require a biological, i.e. rituximab (n = 1000).

Using these assumptions and the current national contract prices, the annual budget impact for the addition of rituximab for this group of patients is approximately R33 500 000/year. See below table for projected budget impact for each scenario:

ANNUAL BUDGET IMPACT	
Projected Cost of current treatment (Triple rx -MTX, SSZ, CHQ)	R37,599,600.00
Projected Cost of leflunomide	R1,868,440.00
Projected Cost of rituximab	R33,488,040.00
Projected Cost of leflunomide plus SSZ plus CHQ	R3,537,532.00
Projected Cost of rituximab plus MTX	R33,909,816.00

Alternative biologicals prices, based on buy-out prices

Medicine	Ave Dose	Frequency	Strength	Pack Size	Cost per pack	Ave Cost per annum	Ave Cost per month
Infliximab	3mg/kg	Every 8 weeks	100mg/ 10ml vials	2	R 7,339.46	R 58,715.68	R 4,892.97
Etanercept	50mg	Weekly	25mg pre-fill syringe	4 injections	R 647.89	R 62,197.44	R 5,183.12

ANNUAL BUDGET IMPACT – alternative biologicals	
Projected costs of infliximab	R58,715,680.00
Projected costs of ertanercept	R62,197,440.00

The annual budget impact with use of alternative biological infliximab and ertanercept, are approximately double that of rituximab.

Economics model:

Assumptions:

- The clinical efficacy of the biologics is similar
- The QALY gains from published studies would be similar to those achieved if modelled in detail in this study
- The treatment scenario is that of a single biologic agent following treatment failure with DMARDs. No switching to another biologic was considered.
- Only medicine costs (and administration costs) would be included
- All patients respond to biologic treatment and continue treatment for the duration of the model
- Serious infections related to the treatment with biologics were not included

	5-year time horizon (with discounting)		
	Incremental Cost	**Incremental QALY**	**ICER (R/QALY)**
vs Triple Therapy			
Infliximab	218,134.27	0.204	1,069,285.66
Etanercept	267,093.60	0.914	292,224.94
Rituximab	137,201.33	0.731	187,689.91
Leflunomide	3,803.38	0.116	32,882.29
vs Methotrexate			
Infliximab	230,775.87	0.204	1,131,254.24
Etanercept	279,735.19	0.914	306,056.01
Rituximab	149,842.92	0.731	204,983.47
Leflunomide	16,444.98	0.116	142,175.59

Only leflunomide and Rituximab below ICER of R 200 000/QALY vs triple therapy

EVIDENCE TO DECISION FRAMEWORK

	JUDGEMENT	SUPPORTING EVIDENCE & ADDITIONAL CONSIDERATIONS
QUALITY OF EVIDENCE	**What is the overall confidence in the evidence of effectiveness?** Confident: [X] Not confident: [ ] Uncertain: [ ]	
BENEFITS & HARMS	**Do the desirable effects outweigh the undesirable effects?** Benefits outweigh harms: [X] Harms outweigh benefits: [ ] Benefits = harms or Uncertain: [ ]	
VALES & PREFERENCES / ACCEPTABILITY	**Is there important uncertainty or variability about how much people value the options?** Minor: [X] Major: [ ] Uncertain: [ ] **Is the option acceptable to key stakeholders?** Yes: [X] No: [ ] Uncertain: [ ]	
RESOURCE USE	**How large are the resource requirements?** More intensive: [X] Less intensive: [ ] Uncertain: [ ]	See costing above
EQUITY	**Would there be an impact on health inequity?** Yes: [ ] No: [X] Uncertain: [ ]	
FEASIBILITY	**Is the implementation of this recommendation feasible?** Yes: [X] No: [ ] Uncertain: [ ]	

Type of recommendation	We recommend against the option and for the alternative	We suggest not to use the option or to use the alternative	We suggest using either the option or the alternative	We suggest using the option	We recommend the option
	☐	☐	☐	☒	☐

NEMLC recommendation:

Rituximab (in combination with methotrexate) is recommended as a bDMARD for refractory RA and should be considered in ppatient's for refractory RA, who have failed treatment with ≥ 3 sDMARDs taken for ≥6 months[7] to be used on a **named-patient** basis as approved by a Pharmacy and Therapeutics Committee. The recommended dose is 2 x 500 mg cycles, 6-monthly.

All Pharmacy and Therapeutics Committees to monitor

Review indicator:

Evidence of efficacy	Evidence of harm	Price reduction
	X	

VEN status:

Vital	Essential	Necessary
	X	

Research priorities:

Rituximab register

Review indicators:

- Alterative biological price decrease

References:

[1] Ally MM. Rheumatoid Arthritis. SA Orthopaedic Journal. Autumn 2010.

[2] Mody GM, Cardiel MH. Challenges in the management of rheumatoid arthritis in developing countries. Best Practice & Research Clin Rheumatol 2008; 22(4):621-41.

[3] Adebajo AO, Reid DM. The pattern of rheumatoid arthritis in West Africa and comparison with a cohort of British patients. Q J Med 1991; 80(292):633-40.

[4] Lopez-Olivo MA, Amezaga Urruela M, McGahan L, Pollono EN, Suarez-Almazor ME . Rituximab for rheumatoid arthritis. Cochrane Database Syst Rev. 2015 Jan 20;1:CD007356. doi: 10.1002/14651858.CD007356.

[5] Rubbert-Roth A, Tak PP, Zerbini C, et al. Efficacy and safety of various repeat treatment dosing regimens of rituximab in patients with active rheumatoid arthritis: results of a Phase III randomized study (MIRROR). Rheumatology 2010; 49:1683–1693.

[6] Aletaha D, Smolen J. The Simplified Disease Activity Index (SDAI) and the Clinical Disease Activity Index (CDAI): a review of their usefulness and validity in rheumatoid arthritis. Clinical and experimental rheumatology, 2005.

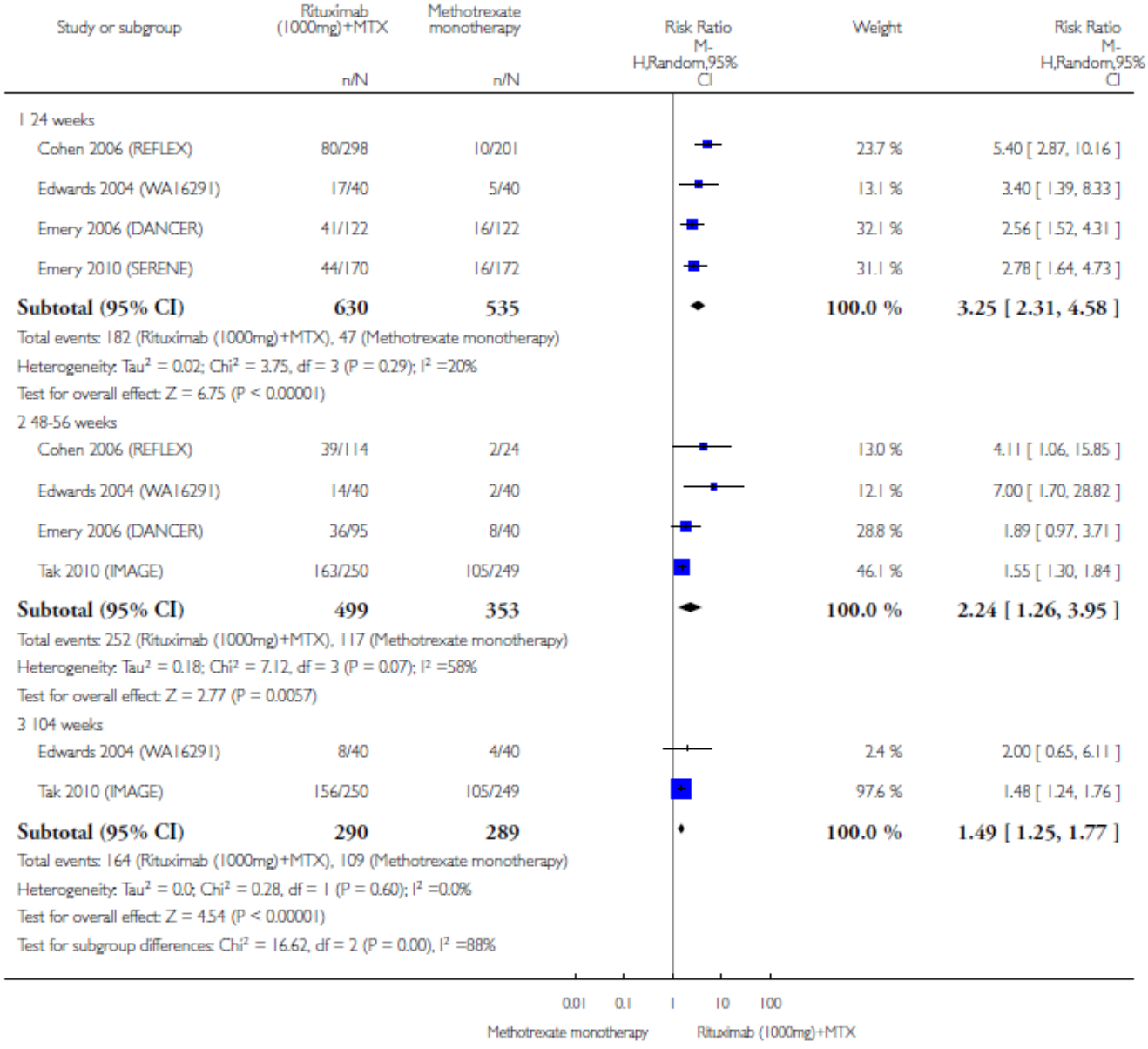
[7] Tikly M, Hodkinson B, Dheda K. Biologic therapy for rheumatoid arthritis in developing countries – a place for non-TNF inhibitors as first line treatment? Rheumatology 2015; 54: 208-209.

Analysis 1.2. Comparison 1 Benefits - RTX (2 x 1000 mg) + MTX versus MTX, Outcome 2 ACR 50.

Review: Rituximab for rheumatoid arthritis

Comparison: 1 Benefits - RTX (2 x 1000 mg) + MTX versus MTX

Outcome: 2 ACR 50



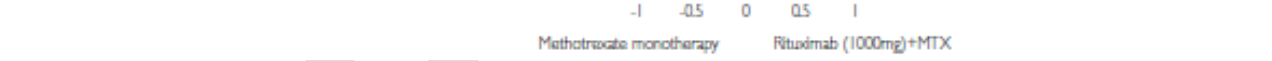
Analysis 1.7. Comparison 1 Benefits - RTX (2 x 1000 mg) + MTX versus MTX, Outcome 7 Clinical Remission (DAS28<2.6).

Review: Rituximab for rheumatoid arthritis

Comparison: 1 Benefits - RTX (2 x 1000 mg) + MTX versus MTX

Outcome: 7 Clinical Remission (DAS28<2.6)

Study or subgroup	Rituximab (1000mg)+MTX n/N	Methotrexate monotherapy n/N	Risk Difference M-H,Random,95% CI	Weight	Risk Difference M-H,Random,95% CI
1 24 weeks					
Cohen 2006 (REFLEX)	27/298	0/201		69.0 %	0.09 [0.06, 0.12]
Emery 2010 (SERENE)	16/169	4/166		31.0 %	0.07 [0.02, 0.12]
Subtotal (95% CI)	**467**	**367**		**100.0 %**	**0.08 [0.06, 0.11]**
Total events: 43 (Rituximab (1000mg)+MTX), 4 (Methotrexate monotherapy)					
Heterogeneity: $Tau^2 = 0.0$; $Chi^2 = 0.45$, df = 1 ($P = 0.50$); $I^2 = 0.0\%$					
Test for overall effect: Z = 5.95 (P < 0.00001)					
2 48-52 weeks					
Cohen 2006 (REFLEX)	14/114	1/24		30.5 %	0.08 [-0.02, 0.18]
Emery 2006 (DANCER)	10/95	2/40		32.4 %	0.06 [-0.04, 0.15]
Tak 2010 (IMAGE)	78/250	32/249		37.1 %	0.18 [0.11, 0.25]
Subtotal (95% CI)	**459**	**313**		**100.0 %**	**0.11 [0.02, 0.20]**
Total events: 102 (Rituximab (1000mg)+MTX), 35 (Methotrexate monotherapy)					
Heterogeneity: $Tau^2 = 0.00$; $Chi^2 = 6.87$, df = 2 ($P = 0.03$); $I^2 = 71\%$					
Test for overall effect: Z = 2.33 (P = 0.020)					
3 104 weeks					
Tak 2010 (IMAGE)	80/250	32/249		100.0 %	0.19 [0.12, 0.26]
Subtotal (95% CI)	**250**	**249**		**100.0 %**	**0.19 [0.12, 0.26]**
Total events: 80 (Rituximab (1000mg)+MTX), 32 (Methotrexate monotherapy)					
Heterogeneity: not applicable					
Test for overall effect: Z = 5.27 (P < 0.00001)					
Test for subgroup differences: $Chi^2 = 7.60$, df = 2 (P = 0.02), $I^2 = 74\%$					

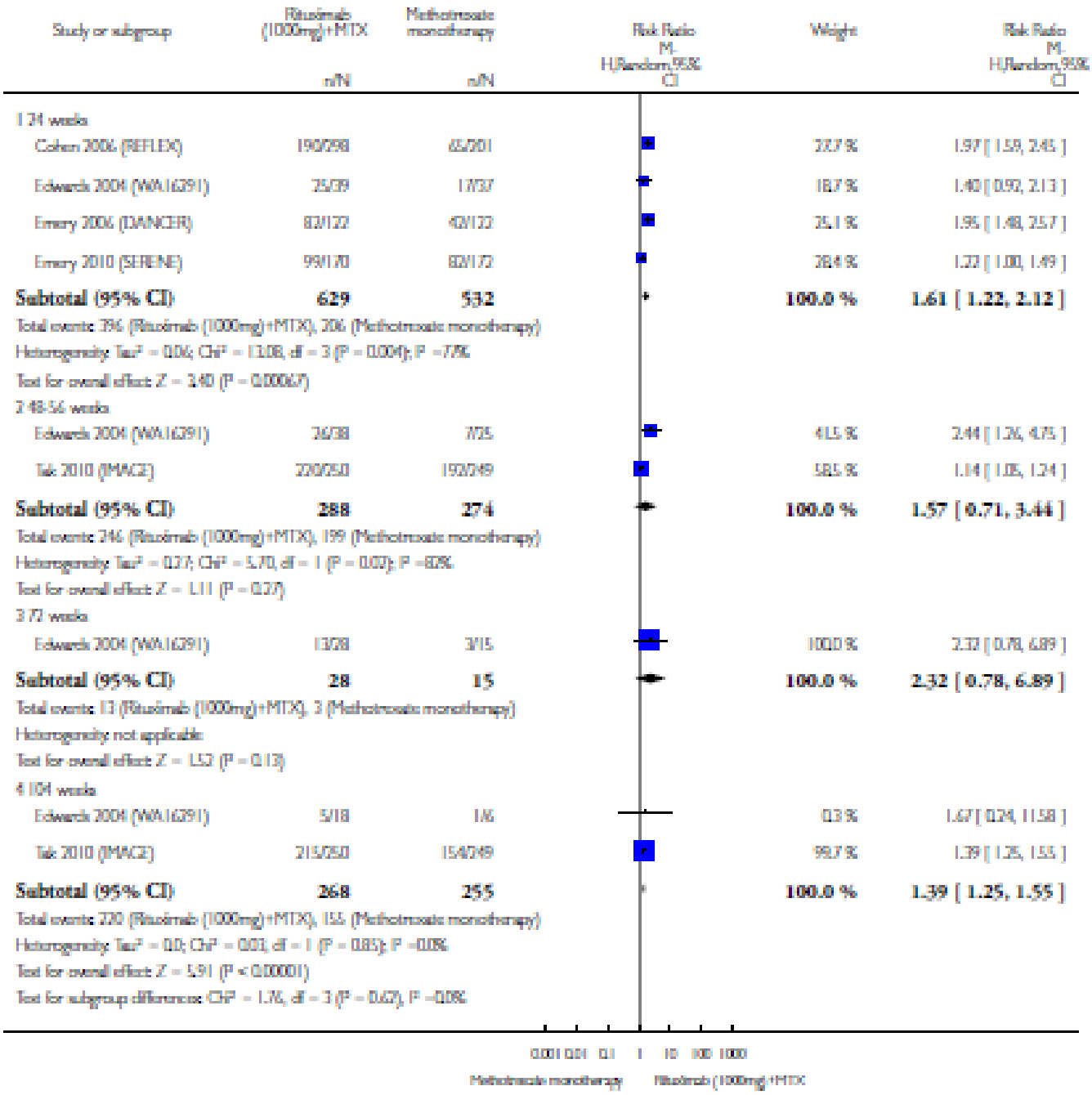


Analysis 1.10. Comparison 1 Benefits - RTX (2 x 1000 mg) + MTX versus MTX, Outcome 10 HAQ-DI MCID=-0.22.

Review: Rituximab for rheumatoid arthritis

Comparison: 1 Benefits - RTX (2 x 1000 mg) + MTX versus MTX

Outcome: 10 HAQ-DI MCID=-0.22



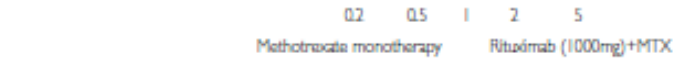
Analysis 1.21. Comparison 1 Benefits - RTX (2 x 1000 mg) + MTX versus MTX, Outcome 21 No radiographic progression.

Review: Rituximab for rheumatoid arthritis

Comparison: 1 Benefits - RTX (2 x 1000 mg) + MTX versus MTX

Outcome: 21 No radiographic progression

Study or subgroup	Rituximab (1000mg)+MTX n/N	Methotrexate monotherapy n/N	Risk Ratio M-H,Fixed,95% CI	Weight	Risk Ratio M-H,Fixed,95% CI
1 24 weeks					
Tak 2010 (IMAGE)	170/244	137/232		100.0 %	1.18 [1.03, 1.35]
Subtotal (95% CI)	**244**	**232**		**100.0 %**	**1.18 [1.03, 1.35]**
Total events: 170 (Rituximab (1000mg)+MTX), 137 (Methotrexate monotherapy)					
Heterogeneity: not applicable					
Test for overall effect: Z = 2.39 (P = 0.017)					
2 52-56 weeks					
Cohen 2006 (REFLEX)	167/278	86/186		45.0 %	1.30 [1.08, 1.56]
Tak 2010 (IMAGE)	156/244	123/232		55.0 %	1.21 [1.03, 1.41]
Subtotal (95% CI)	**522**	**418**		**100.0 %**	**1.25 [1.11, 1.40]**
Total events: 323 (Rituximab (1000mg)+MTX), 209 (Methotrexate monotherapy)					
Heterogeneity: Chi^2 = 0.38, df = 1 (P = 0.54); I^2 =0.0%					
Test for overall effect: Z = 3.68 (P = 0.00023)					
3 104 weeks					
Cohen 2006 (REFLEX)	160/281	73/187		49.9 %	1.46 [1.19, 1.79]
Tak 2010 (IMAGE)	139/244	86/233		50.1 %	1.54 [1.26, 1.89]
Subtotal (95% CI)	**525**	**420**		**100.0 %**	**1.50 [1.30, 1.73]**
Total events: 299 (Rituximab (1000mg)+MTX), 159 (Methotrexate monotherapy)					
Heterogeneity: Chi^2 = 0.15, df = 1 (P = 0.70); I^2 =0.0%					
Test for overall effect: Z = 5.55 (P < 0.00001)					
Test for subgroup differences: Chi^2 = 6.26, df = 2 (P = 0.04), I^2 =68%					



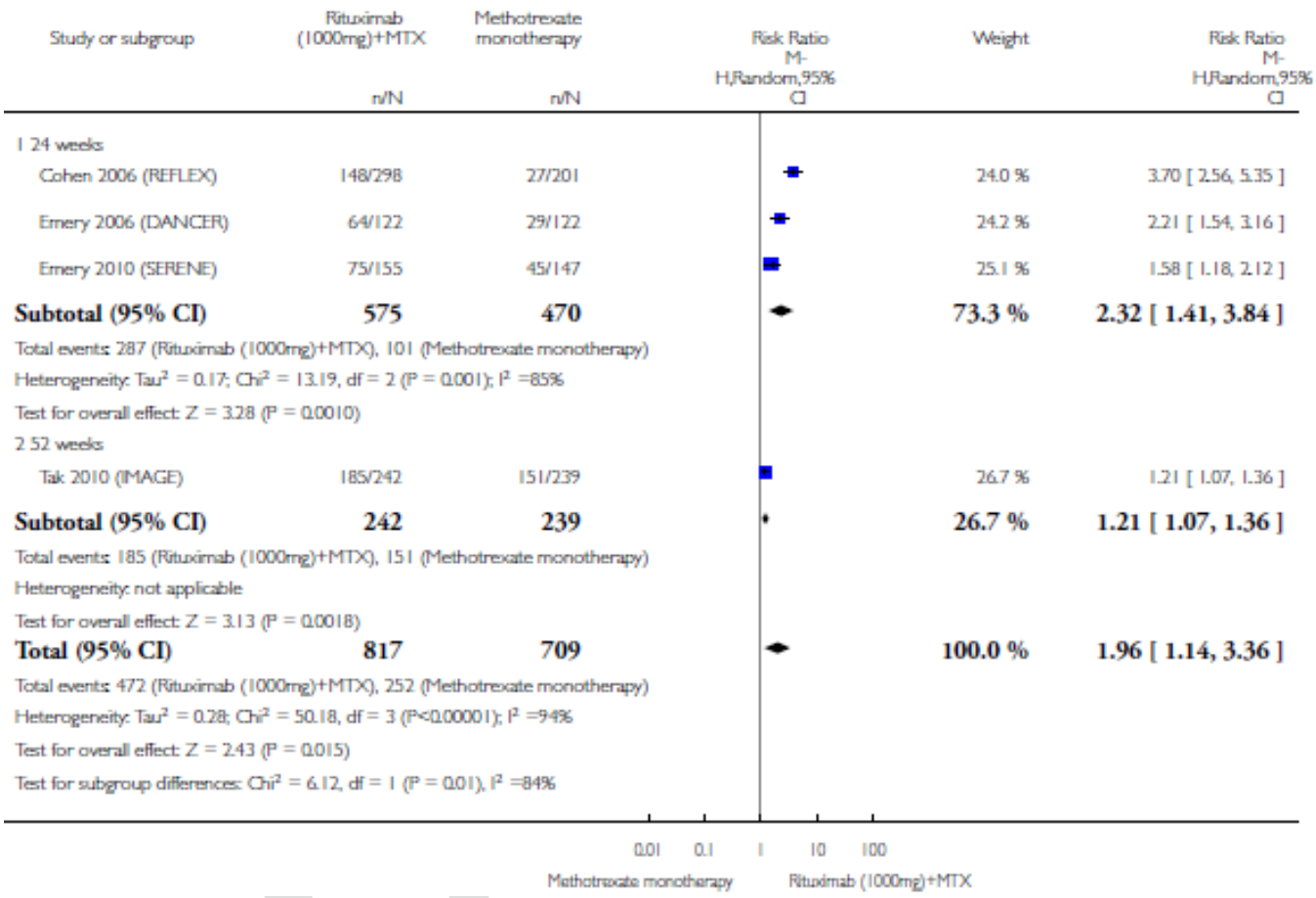
Analysis 1.12. Comparison 1 Benefits - RTX (2 x 1000 mg) + MTX versus MTX, Outcome 12 SF-36 PCS (=or>MCID of 5 or 5.42).

Review: Rituximab for rheumatoid arthritis

Comparison: 1 Benefits - RTX (2 x 1000 mg) + MTX versus MTX

Outcome: 12 SF-36 PCS (=or>MCID of 5 or 5.42)

Study or subgroup	Rituximab (1000mg)+MTX n/N	Methotrexate monotherapy n/N	Risk Ratio M-H,Random,95% CI	Weight	Risk Ratio M-H,Random,95% CI
1 24 weeks					
Cohen 2006 (REFLEX)	148/298	27/201		24.0 %	3.70 [2.56, 5.35]
Emery 2006 (DANCER)	64/122	29/122		24.2 %	2.21 [1.54, 3.16]
Emery 2010 (SERENE)	75/155	45/147		25.1 %	1.58 [1.18, 2.12]
Subtotal (95% CI)	**575**	**470**		**73.3 %**	**2.32 [1.41, 3.84]**
Total events: 287 (Rituximab (1000mg)+MTX), 101 (Methotrexate monotherapy)					
Heterogeneity: $Tau^2 = 0.17$; $Chi^2 = 13.19$, df = 2 ($P = 0.001$); $I^2 = 85\%$					
Test for overall effect: Z = 3.28 (P = 0.0010)					
2 52 weeks					
Tak 2010 (IMAGE)	185/242	151/239		26.7 %	1.21 [1.07, 1.36]
Subtotal (95% CI)	**242**	**239**		**26.7 %**	**1.21 [1.07, 1.36]**
Total events: 185 (Rituximab (1000mg)+MTX), 151 (Methotrexate monotherapy)					
Heterogeneity: not applicable					
Test for overall effect: Z = 3.13 (P = 0.0018)					
Total (95% CI)	**817**	**709**		**100.0 %**	**1.96 [1.14, 3.36]**
Total events: 472 (Rituximab (1000mg)+MTX), 252 (Methotrexate monotherapy)					
Heterogeneity: $Tau^2 = 0.28$; $Chi^2 = 50.18$, df = 3 ($P<0.00001$); $I^2 = 94\%$					
Test for overall effect: Z = 2.43 (P = 0.015)					
Test for subgroup differences: $Chi^2 = 6.12$, df = 1 ($P = 0.01$), $I^2 = 84\%$					

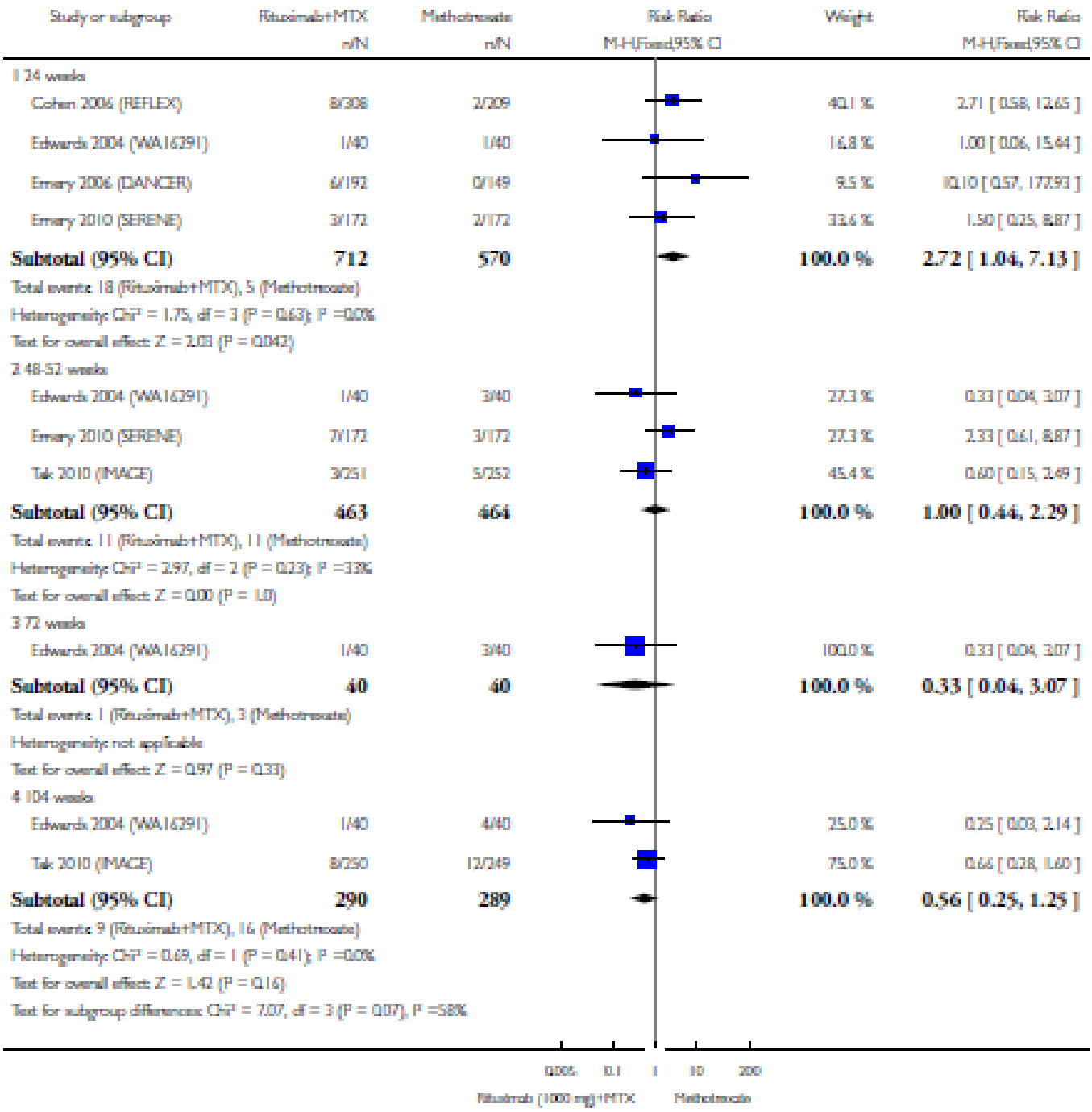


Analysis 6.3. Comparison 6 Withdrawals - RTX (2 x 1000 mg) + MTX versus MTX, Outcome 3 Adverse Events.

Review: Rituximab for rheumatoid arthritis

Comparison: 6 Withdrawals - RTX (2 x 1000 mg) + MTX versus MTX

Outcome: 3 Adverse Events



Analysis 11.2. Comparison 11 Harms - RTX (2 x 1000 mg) + MTX versus MTX, Outcome 2 Serious Adverse Events.

Review: Rituximab for rheumatoid arthritis

Comparison: 11 Harms - RTX (2 x 1000 mg) + MTX versus MTX

Outcome: 2 Serious Adverse Events