Appendix D – GRADE Quality Appraisal

Table D1. Treatment effects for direct, indirect and network meta-analysis evidence and GRADE quality appraisal

		DIRECT EVIDENCE								INDIRECT EVIDENCE			NETWORK META-ANALYSIS	
Intervention	Comparator	Number of trials for direct comparison	Treatment effect (95 % CrI)	Quality of Evidence						Treatment effect (95 % CrI)	P (indirect -direct)	Quality of evidence	Treatment effect (95 % CrI)	Quality of evidence
				Risk of bias	Inconsistency	Indirectness	Imprecision	Publication bias	OVERALL					
MTX-naïve: ACR50 response			OR							OR			OR	
MTX+ABAT (IV)	MTX	1	1.83 (1.29 to 2.61)						High	NE			1.84 (1.01 to 3.42)	High
MTX+ABAT (sc)	MTX	1	1.94 (1.15 to 3.29)						High	NE			1.98 (0.94 to 3.97)	High
MTX+ADA	MTX	4	2.11 (1.76 to 2.51)						High	NE			2.10 (1.52 to 2.87)	High
IM/sc MTX+ADA	MTX	0	NA							2.22 (0.80 to 6.06)		Moderate (imprecision)	2.22 (0.80 to 6.06)	Moderate (imprecision)
MTX+CTZ	MTX	1	1.49 (1.10 to 2.04)	Single study with high amount of incomplete outcome data (C-EARLY)					Moderate (study limitations)	NE			1.49 (0.83 to 2.68)	Moderate (study limitations)
MTX+ETN	MTX	2	2.76 (1.74 to 4.40)						High	3.87 (0.62 to 27.37)	0.72	Low (extreme imprecision)	3.00 (2.02 to 4.59)	High
MTX+GOL (sc)	MTX	1	1.32 (0.84 to 2.08)	Single study with high amount of incomplete outcome data (GO-BEFORE 2013)					Moderate (study limitations)	NE			1.33 (0.68 to 2.59)	Moderate (study limitations)
MTX+IFX	MTX	3	1.92 (1.41 to 2.63)						High	NE			2.03 (1.30 to 3.77)	High
MTX+RTX	MTX	1	2.38 (1.66 to 3.42)						High	NE			2.42 (1.30 to 4.42)	High
MTX+TCZ (4 mg/kg)	MTX	1	1.60 (1.15 to 2.22)	Single study, trial only reported as register, high WD rate (FUNCTION 2013)					Moderate (study limitations)	NE			1.66 (0.95 to 2.92)	Moderate (study limitations)
MTX+TCZ (8 mg/kg)	MTX	2	1.83 (1.32 to 2.55)						High	NE			1.91 (1.09 to 3.36)	High
MTX+TOFA	MTX	1	2.84 (1.11 to 7.47)				Wide CrI; one small study (Conaghan 2015)		Moderate (imprecision)	NE			3.04 (1.05 to 9.37)	Moderate (imprecision)
MTX+CyA	MTX	1	1.88 (0.83 to 4.29)			Single study; Steroids (IA) applied differently to arms (CIMESTRA 2006)	Crl includes no effect and a large effect		Low (indirectness, imprecision)	1.44 (0.41 to 5.07)	0.71	Low (imprecision, study limitations)	1.72 (0.86 to 3.36)	Low (indirectness, imprecision, study limitations)
IM/sc MTX+CyA	MTX	0	NA							1.57 (0.45 to 6.01)		Low (imprecision, study limitations)	1.57 (0.45 to 6.01)	Low (imprecision, study limitations)

MTX+HCQ/CQ	MTX	0	NA							0.78 (0.23 to 2.90)		Moderate (imprecision)	0.78 (0.23 to 2.90)	Moderate (imprecision)
MTX+SSZ	MTX	1	1.58 (0.37 to 7.39)			Low dose MTX in the single study (MASCOT 2007)	CrI includes no effect and a large effect		Low (indirectness, imprecision)	0.93 (0.20 to 4.22)	0.61	Low (imprecision, study limitations)	1.10 (0.41 to 2.78)	Low (indirectness, imprecision, study limitations)
MTX+SSZ+HCQ	MTX	0	NA							2.32 (1.17 to 4.79)		Moderate (indirectness)	2.32 (1.17 to 4.79)	Moderate (indirectness)
IM/sc MTX	MTX	1	1.12 (0.75 to 1.68)	Single study (Braun 2008); EE design					Moderate (study limitations)	NE			1.13 (0.59 to 2.16)	Moderate (study limitations)
ETN	MTX	3	1.57 (1.25 to 1.97)		1 study showed superiority; others showed no difference				Moderate (inconsistency)	NE			1.56 (1.11 to 2.24)	Moderate (inconsistency)
TCZ (8 mg/kg)	MTX	2	1.48 (1.18 to 1.89)						High	NE			1.49 (0.98 to 2.30)	High
CyA	MTX	1	0.33 (0.11 to 1.01)	Single study, open-label (Feraccioli)			CrI includes a large effect		Low (study limitations, imprecision)	0.46 (0.15 to 1.41)	0.65	Low (study limitations, imprecision)	0.40 (0.19 to 0.82)	Low (study limitations, imprecision)
SSZ	MTX	2	0.43 (0.19 to 0.93)	2 studies; larger is open-label					Moderate (study limitations)	NE			0.46 (0.19 to 1.00)	Moderate (study limitations)
IM/sc MTX	IM/sc MTX+ADA	1	0.52 (0.28 to 0.96)						High	NE			0.51 (0.24 to 1.10)	Moderate (imprecision)
MTX+SSZ+HCQ	MTX+ETN	1	0.76 (0.48 to 1.19)				CrI includes a large effect		Moderate (imprecision)	1.03 (0.17 to 6.73)	0.75	Moderate (imprecision)	0.77 (0.43 to 1.46)	Moderate (imprecision)
ETN	MTX+ETN	1	0.41 (0.20 to 0.83)			Single study with partial-MTX exposure (TEMPO 2004)			Moderate (indirectness)	0.68 (0.30 to 1.51)	0.30	Moderate (indirectness)	0.52 (0.32 to 0.84)	Moderate (indirectness)
MTX+TCZ (8 mg/kg)	MTX+TCZ (4 mg/kg)	1	1.15 (0.83 to 1.59)	Single study, trial only reported as register, high WD rate (FUNCTION 2013)					Moderate (study limitations)	NE			1.16 (0.63 to 2.09)	Moderate (study limitations)
TCZ (8 mg/kg)	MTX+TCZ (4 mg/kg)	1	0.88 (0.64 to 1.23)	Single study, trial only reported as register, high WD rate (FUNCTION 2013)					Moderate (study limitations)	NE			0.90 (0.52 to 1.58)	Moderate (study limitations)
TCZ (8 mg/kg)	MTX+TCZ (8 mg/kg)	1	0.77 (0.56 to 1.07)	Single study, trial only reported as register, high WD rate (FUNCTION 2013)					Moderate (study limitations)	NE			0.78 (0.45 to 1.38)	Moderate (study limitations)
CyA	MTX+CyA	2	0.24 (0.11 to 0.53)	One study open-label, the other with high WD rate					Low (study limitations)	0.19 (0.05 to 0.71)	0.74	Low (study limitations)	0.23 (0.12 to 0.43)	Low (study limitations)
IM/sc MTX	IM/sc MTX+CyA	1	0.73 (0.27 to 1.97)	Single study, open-label (Marchesoni 2003)		Low dose MTX in the single study (Marchesoni 2003)	CrI includes no effect and large effect		Low (study limitations, indirectness, imprecision)	NE			0.72 (0.22 to 2.14)	Low (study limitations, indirectness, imprecision)
MTX+SSZ	MTX+HCQ/CQ	1	1.26 (0.41 to 3.85)				CrI includes no effect and a large effect		Moderate (imprecision)	NE			1.36 (0.43 to 4.46)	Moderate (imprecision)
MTX+SSZ+HCQ	MTX+HCQ/CQ	1	2.86 (0.99 to 8.63)				CrI includes no effect and a large effect		Moderate (imprecision)	NE			3.01 (0.93 to 8.89)	Moderate (imprecision)

MTX+SSZ+HCQ	MTX+SSZ	1	2.28 (0.78 to 6.82)				CrI includes no effect and a large effect		Moderate (imprecision)	NE			2.16 (0.85 to 5.64)	Moderate (imprecision)
SSZ	MTX+SSZ	1	0.44 (0.09 to 2.00)			Low dose MTX in the single study (MASCOT 2007)	CrI includes no effect and a large effect		Low (indirectness, imprecision)	0.42 (0.07 to 2.51)	0.97	Low (study limitations, imprecision)	0.41 (0.14 to 1.30)	Low (study limitations, indirectness, imprecision)
SSZ	CyA	1	1.13 (0.39 to 3.34)	Single study, open-label (Feraccioli 2002)			CrI includes no effect and a large effect		Moderate (study limitations, imprecision)	1.33 (0.16 to 8.53)	0.90	Low (study limitations, imprecision)	1.14 (0.45 to 2.81)	Moderate (study limitations, imprecision)
MTX-naïve: Radiographic progression			**SMD**							**SMD**			**SMD**	
MTX+ABAT (IV)	MTX	1	-0.20 (-0.38 to -0.03)						High	NE			-0.20 (-0.60 to 0.19)	Moderate (imprecision)
MTX+ADA	MTX	2	-0.40 (-0.53 to -0.26)						High	NE			-0.37 (-0.64 to -0.08)	High
MTX+CTZ	MTX	2	-0.39 (-0.54 to -0.24)	One study had high rate of WD, other only published as abstract					Moderate (study limitations)	NE			-0.39 (-0.68 to -0.10)	Moderate (study limitations)
MTX+ETN	MTX	3	-0.37 (-0.50 to -0.23)						High	NE			-0.37 (-0.59 to -0.11)	High
MTX+GOL (sc)	MTX	1	-0.13 (-0.35 to 0.09)	Single study with high amount of incomplete outcome data (GO-BEFORE 2013)					Moderate (study limitations)	NE			-0.13 (-0.53 to 0.29)	Low (study limitations, imprecision)
MTX+IFX	MTX	1	-0.43 (-0.59 to -0.26)						High	NE			-0.43 (-0.82 to -0.04)	High
MTX+RTX	MTX	1	-0.38 (-0.57 to -0.20)						High	NE			-0.38 (-0.79 to 0.01)	Moderate (imprecision)
MTX+TCZ (4 mg/kg)	MTX	1	-0.24 (-0.45 to -0.03)	Single study, trial only reported as register, high WD rate (FUNCTION 2013)					Moderate (study limitations)	NE			-0.25 (-0.66 to 0.16)	Moderate (study limitations)
MTX+TCZ (8 mg/kg)	MTX	1	-0.36 (-0.55 to -0.17)	Single study, trial only reported as register, high WD rate (FUNCTION 2013)					Moderate (study limitations)	NE			-0.37 (-0.77 to 0.03)	Moderate (study limitations)
MTX+TOFA	MTX	1	-0.20 (-0.76 to 0.36)				Wide CrI; one small study (Conaghan 2015)		Moderate (imprecision)	NE			-0.21 (-0.85 to 0.47)	Moderate (imprecision)
MTX+CyA	MTX	2	-0.23 (-0.39 to -0.07)			Steroids used in both trials (CARDERA 2008, CIMESTRA 2006), with imbalance in CIMESTRA 2006			Moderate (indirectness)	NE			-0.21 (-0.50 to 0.10)	Low (study limitations, imprecision)
MTX+SSZ+HCQ	MTX	0	NA							-0.03 (-0.75 to 0.72)		Moderate (imprecision)	-0.03 (-0.75 to 0.72)	Moderate (imprecision)
ETN	MTX	3	-0.31 (-0.42 to -0.19)						High	NE			-0.29 (-0.51 to -0.07)	High

TCZ (8 mg/kg)	MTX	1	-0.30 (-0.49 to -0.11)	Single study, trial only reported as register, high WD rate (FUNCTION 2013)					Moderate (study limitations)	NE			-0.30 (-0.70 to 0.09)	Low (study limitations, imprecision)
MTX+SSZ+HCQ	MTX+ETN	2	0.35 (-0.28 to 0.96)						Moderate (imprecision)	NE			0.33 (-0.36 to 1.05)	Moderate (imprecision)
ETN	MTX+ETN	2	0.13 (0.04 to 0.23)						High	NE			0.08 (-0.22 to 0.34)	Moderate (imprecision)
MTX+TCZ (8 mg/kg)	MTX+TCZ (4 mg/kg)	1	-0.12 (-0.26 to 0.03)	Single study, trial only reported as register, high WD rate (FUNCTION 2013)					Moderate (study limitations)	NE			-0.12 (-0.50 to 0.26)	Low (study limitations, imprecision)
TCZ (8 mg/kg)	MTX+TCZ (4 mg/kg)	1	-0.05 (-0.19 to 0.09)	Single study, trial only reported as register, high WD rate (FUNCTION 2013)					Moderate (study limitations)	NE			-0.05 (-0.43 to 0.33)	Low (study limitations, imprecision)
TCZ (8 mg/kg)	MTX+TCZ (8 mg/kg)	1	0.06 (-0.05 to 0.17)	Single study, trial only reported as register, high WD rate (FUNCTION 2013)					Moderate (study limitations)	NE			0.06 (-0.31 to 0.43)	Low (study limitations, imprecision)
MTX-naïve: Withdrawals due to adverse events			**RR**							**RR**			**RR**	
MTX+ABAT (IV)	MTX	1	0.89 (0.68 to 1.16)						High	NE			0.70 (0.21 to 2.35)	High
MTX+ABAT (sc)	MTX	1	0.98 (0.65 to 1.48)						High	NE			0.97 (0.20 to 4.89)	Moderate (imprecision)
MTX+ADA	MTX	4	1.30 (0.92 to 1.88)						High	NE			1.21 (0.63 to 2.18)	High
IM/sc MTX+ADA	MTX	0	NA							0.81 (0.07 to 8.06)		Moderate (imprecision)	0.81 (0.07 to 8.06)	Moderate (imprecision)
MTX+ETN	MTX	3	0.93 (0.45 to 2.75)						High	0.35 (0.05 to 2.14)	0.28	Moderate (imprecision)	0.80 (0.45 to 1.64)	High
MTX+GOL (sc)	MTX	1	1.35 (1.00 to 1.82)	Single study; high rates of early escape (GO-BEFORE 2013)			CrI includes no effect and a large effect		Low (study limitations, imprecision)	NE			2.36 (0.67 to 9.67)	Low (study limitations, imprecision)
MTX+IFX	MTX	4	2.52 (1.36 to 5.15)						High	NE			2.53 (0.94 to 7.81)	Moderate (imprecision)
MTX+RTX	MTX	1	0.95 (0.74 to 1.22)						High	NE			0.83 (0.22 to 3.01)	Moderate (imprecision)
MTX+TCZ (4 mg/kg)	MTX	1	1.22 (0.95 to 1.54)	Single study, trial only reported as register, early escape design and EE patients not reported (FUNCTION 2013)					Low (study limitations)	NE			1.33 (0.46 to 3.77)	Low (study limitations, imprecision)
MTX+TCZ (8 mg/kg)	MTX	1	1.60 (1.26 to 2.05)	Single study, trial only reported as register, early escape design and EE patients not reported (FUNCTION 2013)					Low (study limitations)	NE			2.26 (0.82 to 6.38)	Low (study limitations, imprecision)
MTX+TOFA	MTX	1	0.94 (0.47 to 1.90)						High	NE			0.90 (0.17 to 4.56)	Moderate (imprecision)
MTX+AZA	MTX	3	4.25 (1.67 to 19.05)			Low MTX dosing			Moderate (indirectness)	NE			5.79 (1.58 to 24.31)	Moderate (indirectness)

MTX+CyA	MTX	2	1.17 (0.83 to 1.65)			Steroids used in both trials (CARDERA 2008, CIMESTRA 2006), with imbalance in CIMESTRA 2006			Moderate (indirectness)	NE			1.06 (0.37 to 2.38)	Moderate (indirectness)
IM/sc MTX+CyA	MTX	0	NA							8.89 (0.98 to 139.30)		Very low (extreme imprecision, indirectness)	8.89 (0.98 to 139.30)	Very low (extreme imprecision, indirectness)
MTX+HCQ/CQ	MTX	1	3.72 (0.33 to 118.89)				Very wide CrI		Very low (extreme imprecision)	1.01 (0.21 to 4.48)	0.36	Low (imprecision)	1.35 (0.40 to 5.26)	Low (imprecision)
MTX+SSZ	MTX	4	1.21 (0.70 to 2.12)			Low MTX dosing in all trials			Moderate (indirectness)	NE			1.31 (0.67 to 2.78)	Moderate (indirectness)
MTX+SSZ+HCQ	MTX	2	0.25 (0.05 to 0.84)				Wide CrI		Moderate (imprecision)	NE			0.67 (0.28 to 1.51)	Moderate (imprecision)
IM/sc MTX	MTX	1	1.39 (0.91 to 2.15)				Wide CrI		Moderate (imprecision)	NE			1.85 (0.56 to 6.69)	Moderate (imprecision)
ETN	MTX	3	0.85 (0.59 to 1.20)						High	NE			0.89 (0.49 to 1.78)	High
TCZ (8 mg/kg)	MTX	2	1.31 (0.84 to 2.07)	One study reported only as abstract (Function 2013)	Point estimates of 2 trials showed opposite effects				Low (study limitations, inconsistency)	NE			1.26 (0.55 to 2.78)	Low (study limitations, inconsistency
SSZ+HCQ	MTX	1	0.67 (0.38 to 1.18)				Wide CrI		Moderate (imprecision)	NE			0.48 (0.08 to 2.30)	Moderate (imprecision)
AZA	MTX	3	8.60 (3.67 to 24.57)		1/3 trials found no difference	Low MTX dosing in all trials			Low (inconsistency, indirectness)	NE			8.27 (2.91 to 27.77)	Low (inconsistency, indirectness)
SSZ	MTX	3	1.32 (0.76 to 2.32)			Low MTX dosing			Moderate (indirectness)	NE			1.49 (0.73 to 3.46)	Moderate (indirectness)
IM/sc MTX	IM/sc MTX+ADA	1	1.37 (0.72 to 2.68)						High	NE			2.28 (0.32 to 20.20)	Low (imprecision)
MTX+SSZ+HCQ	MTX+ETN	1	1.08 (0.85 to 1.39)						High	0.47 (0.10 to 1.57)	0.24	High	0.83 (0.31 to 1.87)	High
ETN	MTX+ETN	1	1.12 (0.27 to 4.58)						Moderate (imprecision)	1.05 (0.21 to 4.06)	0.95	Moderate (imprecision)	1.12 (0.49 to 2.45)	High
MTX+TCZ (8 mg/kg)	MTX+TCZ (4 mg/kg)	1	1.32 (1.04 to 1.67)	Single study, trial only reported as register, early escape design and EE patients not reported (FUNCTION 2013)					Low (study limitations)	NE			1.71 (0.58 to 5.02)	Low (study limitations)
TCZ (8 mg/kg)	MTX+TCZ (4 mg/kg)	1	1.04 (0.82 to 1.31)	Single study, trial only reported as register, early escape design and EE patients not reported (FUNCTION 2013)					Low (study limitations)	NE			0.95 (0.33 to 2.57)	Low (study limitations)
TCZ (8 mg/kg)	MTX+TCZ (8 mg/kg)	1	0.79 (0.62 to 0.99)	Single study, trial only reported as register, early escape design and EE patients not reported (FUNCTION 2013)					Low (study limitations)	NE			0.56 (0.20 to 1.48)	Low (study limitations)

IM/sc MTX	IM/sc MTX+CyA	1	0.47 (0.20 to 0.99)	Single study, open-label (Marchesoni 2003)		Low dose MTX in the single study (Marchesoni 2003)			Low (study limitations, indirectness)	NE			0.21 (0.02 to 1.26)	Very low (study limitations, indirectness, imprecision)
MTX+SSZ	MTX+HCQ/CQ	1	1.11 (0.21 to 6.14)				Wide CrI		Moderate (imprecision)	0.31 (0.006 to 5.05)	0.44	Low (imprecision)	0.96 (0.26 to 3.45)	Moderate (imprecision)
MTX+SSZ+HCQ	MTX+HCQ/CQ	1	0.73 (0.12 to 4.13)				Wide CrI		Moderate (imprecision)	0.15 (0.004 to 2.06)	0.33	Low (imprecision)	0.49 (0.12 to 1.77)	Moderate (imprecision)
MTX+SSZ+HCQ	MTX+SSZ	1	0.63 (0.11 to 3.58)				Wide CrI		Moderate (imprecision)	0.42 (0.09 to 1.41)	0.71	Low (imprecision)	0.51 (0.18 to 1.29)	Moderate (imprecision)
SSZ	MTX+SSZ	3	1.18 (0.69 to 2.01)			Low MTX dosing			Moderate (indirectness)	NE			1.15 (0.55 to 2.48)	Moderate (indirectness)
SSZ+HCQ	MTX+SSZ+HCQ	1	1.04 (0.59 to 1.86)						High	NE			0.71 (0.11 to 3.50)	Moderate (imprecision)
MTX-inadequate response: ACR50 response			**OR**							**OR**			**OR**	
MTX+ABAT (IV)	MTX	5	3.76 (2.54 to 5.65)						High	3.65 (1.49 to 9.00)	0.95	High	3.81 (2.80 to 5.33)	High
MTX+ABAT (sc)	MTX	0	NA							4.16 (2.72 to 6.53)		High	4.16 (2.72 to 6.53)	High
MTX+ADA	MTX	10	4.46 (3.28 to 6.16)						High	4.68 (1.91 to 11.85)	0.91	High	4.37 (3.38 to 5.89)	High
MTX+ETN	MTX	3	12.29 (6.13 to 26.95)	Largest trial had open-label MTX+ETN arm (ESCAPE 2010)					Moderate (study limitations)	NE			12.31 (5.76 to 30.78)	Moderate (study limitations)
MTX+GOL (sc)	MTX	3	4.39 (2.79 to 7.07)	Relatively high WD/EE rates across trials.		Low MTX dosing			Moderate (study limitations, indirectness)	NE			4.49 (2.57 to 8.01)	Moderate (study limitations, indirectness)
MTX+GOL (IV)	MTX	1	3.47 (2.21 to 5.56)	Single trial, EE design with imputation only of PBO arm					Moderate (study limitations)	NE			3.58 (1.79 to 7.25)	Moderate (study limitations)
MTX+IFX	MTX	6	3.42 (2.61 to 4.51)						High	NE			3.46 (2.46 to 5.00)	High
MTX+RTX	MTX	3	3.62 (2.43 to 5.52)						High	NE			3.59 (2.18 to 6.27)	High
MTX+TCZ (4 mg/kg)	MTX	2	2.96 (1.94 to 4.61)						High	NE			2.57 (1.42 to 4.56)	High
MTX+TCZ (8 mg/kg)	MTX	3	4.65 (3.17 to 6.98)						High	NE			4.16 (2.46 to 6.85)	High
MTX+TOFA	MTX	3	4.22 (2.69 to 6.78)						High	NE			5.42 (3.31 to 9.01)	High
MTX+HCQ/CQ	MTX	0	NA							8.94 (2.18 to 46.14)		Low (high imprecision)	8.94 (2.18 to 46.14)	Low (high imprecision)
MTX+IMGold	MTX	1	5.89 (1.32 to 44.75)						Low (high imprecision)	NE			16.34 (2.03 to 553.42)	Low (high imprecision)
MTX+LEF	MTX	1	5.18 (2.46 to 12.08)						Moderate (imprecision)	NE			5.69 (2.23 to 16.27)	Moderate (imprecision)
MTX+SSZ	MTX	0	NA						Low (high imprecision)	2.50 (0.49 to 13.76)			2.50 (0.49 to 13.76)	Low (high imprecision)
MTX+SSZ+HCQ	MTX	0	NA						Moderate (study limitations)	10.51 (4.46 to 30.81)			10.51 (4.46 to 30.81)	Moderate (study limitations)
TCZ (4 mg/kg)	MTX	1	0.96 (0.41 to 2.25)	Single trial with moderate WD rate					Moderate (study limitations)	NE			1.43 (0.58 to 3.37)	Moderate (study limitations)

TCZ (8 mg/kg)	MTX	1	1.68 (0.62 to 4.56)	Single trial with moderate WD rate					Moderate (study limitations)	4.15 (1.72 to 9.63)	0.17	Moderate (imprecision)	3.01 (1.52 to 5.59)	Low (study limitations, imprecision, inconsistency)
MTX+ABAT (sc)	MTX+ABAT (IV)	1	1.10 (0.70 to 1.77)						High	1.04 (0.46 to 2.38)	0.88	High	1.09 (0.75 to 1.60)	High
MTX+IFX	MTX+ABAT (IV)	1	0.86 (0.42 to 1.81)						High	0.95 (0.52 to 1.72)	0.81	High	0.91 (0.58 to 1.41)	High
MTX+ADA	MTX+ABAT (sc)	1	1.08 (0.55 to 2.11)						High	1.01 (0.53 to 1.97)	0.88	High	1.05 (0.68 to 1.65)	High
MTX+TOFA	MTX+ADA	1	1.52 (0.99 to 2.33)						High	1.01 (0.46 to 2.43)	0.45	High	1.24 (0.74 to 2.06)	High
MTX+SSZ+HCQ	MTX+ETN	2	0.87 (0.63 to 1.21)		1 trial favoured MTX+ETN (RACAT 2013), the other showed no difference (TEAR 2012)	TEAR 2012 compared step-up therapy (did not randomize after MTX-IR)			Moderate (inconsistency, indirectness)	NE			0.86 (0.53 to 1.42)	Moderate (inconsistency, indirectness)
MTX+TCZ (8 mg/kg)	MTX+TCZ (4 mg/kg)	2	1.74 (1.22 to 2.48)						High	NE			1.61 (0.96 to 2.70)	Moderate (imprecision)
TCZ (4 mg/kg)	MTX+TCZ (4 mg/kg)	1	0.67 (0.29 to 1.53)				Wide CrI		Moderate (imprecision)	NE			0.55 (0.22 to 1.31)	Moderate (imprecision)
TCZ (8 mg/kg)	MTX+TCZ (4 mg/kg)	1	1.18 (0.44 to 3.14)						High	1.18 (0.45 to 2.93)	0.99	High	1.16 (0.60 to 2.17)	High
TCZ (4 mg/kg)	MTX+TCZ (8 mg/kg)	1	0.37 (0.16 to 0.81)				Wide CrI		Moderate (imprecision)	NE			0.34 (0.15 to 0.79)	Moderate (imprecision)
TCZ (8 mg/kg)	MTX+TCZ (8 mg/kg)	1	0.77 (0.57 to 1.06)						High	NE			0.73 (0.43 to 1.18)	High
MTX+SSZ	MTX+HCQ/CQ	1	0.32 (0.10 to 0.96)	Single study with high WD rate (O'Dell 2002)			Wide CrI		Moderate (study limitations, imprecision)	NE			0.28 (0.07 to 1.02)	Moderate (study limitations, imprecision)
MTX+SSZ+HCQ	MTX+HCQ/CQ	1	1.15 (0.42 to 3.18)	Single study with high WD rate (O'Dell 2002)					Moderate (study limitations)	NE			1.16 (0.35 to 3.71)	Moderate (study limitations)
MTX+SSZ+HCQ	MTX+SSZ	1	3.57 (1.16 to 12.19)	Single study with high WD rate (O'Dell 2002)			Wide CrI		Moderate (study limitations, imprecision)	NE			4.11 (1.07 to 17.49)	Moderate (study limitations, imprecision)
TCZ (8 mg/kg)	TCZ (4 mg/kg)	1	1.74 (0.78 to 3.91)						High	NE			2.11 (0.88 to 5.08)	High
MTX-inadequate response: Radiographic progression			**SMD**							**SMD**			**SMD**	
MTX+ABAT (IV)	MTX	1	-0.29 (-0.50 to -0.09)						High	NE			-0.30 (-1.44 to 0.85)	Moderate (imprecision)
MTX+ABAT (sc)	MTX	0	NA							-0.48 (-2.03 to 1.21)		Moderate (imprecision)	-0.48 (-2.03 to 1.21)	Moderate (imprecision)
MTX+ADA	MTX	1	-0.44 (-0.65 to -0.23)	Single trial, relatively high WD/EE rate					Moderate (study limitations)	NE			-0.44 (-1.53 to 0.72)	Moderate (study limitations, imprecision)
MTX+ETN	MTX	0	NA							-0.60 (-2.41 to 1.21)		Moderate (imprecision)	-0.60 (-2.41 to 1.21)	Moderate (imprecision)
MTX+GOL (sc)	MTX	2	-0.13 (-0.34 to 0.08)	High rates of escape/WD	Different effects in the 2 trials	Low MTX in 1 of trials (the trial that favoured GOL)			Low (study limitations, inconsistency, indirectness)	NE			-0.14 (-0.96 to 0.67)	Low (study limitations, inconsistency, indirectness, imprecision)

MTX+GOL (IV)	MTX	1	-0.44 (-0.64 to -0.24)	Single trial, relatively high EE					Moderate (study limitations)	NE			-0.44 (-1.55 to 0.73)	Low (study limitations, imprecision)
MTX+IFX	MTX	1	-0.68 (-1.03 to -0.34)	Single trial, relatively high WD					Moderate (study limitations)	NE			-0.69 (-1.83 to 0.47)	Low (study limitations, imprecision)
MTX+SSZ+HCQ	MTX	0	NA							-0.41 (-2.02 to 1.20)		Low (indirectness, imprecision)	-0.41 (-2.02 to 1.20)	Low (indirectness, imprecision)
MTX+ADA	MTX+ABAT (sc)	1	0.04 (-0.14 to 0.21)						High	NE			0.04 (-1.11 to 1.17)	Moderate (imprecision)
MTX+SSZ+HCQ	MTX+ETN	2	0.18 (-0.007 to 0.36)			TEAR compared step-up therapy (did not randomize after MTX-IR)			Moderate (indirectness)	NE			0.19 (-0.62 to 0.99)	Low (indirectness, imprecision)
MTX+SSZ+HCQ	MTX+IFX	1	0.28 (0.02 to 0.55)	Single trial, open-label (SWEFOT)					Moderate (study limitations)	NE			0.28 (-0.85 to 1.43)	Low (study limitations, imprecision)
MTX- inadequate response: Withdrawals due to adverse events			**RR**							**RR**			**RR**	
MTX+ABAT (IV)	MTX	6	0.82 (0.42 to 1.52)		2 largest trials showed trends towards opposite effects				Moderate (inconsistency)	0.77 (0.25 to 2.48)		Moderate (imprecision)	0.76 (0.44 to 1.30)	Moderate (inconsistency)
MTX+ABAT (sc)	MTX	0	NA							0.55 (0.28 to 1.03)		Moderate (indirectness)	0.55 (0.28 to 1.03)	Moderate (indirectness)
MTX+ADA	MTX	8	1.64 (0.94 to 2.70)						High	1.37 (0.40 to 4.59)	0.81	Moderate (indirectness)	1.44 (0.95 to 2.30)	High
MTX+CTZ	MTX	4	1.40 (0.77 to 2.68)	High rates of EE		Low MTX dosing			Low (study limitations, indirectness)	NE			1.42 (0.79 to 2.99)	Low (study limitations, indirectness)
MTX+ETN	MTX	3	1.21 (0.42 to 3.90)	Largest trial had open-label MTX+ETN arm (ESCAPE 2010)					Moderate (study limitations)	1.38 (0.42 to 4.37)	0.88	Moderate (study limitations)	1.28 (0.56 to 2.96)	Moderate (study limitations)
MTX+GOL (sc)	MTX	3	0.99 (0.39 to 2.54)	High rates of EE/WD in all trials		Low MTX dosing			Low (study limitations, indirectness)	NE			1.02 (0.39 to 2.78)	Low (study limitations, indirectness)
MTX+GOL (IV)	MTX	1	1.10 (0.73 to 1.67)	Single trial, relatively high EE					Moderate (study limitations)	NE			1.32 (0.36 to 6.31)	Low (study limitations, imprecision)
MTX+IFX	MTX	6	1.68 (0.94 to 3.09)		Inconsistent findings across trials				Moderate (inconsistency)	1.50 (0.32 to 7.45)	0.88	Moderate (imprecision)	1.62 (0.99 to 2.70)	Moderate (inconsistency)
MTX+RTX	MTX	3	2.20 (0.74 to 8.28)						Moderate (imprecision)	NE			2.07 (0.74 to 6.45)	Moderate (imprecision)
MTX+TCZ (4 mg/kg)	MTX	3	1.75 (1.09 to 2.90)						High	NE			1.63 (0.95 to 2.90)	High
MTX+TCZ (8 mg/kg)	MTX	5	1.74 (1.12 to 2.79)						High	NE			1.71 (1.01 to 2.84)	High
MTX+TOFA	MTX	4	1.15 (0.64 to 2.17)						High	NE			1.24 (0.74 to 2.26)	High
MTX+CyA	MTX	2	2.95 (1.11 to 9.40)			Low MTX dosing	Wide CrI		Low (indirectness, imprecision)	NE			3.27 (1.20 to 9.57)	Low (indirectness, imprecision)
MTX+IMGold	MTX	1	1.55 (0.66 to 3.66)				Very wide CrI		Low (imprecision)	NE			4.12 (0.49 to 102.75)	Very low (extreme imprecision)
MTX+LEF	MTX	1	1.50 (0.87 to 2.66)				Wide CrI		Moderate (imprecision)	NE			1.86 (0.74 to 4.68)	Moderate (imprecision)

MTX+SSZ+HCQ	MTX	0	NA							1.82 (0.87 to 3.92)		Moderate (imprecision)	1.82 (0.87 to 3.92)	Moderate (imprecision)
TCZ (4 mg/kg)	MTX	1	1.29 (0.47 to 3.81)				Wide CrI		Moderate (imprecision)	NE			1.52 (0.49 to 4.13)	Moderate (imprecision)
TCZ (8 mg/kg)	MTX	1	1.12 (0.30 to 5.21)				Wide CrI		Moderate (imprecision)	1.35 (0.42 to 4.33)	0.84	Moderate (imprecision)	1.33 (0.58 to 2.89)	Moderate (imprecision)
MTX+ABAT (sc)	MTX+ABAT (IV)	3	0.72 (0.37 to 1.31)			2 of 3 trials had low MTX dosing			Moderate (study limitations)	0.78 (0.23 to 2.38)	0.89	Moderate (imprecision)	0.72 (0.42 to 1.26)	Moderate (study limitations)
MTX+IFX	MTX+ABAT (IV)	1	3.34 (0.82 to 16.50)				Wide CrI		Moderate (imprecision)	1.86 (0.84 to 3.87)	0.47	Moderate (imprecision)	2.14 (1.11 to 4.56)	Moderate (imprecision)
MTX+ADA	MTX+ABAT (sc)	1	2.69 (1.20 to 6.28)				Wide CrI		Moderate (imprecision)	2.79 (1.02 to 7.81)	0.97	Moderate (imprecision)	2.67 (1.42 to 4.89)	Moderate (imprecision)
MTX+TOFA	MTX+ADA	1	0.97 (0.74 to 1.27)						High	0.67 (0.28 to 1.64)	0.51	High	0.86 (0.49 to 1.54)	High
MTX+SSZ+HCQ	MTX+ETN	2	1.39 (0.75 to 2.60)			TEAR compared step-up therapy (did not randomize after MTX-IR)			Moderate (indirectness)	1.56 (0.34 to 6.72)	0.92	Low (Study limitations, imprecision)	1.43 (0.78 to 2.83)	Moderate
MTX+SSZ+HCQ	MTX+IFX	1	1.07 (0.82 to 1.40)	Single trial, open-label (SWEFOT)					Moderate (study limitations)	1.14 (0.25 to 6.07)	0.95	Moderate (imprecision)	1.13 (0.57 to 2.20)	Moderate
MTX+TCZ (8 mg/kg)	MTX+TCZ (4 mg/kg)	3	1.10 (0.74 to 1.63)						High	NE			1.05 (0.64 to 1.65)	High
TCZ (4 mg/kg)	MTX+TCZ (4 mg/kg)	1	0.95 (0.30 to 2.88)						High	NE			0.92 (0.32 to 2.39)	High
TCZ (8 mg/kg)	MTX+TCZ (4 mg/kg)	1	0.81 (0.20 to 2.77)						High	0.83 (0.26 to 2.42)	0.97	High	0.80 (0.37 to 1.70)	High
TCZ (4 mg/kg)	MTX+TCZ (8 mg/kg)	1	0.97 (0.31 to 2.92)						High	NE			0.89 (0.31 to 2.26)	High
TCZ (8 mg/kg)	MTX+TCZ (8 mg/kg)	2	0.79 (0.39 to 1.55)						High	NE			0.77 (0.39 to 1.51)	High
TCZ (8 mg/kg)	TCZ (4 mg/kg)	1	0.87 (0.30 to 2.45)						High	NE			0.86 (0.31 to 2.80)	High

Treatment effects and evidence quality were assessed for all treatments compared to MTX and additional treatment comparisons where direct evidence was available.
Abbreviations: ABAT, abatacept; ADA, adalimumab; CTZ, certolizumab; CyA, cyclosporine; ETN, etanercept; GOL, golimumab; HCQ, hydroxychloroquine; IFX, infliximab; IM, intra-muscular; IV, intravenous; LEF, leflunomide; MTX, methotrexate; NA, not applicable (no evidence); NE, not estimable; OR, odds ratio; RR, rate ratio; RTX, rituximab; sc, subcutaneous; SMD, standardized mean difference; SSZ, sulphasalazine; TCZ, tocilizumab; TOFA, tofacitinib