Supplementary Material

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Issue Addressed	Fournier 2019	Chen_2019	Navarro _2020	Lei Tian 2020	Van De Laar_2020	Muszsbek 2019	Min young lee_2015	So Young Ha_2021	Schleuter 2019	Jansen 2017	Claxton 2018	Fatemi 2020	Tan 2021(1)	Tan 2021(2)	SiniLI _2021 (1)	SiniLI _2021 (2)	Kuwana _2022
Narrow perspective bias	Р	Υ	Υ	Υ	Y	Υ	Υ	Υ	Y	Υ	Υ	Y	Y	Υ	Υ	Y	Y
Inefficient comparator bias	Y	Y	Y	Y	Y	Υ	Y	Y	Y	Y	Y	Y	Y	Y	Υ	Y	Y
Cost measurement omission bias	Р	Υ	Р	Υ	Р	Υ	Υ	Y	Y	Y	Υ	Y	Y	Υ	Υ	Y	Р
Intermittent data collection bias	Y	Y	Р	Υ	Р	Υ	Υ	Y	Р	Y	Y	Y	Y	Υ	Υ	Y	Р
Invalid valuation bias	Р	Υ	Р	Υ	Р	Υ	Υ	Y	Р	Υ	Р	Y	Y	Υ	Р	Y	Р
Ordinal ICER bias	Y	Y	Р	Р	U	Υ	Υ	Y	Р	Y	Р	Y	Y	U	Р	Y	Р
Double-counting bias	Р	Р	U	Υ	U	Υ	Р	Y	Р	Υ	Р	Р	Y	Υ	U	U	U
Inappropriate discounting bias	Y	Y	Υ	Υ	Y	Υ	Υ	Y	Y	Y	Y	Y	Y	Υ	Υ	Y	Y
Limited sensitivity analysis bias	U	Р	Р	Р	U	Υ	U	Р	Р	Y	Р	Y	Y	Р	Υ	Р	Р
Sponsor bias	Y	Y	Υ	Υ	Y	Υ	Υ	Y	Y	Y	Y	Y	Y	Υ	Υ	Y	Y
Reporting and dissemination bias	U	U	U	U	U	Υ	U	U	Y	Y	Υ	U	Y	Υ	Υ	Y	Υ
Structural assumptions bias	Y	Y	Υ	Υ	Υ	Υ	Υ	Y	Y	Y	Y	Y	Р	Р	Υ	Y	Υ
No treatment comparator bias	Y	Y	Υ	Υ	Y	Υ	Υ	Y	Y	Y	Y	Y	Y	Υ	Υ	Y	Υ
Wrong model bias	Y	Y	Υ	Υ	Υ	Υ	Υ	Y	Y	Y	Y	Y	Y	Υ	Υ	Y	Y
Limited time horizon bias	Р	Y	Υ	Υ	Y	Υ	Υ	Y	Y	Y	Y	Y	Y	Υ	Υ	Y	Y
Bias related to data identification	Р	Y	Р	Υ	Р	Υ	U	Р	Р	Υ	Р	Y	Y	Υ	Υ	Y	Y
Bias related to baseline data	Y	Y	Р	Р	Р	Υ	U	Р	Р	Р	Р	Р	Р	Р	Р	Y	U
Bias related to treatment effects	Р	Υ	Р	Р	U	Υ	Р	Р	Р	Υ	Р	Р	Р	Υ	Υ	Y	Р
Bias related to quality-of-life weights	Р	Y	Р	Υ	Р	Υ	U	Y	Y	Y	Y	Y	Y	Υ	Р	Y	Р
Non-transparent data incorporation bias	Р	Υ	Р	Υ	Р	Υ	Υ	Y	Y	Y	Y	Y	Р	Υ	Υ	Y	Р
Limited scope bias	U	Р	Р	Y	Р	Υ	Р	Р	Р	Y	Y	Y	U	Y	Р	Р	U
Bias related to internal consistency	U	U	U	U	U	U	U	U	U	U	U	U	U	U	U	U	U

Supplementary Figure 1- Assessment of Risk of Bias using ECOBIAS Checklist

Y- Yes, N-No, P-Partly, U-Unclear, NA- Not Applicable |

Source: http://dx.doi.org/10.1586/14737167.2015.1103185

Supplementary Figure 2- Pooled INBs for JAKi vs csDMARDs/bDMARDS

of the t						
Ohida			1	INB		Weight
Siudy		NT.		with 95% C	1	(%)
Min young lee_2015			13,495 [-4,465,	31,456]	9.17
Jansen_2017	2		48,031 [-30,775,	126,838]	3.50
Claxton_2018			103,005 [98,133,	107,878]	9.99
Chen_2019	<	•	798 [-255,674,	257,269]	0.48
Muszsbek_2019	< .		-14,492 [-270,964,	241,979]	0.48
Max Schleuter_2019			5,383 [2,946,	7,819]	10.05
Navarro_2020			43,111 [38,892,	47,331]	10.01
Lei Tian_2020			24,602 [6,642,	42,563]	9.17
Celine Van De Laar_2020	۰ ۱		-1,407 [-123,449,	120,635]	1.83
Fatemi_2020	аў.		16,184 [-75,028,	107,395]	2.86
So Young Ha_2021			9,783 [6,337,	13,228]	10.03
Tan_2021(1)			10,554 [-25,367,	46,475]	7.24
Tan_2021(2)	←		-88,646 [-145,441,	-31,850]	5.10
SiNi Li_2021(1)	1		1,151 [-1,286,	3,587]	10.05
Kuwana_2022			18,402 [14,957,	21,848]	10.03
Overall		-	19,886 [1,635,	38,137]	
Heterogeneity: $\tau^2 = 8.61e+08$, $I^2 = 99.14\%$, $H^2 = 116.17$ Test of $\theta_i = \theta_i$: Q(14) = 1626.38, p = 0.00	Not Cost-effective	Cost-effective				
na mananana dan kata kata kata kata kata kata kata ka	-100000-50000	0 50000 1000 n US\$	00			
	1110	1,03 COC 5 123				

JAKi vs csDMARDs/bDMARDs

Random-effects DerSimonian-Laird model Sorted by: Year

Omitted study		INB with 95% CI	p-value
Chen 2019		19976.92 [1676.61, 382	77.24] 0.032
Navarro 2020 -	•	17210.33 [-2299.60, 367	20.26] 0.084
Lei Tian_2020		19385.47 [170.19, 386	00.74] 0.048
Celine Van De Laar_2020		20281.22 [1854.98, 387	07.46] 0.031
Muszsbek_2019		20051.11 [1751.00, 383	51.22] 0.032
Min young lee_2015	•	20505.48 [1287.29, 397	23.68] 0.037
So Young Ha_2021		20376.20 [-534.12, 412	86.52] 0.056
Max Schleuter_2019 -	e	20527.07 [-1323.01, 423	77.16] 0.066
Jansen_2017	•	18863.47 [279.22, 374	47.72] 0.047
Claxton_2018		13512.62 [3317.69, 237	07.54] 0.009
Fatemi_2020	·	19992.80 [1467.15, 385	18.45] 0.034
Tan_2021(1)	•	20607.54 [1636.96, 395	78.11] 0.033
Tan_2021(2)		25720.90 [7043.32, 443	98.48] 0.007
SiNi Li_2021(1)	•	21213.54 [23.63, 424	03.46] 0.050
Kuwana_2022 -		19406.57 [-1606.09, 404	19.24] 0.070
(10000 20000 30000 40000 INB in US\$		

Supplementary Figure 3- Leave one out analysis for JAKi vs csDMARDs/bDMARDS

Random-effects DerSimonian-Laird model

JAKi- Janus Kinase Inhibitor, csDMARD- conventional synthetic disease modifying anti rheumatic drugs, bDMARDs- biologic disease modifying anti rheumatic drugs, CI- confidence interval



Supplementary Figure 4- Galbraith plot for JAKi vs csDMARDs/bDMARDS

JAKi- Janus Kinase Inhibitor, csDMARD- conventional synthetic disease modifying anti rheumatic drugs, bDMARDs- biologic disease modifying anti rheumatic drugs, CI- confidence interval



Supplementary Figure 5- Funnel plot for JAKi vs csDMARDs/bDMARDS

JAKi- Janus Kinase Inhibitor, csDMARD- conventional synthetic disease modifying anti rheumatic drugs, bDMARDs- biologic disease modifying anti rheumatic drugs, CI- confidence interval

Supplementary Figure 6	- Subgroup	analysis of	pooled INBs bas	sed on study perspecti	ves
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Subgroup a	analysis:	by	perspective
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Subgrou	p analysis. by p	erspective				
Study				INB	a.	Weight
		<u> </u>	y	VIII1 95 % C	4	(70)
Health System		-	10 111 1		47 0041	40.04
Navarro_2020			43,111[38,892,	47,331]	10.01
Lei Tian_2020	23		24,602 [6,642,	42,563]	9.17
Muszsbek_2019	<		> -14,492 [-270,964,	241,979]	0.48
Max Schleuter_2019			5,383 [2,946,	7,819]	10.05
Claxton_2018		1. THE	> 103,005 [98,133,	107,878]	9.99
Tan_2021(1)		-	10,554 [-25,367,	46,475]	7.24
Tan_2021(2)			-88,646 [-145,441,	-31,850]	5.10
SiNi Li_2021(1)			1,151 [-1,286,	3,587]	10.05
Kuwana_2022			18,402 [14,957,	21,848]	10.03
Heterogeneity: τ ² = 1.06e+09, I ² = 99.50%, H ² = 200.79		-	20,681 [-2,965,	44,328]	
Test of $\theta_i = \theta_j$: Q(8) = 1606.35, p = 0.00						
Payer						
Chen_2019	<	-	> 798 [-255,674,	257,269]	0.48
Fatemi_2020	8	-	> 16,184 [-75,028,	107,395]	2.86
Heterogeneity: $r^2 = 0.00$, $l^2 = 0.00\%$, $H^2 = 1.00$	-		- 14,456 [-71,483,	100,395]	
Test of $\theta_i = \theta_j$: Q(1) = 0.01, p = 0.91						
Societal						
Celine Van De Laar_2020	~ 1		> -1,407 [-123,449,	120,635]	1.83
Min young lee_2015	19 19	-	13,495 [-4,465,	31,456]	9.17
So Young Ha 2021			9,783 [6,337,	13,228]	10.03
Jansen 2017		-	> 48,031 [-30,775,	126,838]	3.50
Heterogeneity: $\tau^2 = 0.00$, $I^2 = 0.00\%$, $H^2 = 1.00$		•	9,976 [6,596.	13,355]	
Test of $\theta_i = \theta_j$: Q(3) = 1.09, p = 0.78					•	
Overall		-	19,886 [1,635,	38,137]	
Heterogeneity: r ² = 8.61e+08, I ² = 99.14%, H ² = 116.17					Anno 2007 (2007) (2007)	
Test of θ _i = θ _j : Q(14) = 1626.38, p = 0.00	Not Cost-effective	Cost-effective				
Test of group differences: $Q_b(2) = 0.78$, p = 0.68			-10			
2	100000 -50000	0 50000 10	0000			
	INB I	n US\$				

Random-effects DerSimonian-Laird model

Supplementary	Figure	7- Subgroup	analysis	of Pooled	INBs	based on	Income	classification
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Subgroup ana	lysis: by	Income	Classification
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Study			v	INB vith 95% C	I	Weight (%)
High income						
Min young lee_2015	17		13,495 [-4,465,	31,456]	9.17
Jansen_2017			48,031 [-30,775,	126,838]	3.50
Claxton_2018		>	103,005 [98,133,	107,878]	9.99
Chen_2019	<	•	798 [-255,674,	257,269]	0.48
Muszsbek_2019	<	>	-14,492 [-270,964,	241,979]	0.48
Max Schleuter_2019			5,383 [2,946,	7,819]	10.05
Navarro_2020			43,111 [38,892,	47,331]	10.01
Celine Van De Laar_2020	← •	>	-1,407 [-123,449,	120,635]	1.83
So Young Ha_2021			9,783 [6,337,	13,228]	10.03
Kuwana_2022			18,402 [14,957,	21,848]	10.03
Heterogeneity: $\tau^2 = 1.09e+09$, $I^2 = 99.35\%$, $H^2 = 154.3$	3		31,502 [6,440,	56,564]	
Test of $\theta_i = \theta_j$: Q(9) = 1388.94, p = 0.00						
Lower middle income						
Fatemi_2020	13		16,184 [-75,028,	107,395]	2.86
Heterogeneity: $\tau^2 = 0.00$, $I^2 = .\%$, $H^2 = .$			- 16,184 [-75,028,	107,395]	
Test of $\theta_i = \theta_j$: Q(0) = 0.00, p = .						
Upper middle income						
Lei Tian_2020			24,602 [6,642,	42,563]	9.17
Tan_2021(1)	() <u> </u>		10,554 [-25,367,	46,475]	7.24
Tan_2021(2)	<		-88,646 [-145,441,	-31,850]	5.10
SiNi Li_2021(1)			1,151 [-1,286,	3,587]	10.05
Heterogeneity: τ^2 = 4.23e+08, I^2 = 81.66%, H^2 = 5.45	-		-791 [-25,230,	23,648]	
Test of $\theta_i = \theta_j$: Q(3) = 16.35, p = 0.00						
Overall		-	19,886 [1,635,	38,137]	
Heterogeneity: τ^2 = 8.61e+08, I^2 = 99.14%, H^2 = 116.1	7					
Test of $\theta_i = \theta_j$: Q(14) = 1626.38, p = 0.00	Not Cost-effective	Cost-effective				
Test of group differences: $Q_b(2) = 3.27$, p = 0.19			-			
	-100000 -50000	50000 100	000			
Pandom offects DerSimonian Laird model	INB I	1022				

Random-effects DerSimonian-Laird model Sorted by: Year

Study			٧	INB vith 95% C	I	Weight (%)
Threshold lessthan median						
Lei Tian_2020			24,602 [6,642,	42,563]	9.17
Min young lee_2015	9 7		13,495 [-4,465,	31,456]	9.17
So Young Ha_2021			9,783 [6,337,	13,228]	10.03
Fatemi_2020	10	•	16,184 [-75,028,	107,395]	2.86
Tan_2021(1)	3		10,554 [-25,367,	46,475]	7.24
Tan_2021(2)	<∎		-88,646 [-145,441,	-31,850]	5.10
SiNi Li_2021(1)			1,151 [-1,286,	3,587]	10.05
Heterogeneity: τ ² = 5.59e+07, I ² = 81.56%, H ² = 5.42		٠	7,455 [-1,074,	15,984]	
Test of $\theta_i = \theta_j$: Q(6) = 32.53, p = 0.00						
Threshold morethan median						
Chen_2019	<	•>	798 [-255,674,	257,269]	0.48
Navarro_2020			43,111 [38,892,	47,331]	10.01
Celine Van De Laar_2020	← •	>	-1,407 [-123,449,	120,635]	1.83
Muszsbek_2019	<	>	-14,492 [-270,964,	241,979]	0.48
Max Schleuter_2019			5,383 [2,946,	7,819]	10.05
Jansen_2017		 >	48,031 [-30,775,	126,838]	3.50
Claxton_2018		>	103,005 [98,133,	107,878]	9.99
Kuwana_2022			18,402 [14,957,	21,848]	10.03
Heterogeneity: τ^2 = 1.44e+09, I ² = 99.47%, H ² = 188.14			38,972 [5,289,	72,655]	
Test of $\theta_i = \theta_j$: Q(7) = 1316.99, p = 0.00						
Overall		-	19,886 [1,635,	38,137]	
Heterogeneity: $\tau^2 = 8.61e+08$, $I^2 = 99.14\%$, $H^2 = 116.17$						
Test of $\theta_i = \theta_j$: Q(14) = 1626.38, p = 0.00	Not Cost-effective	Cost-effective				
Test of group differences: $Q_{b}(1) = 3.16$, p = 0.08						
	100000 -50000 (INB ii	0 50000 100 n US\$	000			

Supplementary Figure 8- Subgroup analysis of pooled INBs based on threshold

Subgroup analysis: by Median Threshold (\$41118)

Random-effects DerSimonian-Laird model

Supplementary	Figure 9-	Subgroup	analysis	of pooled	INBs	based of	on scenario
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Subgroup	analysis:	by	Scenario
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Subgro	Sup analysis. by	Scenario				
Study			v	INB vith 95% C	1	Weight (%)
Five					·	
Navarro_2020			43,111 [38,892,	47,331]	10.01
Muszsbek 2019	←		→ -14,492 [-270,964,	241,979]	0.48
Min young lee 2015		-	13,495 [-4,465,	31,456]	9.17
So Young Ha 2021			9,783 [6,337,	13,228]	10.03
Claxton 2018			> 103,005 [98,133,	107,878]	9.99
Tan_2021(1)		-	10,554 [-25,367,	46,475]	7.24
Tan_2021(2)	<		-88,646 [-145,441,	-31,850]	5.10
SiNi Li_2021(1)			1,151 [-1,286,	3,587]	10.05
Kuwana_2022			18,402 [14,957,	21,848]	10.03
Heterogeneity: $\tau^2 = 1.18e+09$, $l^2 = 99.47\%$, $H^2 = 188.33$	5 -		19,445 [-5,374,	44,264]	
Test of $\theta_i = \theta_i$: Q(8) = 1506.77, p = 0.00		1000			10	
Four						
Chen_2019	<	•	→ 798 [-255,674,	257,269]	0.48
Lei Tian_2020			24,602 [6,642,	42,563]	9.17
Max Schleuter_2019			5,383 [2,946,	7,819]	10.05
Fatemi_2020	13	-	→ 16,184 [-75,028,	107,395]	2.86
Heterogeneity: r^2 = 5.62e+07, I^2 = 31.37%, H^2 = 1.46		-	11,060 [-1,345,	23,464]	
Test of $\theta_i = \theta_j$: Q(3) = 4.37, p = 0.22						
One						
Jansen_2017			→ 48,031 [-30,775,	126,838]	3.50
Heterogeneity: $\tau^2 = 0.00$, $I^2 = .\%$, $H^2 = .$		and see the	48,031 [-30,775,	126,838]	
Test of $\theta_i = \theta_j$: Q(0) = 0.00, p = .						
Three concerns				100 110	100 0051	4.00
Celine Van De Laar_2020	<		→ -1,407[-123,449,	120,635]	1.83
Heterogeneity: $T^{*} = 0.00$, $T^{*} = .\%$, $H^{*} = .$			1,407 [-123,449,	120,635]	
Test of $\theta_i = \theta_j$: Q(0) = -0.00, p = .						
Overall			10 996 [1 6 2 5	20 1271	
Heterogeneity: $t^2 = 8.61 \pm 0.01^2 = 0.0140$, $\mu^2 = 146.4^2$	7		19,000 [1,035,	30,137]	
Test of $P_{-} = P_{+} O(14) = 1626.28 \text{ p} = 0.00$	Not Cost offective	Cost offective				
Test of $\theta_i = \theta_j$. Q(14) = 1626.36, p = 0.00	Not Cost-enective	Cost-enective				
Test of group differences: $Q_b(3) = 1.16$, p = 0.76	[]	S 20				
	-100000 -50000	0 50000 10	00000			
Random-effects DerSimonian-Laird model	IND I	1000				

Study					INB with 95% CI			
5 Year								
Celine Van De Laar_2020	~ 1		-1,407 [-123,449,	120,635]	1.83		
Heterogeneity: $\tau^2 = 0.00$, $I^2 = .\%$, $H^2 = .$				-123,449,	120,635]			
Test of $\theta_i = \theta_j$: Q(0) = -0.00, p = .								
Lifetime								
Chen_2019	<	• >	> 798 [-255,674,	257,269]	0.48		
Navarro_2020			43,111 [38,892,	47,331]	10.01		
Lei Tian_2020			24,602 [6,642,	42,563]	9.17		
Muszsbek_2019	<	;	-14,492 [-270,964,	241,979]	0.48		
Min young lee_2015	85		13,495 [-4,465,	31,456]	9.17		
So Young Ha_2021			9,783 [6,337,	13,228]	10.03		
Max Schleuter_2019	()		5,383 [2,946,	7,819]	10.05		
Jansen_2017			48,031 [-30,775,	126,838]	3.50		
Claxton_2018		2	> 103,005 [98,133,	107,878]	9.99		
Fatemi_2020	ö <u></u>	-	> 16,184 [-75,028,	107,395]	2.86		
Tan_2021(1)	11 <u></u>	-	10,554 [-25,367,	46,475]	7.24		
Tan_2021(2)			-88,646 [-145,441,	-31,850]	5.10		
SiNi Li_2021(1)	1		1,151 [-1,286,	3,587]	10.05		
Kuwana_2022			18,402 [14,957,	21,848]	10.03		
Heterogeneity: τ^2 = 8.62e+08, I ² = 99.20%, H ² = 125.10		-	20,281 [1,855,	38,707]			
Test of $\theta_i = \theta_j$: Q(13) = 1626.30, p = 0.00								
Overall		-	19,886 [1,635,	38,137]			
Heterogeneity: τ^2 = 8.61e+08, I ² = 99.14%, H ² = 116.17								
Test of $\theta_i = \theta_j$: Q(14) = 1626.38, p = 0.00	Not Cost-effective	Cost-effective						
Test of group differences: $Q_b(1) = 0.12$, p = 0.73			7					
8	100000 -50000	0 50000 100	0000					
	INDI	1000						

Supplementary Figure 10- Subgroup analysis of pooled INBs based on time horizon

Subgroup analysis: by Time Horizon

Random-effects DerSimonian-Laird model

Supplementary Figure 11- Second line JAKi vs TNF-a-i for csDMARD failed RA

JAKi vs	TNF-a-i for	csDMARD	failed RA
0/ 11 11 10		0000100 0100	iuncu iui

Study			v	INB vith 95% C	I	Weight (%)
Min young lee_2015	-		13,495 [-4,465,	31,456]	12.30
Claxton_2018			117,382 [113,936,	120,827]	12.79
Chen_2019	< <u> </u> ।		798 [-255,674,	257,269]	1.35
Max Schleuter_2019	1	а. —	5,383 [2,946,	7,819]	12.80
Navarro_2020			12,516 [10,079,	14,952]	12.80
Lei Tian_2020			24,602 [6,642,	42,563]	12.30
Celine Van De Laar_2020		>	-1,407 [-123,449,	120,635]	4.39
Fatemi_2020	3	-	16,184 [-75,028,	107,395]	6.18
Tan_2021(1)			22,183 [4,222,	40,143]	12.30
SiNi Li_2021(1)			1,151 [-1,286,	3,587]	12.80
Overall	1		25,813 [-5,714,	57,340]	
Heterogeneity: $\tau^2 = 2.02e+09$, $I^2 = 99.74\%$, $H^2 = 384.83$ Test of $\theta_i = \theta_j$: Q(9) = 3463.46, p = 0.00	Not Cost-effective	Cost-effective				
	-100000-50000 (INB ir	0 50000 10000 n US\$	00			
Random-effects DerSimonian-Laird model						

Sorted by: Year

INB- incremental net benefit, JAKi- Janus Kinase Inhibitor, CI- confidence interval, DMARDdisease modifying anti rheumatic drugs, csDMARD- conventional synthetic disease modifying anti rheumatic drugs, RA- Rheumatoid Arthritis.

Supplementary Figure 12- Leave one out analysis for JAKi vs TNF-a-i for csDMARD

failed RA



Random-effects DerSimonian-Laird model Sorted by: Year

JAKi- Janus Kinase Inhibitor, CI- confidence interval, TNF-a-i - Tumor necrosis factor -alphainhibitors, csDMARD- conventional synthetic disease modifying anti rheumatic drugs, RA-Rheumatoid Arthritis.

Supplementary Figure 13- Leave one out analysis for JAKi vs TNFa-i in csDMARD failure patients after removing the outlier (Claxton, 2018)



JAKi vs TNF-a-i in csDMARD failure:Leave-One-Out

Random-effects DerSimonian-Laird model Sorted by: Year

JAKi- Janus Kinase Inhibitor, CI- confidence interval, TNF-a-i - Tumor necrosis factor -alphainhibitors, csDMARD- conventional synthetic disease modifying anti rheumatic drugs.

Online Supplementary Material

Appendix I: Search Strategy

PICOS	PUBMED search terms	Hits on date 12 th Feb 2021	Hits on date 5 th May 2022
Р	"arthritis, rheumatoid"[MeSH Terms] OR rheumatoid arthritis	153,377	161,308
Ι	tnf OR "Tumor Necrosis Factor" OR "JAK inhibitor" OR "JAK inhibitors" OR "Janus kinase inhibitor" OR DMARD OR "disease modifying anti- rheumatic drugs" OR biologics OR upadacitinib OR Rinvoq OR baricitinib OR Olumiant OR Simponi OR Simponi Aria OR golimumab OR certolizumab pegol OR certolizumab OR Inflectra OR infliximab-dyyb OR infliximab OR Remicade OR etanercept-szzs OR Erelzi OR etanercept OR Enbrel OR adalimumab-atto OR Amjevita OR adalimumab OR Humira OR Cyltezo OR Hyrimoz OR Cimzia OR methotrexate OR Amethopterin OR MTX OR Otrexup OR Trexall OR Rheumatrex OR Rasuvo OR tofacitinib OR Xeljanz OR Rituximab OR Rituxan OR Truxima OR Mabthera OR Ocrelizumab OR Ofatumumab OR Ublituximab	7,018,085	7,601,344
0	QALY OR "quality adjusted" OR "life year" OR "life years" OR DALY OR "disability adjusted" OR "cost effective" OR cost-utility OR "cost utility" OR ICER OR ICERS OR INB OR "economics"[MeSH Terms] OR "economics, pharmaceutical"[MeSH Terms]	703,048	743,921
PICS	PIO	1,353	1,455
	From 2021 to 5 th May 2022		90

PICOS	Embase Search terms	Hits on date 12 th Feb 2021	Hits on date 5 th May 2022
Р	'rheumatoid arthritis'/exp OR 'arthritis deformans' OR 'arthritis, rheumatoid' OR 'arthrosis deformans' OR 'beauvais disease' OR 'chronic articular rheumatism' OR 'chronic polyarthritis' OR 'chronic progressive poly arthritis' OR 'chronic progressive polyarthritis' OR 'chronic rheumatoid arthritis' OR 'disease, beauvais' OR 'inflammatory arthritis' OR 'polyarthritis, primary chronic' OR 'primary chronic polyarthritis' OR 'progressive polyarthritis, chronic' OR 'rheumarthritis' OR 'rheumatic arthritis' OR 'rheumatic polyarthritis' OR 'rheumatism, chronic articular' OR 'rheumatoid arthritis'	249,996	272,136
Ι	'tumor necrosis factor inhibitor'/exp OR 'tnf alpha inhibitor' OR 'tnf inhibitor' OR 'anti tnf agent' OR 'anti tnf alpha agent' OR 'anti tumor necrosis factor agent' OR 'anti tumour necrosis factor agent' OR 'tumor necrosis factor alpha inhibitor' OR 'tumor necrosis factor inhibitor' OR 'tumor necrosis factor inhibitors' OR 'tumour necrosis factor alpha inhibitor' OR 'tumour necrosis factor inhibitor' OR 'janus kinase inhibitor'/exp OR 'jak inhibitor' OR 'janus kinase inhibitor' OR 'janus kinase inhibitors' OR 'janus tyrosine kinase inhibitor' OR 'disease modifying antirheumatic drug'/exp OR 'disease modifying antirheumatic agent' OR 'disease modifying antirheumatic drug' OR 'disease modifying antirheumatic drugs' OR 'baricitinib'/exp OR 'baricitinib' OR 'olumiant' OR 'upadacitinib'/exp OR 'rinvoq' OR 'upadacitinib' OR 'upadacitinib 2, 3 dihydroxybutanedioate' OR 'upadacitinib hemihydrate' OR 'upadacitinib hydrate' OR 'upadacitinib tartrate' OR	356,629	396,592

	'golimumab/exp OR 'golimumab' OR 'simponi 'OR 'simponi aria' OR 'certolizumab pegol'/exp OR 'certolizumab pegol' OR 'cimzia' OR 'pegylated tumor necrosis factor alpha antibody fab fragment' OR 'pegylated tumour necrosis factor alpha antibody fab fragment' OR 'certolizumab'/exp OR 'etanercept/exp OR 'avent' OR 'benepali' OR 'brenzys' OR 'embrel' OR 'enbrel' OR 'enerceptan' OR 'erelzi' OR 'etanercept' OR 'etanercept szzs' OR 'etanercept ykro' OR 'etanercept-szzs' OR 'etanercept ykro' OR 'etanercept szzs' OR 'etanercept ykro' OR 'etanercept-szzs' OR 'etanercept 'OR 'recombinant tumor necrosis factor receptor fc fusion protein' OR 'recombinant tumour necrosis factor receptor fc fusion protein' OR 'recombinant tumour necrosis factor receptor fc fusion protein' OR 'tasocitinib cirtrate' OR 'tofacitinib' OR 'tofacitinib'/exp OR 'tasocitinib' OR 'tasocitinib cirtrate' OR 'tofacitinib' OR 'tofacitinib cirtrate' OR 'xeljanz' OR 'xeljanz xr' OR 'adalimumab'/exp OR 'tofacitinib cirtrate' OR 'amjevita' OR 'gp 2017' OR 'hulio' OR 'humira' OR 'ibi303' OR 'm 923' OR 'm923' OR 'monoclonal antibody d2e7' OR 'sb 5' OR 'sb5' OR 'amgevita' OR 'amjevita' OR 'adalimumab-bwwd' OR 'adaly' OR 'adalimumab' OR 'infliximab/exp OR 'inflectra' OR 'infliximab' OR 'remicade' OR 'remsima' OR 'renflexis' OR 'methotrexate'/exp OR '4 amino 10 methylpteroylglutamic acid' OR '4 amino 10 methylpteroylglutamic acid' OR 'mtx' OR 'amethopterin' OR 'methotrexate' OR 'methotrexate' OR 'methotrexate' OR 'methotrexate' OR 'methotrexate' OR 'metotrexate' OR 'metotrexate' OR 'methotrexate' OR 'metotrexate' OR 'metotrexate' OR 'methotrexate' OR 'rheumatrex' OR 'texate' OR 'metotrexate' OR 'metecil' OR 'metothrexate' OR 'metotrexate' OR 'metotrexate' OR 'metecil' OR 'rituximab'/exp OR 'mabthera' OR 'reditux' OR 'ritumai' OR 'ritumax' OR 'rituximab'/exp OR 'mabthera' OR 'reditux' OR 'ritemvia' OR 'ritumax' OR 'rituxin' OR 'rituximab' OR 'rituxima' OR 'orelizumab'/exp OR 'ocrelizumab' OR 'ocrevus' OR 'ofatumumab'/exp OR 'arzerra' OR 'humaxcd20' OR 'ofatumumab' OR		
Ο	'cost benefit analysis'/exp OR 'cost analysis' OR 'cost benefit' OR 'cost benefit analysis' OR 'cost benefit ratio' OR 'cost-benefit analysis' OR 'cost minimization analysis'/exp OR 'cost minimization' OR 'cost minimization analysis' OR 'quality of life' OR 'QALY' OR 'quality adjusted' OR 'life year' OR 'life years' OR 'DALY' OR 'disability adjusted' OR 'ICER' OR 'ICERS' OR INB OR 'cost effectiveness analysis'/exp OR 'cost effectiveness' OR 'cost effectiveness analysis' OR 'cost effectiveness ratio' OR 'cost efficiency analysis' OR 'willingness to pay' OR 'cost utility analysis'/exp OR 'cost utility' OR 'cost utility analysis'	877,755	970,430
PICS	PIO	4,822	5,295
	PIO with #5 AND ('crohn disease'/dm OR 'rheumatic disease'/dm OR 'rheumatoid arthritis'/dm) AND 'human'/de AND ('article'/it OR 'article in press'/it) AND ([adult]/lim OR [aged]/lim OR [middle aged]/lim OR [very elderly]/lim OR [young adult]/lim)	863	1,000
	From 2021 to 5 th May 2022		157

Appendices

PICOS	Scopus search terms	Hits on date 12 th Feb 2021	Hits on date 5 th May 2022
Р	"Rheumatoid arthritis" OR rheumatoid	560,511 results	611,784 results
Ι	tnf OR "Tumor Necrosis Factor" OR "JAK inhibitor" OR "JAK inhibitors" OR "Janus kinase inhibitor" OR DMARD OR "disease modifying anti- rheumatic drugs" OR biologics OR upadacitinib OR Rinvoq OR baricitinib OR Olumiant OR Simponi OR "Simponi Aria" OR golimumab OR "certolizumab pegol" OR certolizumab OR Inflectra OR infliximab-dyyb OR infliximab OR Remicade OR etanercept-szzs OR Erelzi OR etanercept OR Enbrel OR adalimumab-atto OR Amjevita OR adalimumab OR Humira OR Cyltezo OR Hyrimoz OR Cimzia OR methotrexate OR Amethopterin OR MTX OR Otrexup OR Trexall OR Rheumatrex OR Rasuvo OR tofacitinib OR Xeljanz OR Rituximab OR Rituxan OR Truxima OR Mabthera OR Ocrelizumab OR Ofatumumab OR Ublituximab	1,733,118 results	1,902,804 results
0	"cost effectiv*" OR "cost utility" OR "cost benefit" OR "cost-benefit" OR "quality adjusted life years" OR qaly OR ly OR "life year\$" OR daly OR "disability adjusted" OR "incremental cost effective ratio" OR "ICER" OR "incremental net benefit" OR inb OR "benefit ratio" OR 'cost benefit' OR 'cost minimi?ation' OR "cost-effectiveness" OR "cost effectiveness ratio" OR "cost efficiency analys?s"	586,742 results	639,644 results
PIO		6,099 results	
	TITLE-ABS-KEY ("Rheumatoid arthritis" OR rheumatoid) AND (tnf OR "Tumor Necrosis Factor" OR "JAK inhibitor" OR "JAK inhibitors" OR "Janus kinase inhibitor" OR dmard OR "disease modifying anti- rheumatic drugs" OR biologics OR upadacitinib OR rinvoq OR baricitinib OR olumiant OR simponi OR "Simponi Aria" OR golimumab OR "certolizumab pegol" OR certolizumab OR inflectra OR infliximab-dyyb OR infliximab OR remicade OR etanercept-szzs OR erelzi OR etanercept OR enbrel OR adalimumab-atto OR amjevita OR adalimumab OR humira OR cyltezo OR hyrimoz OR cimzia OR methotrexate OR amethopterin OR mtx OR otrexup OR trexall OR rheumatrex OR rasuvo OR tofacitinib OR xeljanz OR rituximab OR rituxan OR truxima OR mabthera OR ocrelizumab OR ofatumumab OR ublituximab) AND ("cost effectiv*" OR "cost utility" OR "cost benefit" OR "cost-benefit" OR "quality adjusted life years" OR qaly OR ly OR "life year\$" OR daly OR "incremental net benefit" OR inb OR "benefit ratio" OR 'cost AND benefit' OR 'cost AND minimi?ation' OR "cost-effectiveness" OR "cost utility") AND (LIMIT-TO (DOCTYPE , "ar")) AND (LIMIT-TO (SRCTYPE , "j"))	1,542 results	1,716 results
	From 2021 to 5th May 2022 TITLE-ABS-KEY ("Rheumatoid arthritis" OR rheumatoid) AND (tnf OR "Tumor Necrosis Factor" OR "JAK inhibitor" OR "JAK inhibitors" OR "Janus kinase inhibitor" OR dmard OR "disease modifying anti- rheumatic drugs" OR biologics OR upadacitinib OR rinvoq OR baricitinib OR olumiant OR simponi OR "Simponi Aria" OR golimumab OR "certolizumab pegol" OR certolizumab OR inflectra OR		171 results

	infliximab-dyyb OR infliximab OR remicade OR etanercept-szzs OR erelzi OR etanercept OR enbrel OR adalimumab-atto OR amjevita OR adalimumab OR humira OR cyltezo OR hyrimoz OR cimzia OR methotrexate OR amethopterin OR mtx OR otrexup OR trexall OR rheumatrex OR rasuvo OR tofacitinib OR xeljanz OR rituximab OR rituxan OR truxima OR mabthera OR ocrelizumab OR ofatumumab OR ublituximab) AND ("cost effectiv*" OR "cost utility" OR "cost benefit" OR "cost-benefit" OR "quality adjusted life years" OR qaly OR ly OR "life year\$" OR daly OR "disability adjusted" OR "incremental cost effective ratio" OR "ICER" OR "incremental net benefit" OR inb OR "benefit ratio" OR 'cost aND benefit' OR 'cost AND minimi?ation' OR "cost-effectiveness" OR "cost effectiveness ratio" OR "cost efficiency analys?s" OR "cost utility") AND (LIMIT-TO (SRCTYPE ,		
	"j")) AND (LIMIT-TO (DOCTYPE, "ar")) AND (LIMIT-TO (PUBYEAR, 2022) OR LIMIT-TO (PUBYEAR, 2021))		

Appendix II: Methods

A) Incremental net benefit (INB) can be estimated as follows:

2

or

or

2

K is the Willingness to pay (WTP), ΔC and ΔE are incremental cost and incremental effectiveness, $\sigma^2_{\Delta C}$, $\sigma^2_{\Delta E}$, $\rho_{\Delta C\Delta E}$ were variances of ΔC and ΔE and their covariance, and σ^{2}_{ICER} was variance of ICER. The WTP was used as reported in the original included studies, i.e., a standard/country specific or GDP based WTP threshold. A positive INB favours treatment, i.e., intervention is cost-effective, whereas a negative INB favours the comparator, i.e., intervention is not cost-effective.

Currency conversions and standardization

The monetary units were converted to purchasing power parity (PPP), adjusted to US\$ for the year 2021 before INB calculation. For instance, if a study reported cost, ICER, and thresholds in Euros for 2012, this currency was first converted to 2021 Euros using the historical consumer price index (CPI) of that country. The Euro 2021 value was next converted to PPP adjusted US\$ rate using conversion rates from the International Monetary Fund²⁵. In addition, the K value from GDP-based threshold was corrected for both latest CPI (2021) and PPP, while for standard/country specific or fixed K, only PPP was corrected. For the variance monetary value conversion, the specific study variance was multiplied by the square of total factors (i.e., CPI and PPP) for the year

2021. For example, if Y is variance of ICER in Euros 2012, this was converted into 2021 PPP adjusted US\$ as

$$Var_{PPP_{2021}} = Var_{Euros_{2012}} x \left(\frac{CPI_{Euros_{2021}}}{CPI_{Euros_{2012}}} x \frac{1}{PPP_{2021}}\right)^2 - - - - (5)$$

B) Meta-analysis

i. A fixed effect model

ii. A random effect model

$$INB_{p} = \frac{\sum_{i=1}^{S} w_{i}^{*} \cdot INB_{i}}{\sum_{i=1}^{S} w_{i}^{*}} - \dots - (3)$$
$$w_{i}^{*} = \frac{1}{Var(INB_{i}) + \tau^{2}} - \dots - (4)$$
$$\tau^{2} = \frac{Q - (S - 1)}{\sum w_{i} - \frac{\sum w_{i}^{2}}{\sum w_{i}}} - \dots - (5)$$

Q is the Cochrane Q-statistic, where Q = 0 if Q < S-1; and s is the number of included studies/comparisons. The heterogeneity of INB was assessed using Cochrane Q-test and I² statistic calculated as equations below.

$$Q = \sum_{i=1}^{S} w_i (INB_i - INB_p)^2 - (6)$$
$$I^2 = 100\% x \frac{Q - (S - 1)}{Q} - (7)$$

- C) Scenarios developed to obtain variance
- Scenario-1: studies which reports the point estimates & variances for every parameter required for calculation
- Scenario-2: studies which reports the means and 95% CIs of incremental costs & outcomes, and ICER

95% CI of $\mu_{ICER} = \hat{\mu}_{ICER} \pm Z_{\alpha/2} \times SE$ $UL_{ICER} = \hat{\mu}_{ICER} \pm Z_{\alpha/2} \times SE$ $SE = \frac{UL_{ICER} - \hat{\mu}_{ICER}}{Z_{\alpha/2}}$ $\hat{\sigma}^{2}_{ICER} = SE^{2}$ $UL_{ICER} = Upper limit of ICER$ $Z_{\alpha/2} = Standard Normal = 1.96$ $\hat{\mu}_{ICER} = mean ICER$

• Scenario-3: studies which reports means and 95% CI of costs/outcomes, or $\Delta C \& \Delta E$, but not ICER or its variance.

Monte Carlo simulation with a gamma and normal distributions for ΔC and ΔE is performed to estimate covariance between ΔC and ΔE .

• Scenario-4: studies which does not report any dispersion, but provides the CE plane graphs,

Data can be directly extracted from the CE plane using Web-Plot Digitizer software. The means of ΔC , ΔE , and their variances and co-variance can be estimated accordingly.

• Scenario-5: The study reports only the means (or point estimates) of costs, outcomes, and ICER.

The measures of dispersions can be borrowed from another similar study if they fulfil the following criteria:

- They are in the same stratum of country income level, perspective, intervention, comparator, time period, country region, model type, and inputs (i.e., discounting, time horizon).
- \circ Their ICERs are not much different, e.g., $\pm 50\%$ to 75%

Appendix III: Summary of Findings of GRADE Assessment

Evidence Profile using Grading of Recommendation, Assessment, Development, and Evaluation (GRADE) instrument

P: Adult patients with moderate to severe RA

I: JAK inhibitors alone or combination/sequence with csDMARDs

C: Any others

O: Incremental cost-effectiveness ratio (ICER), or Incremental Net Benefit.

	Outcome: Cost-effectiveness (assessed with meta-analysis of cost utility analysis)								
Quality assessment*						Su	mmary of	findings	
No of	Risk of	.	T 11	.		Effect	(US\$)		Comments
studies	Bias	Inconsistency	Indirectness	Imprecision	Publication Bias	INB	95%CI	Certainty/Quality	
Cost-ef	Cost-effectiveness of JAKi compared to csDMARD/bDMARD (Assessed with meta-analysis).								
15	not serious	serious ^a	serious ^b	serious ^c	unlikely	19,886	(1,635 to 38,137)	⊕⊕○○ Very Low	Less evidence from low-middle income countries and high unexplained heterogeneity. Varying population with sequential treatment strategy.
Cost-eff	ectivene	ss of Second lir	ne JAK-i vs c	sDMARDs/bl	DMARDs for csDMARD failed	RA patients (Assessed wi	ith meta-analysis).	
13	not serious	serious ^a	serious ^b	serious ^c	unlikely	23,144	(74.1 to 46,214)	⊕⊕⊖O Low	Less evidence from low-middle income countries and high unexplained heterogeneity. Varying population.
Cost-eff	ectivene	ss of JAKi com	pared to othe	rs from socie	tal perspective (Assessed with n	neta-analysis).		•	
4	not serious	not serious	not serious	serious	unlikely	9,976	(6,596 to 13,355)	⊕⊕OO Low	Less number of studies. Varying population with sequential treatment strategy.
Cost-ef	fectivene	ess of JAKi con	npared to othe	ers from high	income countries (Assessed wit	h meta-analys	is).		
10	not serious	serious ^a	serious	serious ^c	unlikely	31,502	(6,440 to 56,564)	⊕⊕OO Low	High unexplained heterogeneity. Varying population with sequential treatment strategy.
Cost-eff	ectivene	ss of JAKi com	pared to othe	rs from lifetir	me horizon (Assessed with meta	-analysis).		•	
14	not serious	serious ^a	serious ^b	serious ^c	unlikely	20,281	(1,855 to 38,707)	⊕⊕OO Low	Less evidence from low-middle income countries and high unexplained heterogeneity. Varying population with sequential treatment strategy.

^a high heterogeneity ^b studies included have reported a wide confidence intervals ^c Lack of generalisability

Appendix IV: PRISMA Checklist for Abstract

Section and Topic	ltem #	Checklist item	Reported (Yes/No)	
TITLE: Cost-effectiveness of Janus Kinase inhibitors for Rheumatoid Arthritis: A systematic review and meta-analysis of cost- utility studies				
Title	1	Identify the report as a systematic review.	Yes, Page 1	
BACKGROUND				
Objectives	2	Provide an explicit statement of the main objective(s) or question(s) the review addresses.	Yes, Page 2	
METHODS				
Eligibility criteria	3	Specify the inclusion and exclusion criteria for the review.	Yes, Page 2	
Information sources	4	Specify the information sources (e.g. databases, registers) used to identify studies and the date when each was last searched.	Yes, Page 2	
Risk of bias	5	Specify the methods used to assess risk of bias in the included studies.	Yes, Page 2	
Synthesis of results	6	Specify the methods used to present and synthesise results.	Yes, Page 2	
RESULTS				
Included studies	7	Give the total number of included studies and participants and summarise relevant characteristics of studies.		
Synthesis of results	8	Present results for main outcomes, preferably indicating the number of included studies and participants for each. If meta-analysis was done, report the summary estimate and confidence/credible interval. If comparing groups, indicate the direction of the effect (i.e. which group is favoured).		
DISCUSSION				
Limitations of evidence	evidence 9 Provide a brief summary of the limitations of the evidence included in the review (e.g. study risk of bias, inconsistency and imprecision).		Yes, Page 2	
Interpretation	10	Provide a general interpretation of the results and important implications.	Yes, Page 2	
OTHER				
Funding	11	Specify the primary source of funding for the review.	Yes, Page 2	
Registration	12	Provide the register name and registration number.	Yes, Page 2	

From: Page MJ, McKenzie JE, Bossuyt PM, Boutron I, Hoffmann TC, Mulrow CD, et al. The PRISMA 2020 statement: an updated guideline for reporting systematic reviews. BMJ 2021;372:n71. doi: 10.1136/bmj.n71

Appendix	V:	PRISMA	checklist
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Item #	Checklist item	Location where item is reported					
TITLE: Cost-effectiveness of Janus Kinase inhibitors for Rheumatoid Arthritis: A systematic review and meta-analysis of cost-utility studies							
1	Identify the report as a systematic review.	Yes, Page 1					
2	See the PRISMA 2020 for Abstracts checklist.	Yes					
1							
3	Describe the rationale for the review in the context of existing knowledge.	Yes, Page 3					
4	Provide an explicit statement of the objective(s) or question(s) the review addresses.	Yes, Page 3 to 4					
1							
5	Specify the inclusion and exclusion criteria for the review and how studies were grouped for the syntheses.	Yes, Page 4					
6	Specify all databases, registers, websites, organisations, reference lists and other sources searched or consulted to identify studies. Specify the date when each source was last searched or consulted.	Yes, Page 4					
7	Present the full search strategies for all databases, registers and websites, including any filters and limits used.	Yes, Page 4 to 5, Appendix 1					
8	Specify the methods used to decide whether a study met the inclusion criteria of the review, including how many reviewers screened each record and each report retrieved, whether they worked independently, and if applicable, details of automation tools used in the process.	Yes, Page 4 to 5, Figure 1					
9	Specify the methods used to collect data from reports, including how many reviewers collected data from each report, whether they worked independently, any processes for obtaining or confirming data from study investigators, and if applicable, details of automation tools used in the process.	Yes, Page 4 to 5					
10a	List and define all outcomes for which data were sought. Specify whether all results that were compatible with each outcome domain in each study were sought (e.g. for all measures, time points, analyses), and if not, the methods used to decide which results to collect.	Yes, Page 5 to 6					
10b	List and define all other variables for which data were sought (e.g. participant and intervention characteristics, funding sources). Describe any assumptions made about any missing or unclear information.	Yes,					
11	Specify the methods used to assess risk of bias in the included studies, including details of the tool(s) used, how many reviewers assessed each study and whether they worked independently, and if applicable, details of automation tools used in the process.	Yes, Page 6					
12	Specify for each outcome the effect measure(s) (e.g. risk ratio, mean difference) used in the synthesis or presentation of results.	Yes, Page 5 to 6, Appendix II					
13a	Describe the processes used to decide which studies were eligible for each synthesis (e.g. tabulating the study intervention characteristics and comparing against the planned groups for each synthesis (item #5)).	Yes, Page 5 to 6, Appendix II					
13b	Describe any methods required to prepare the data for presentation or synthesis, such as handling of missing summary statistics, or data conversions.	Yes, Page 5 to 6, Appendix II					
13c	Describe any methods used to tabulate or visually display results of individual studies and syntheses.	Yes, Page 5 to 6, Appendix II					
13d	Describe any methods used to synthesize results and provide a rationale for the choice(s). If meta-analysis was performed, describe the model(s), method(s) to identify the presence and extent of statistical heterogeneity, and software package(s) used.	Yes, Page 5 to 6, Appendix II					
13e	Describe any methods used to explore possible causes of heterogeneity among study results (e.g. subgroup analysis, meta-regression).	Yes, Page 5 to 6, Appendix II					
13f	Describe any sensitivity analyses conducted to assess robustness of the synthesized results.	Yes, Page 5 to 6, Appendix II					
14	Describe any methods used to assess risk of bias due to missing results in a synthesis (arising from reporting biases).	Yes, Page 6					
15	Describe any methods used to assess certainty (or confidence) in the body of evidence for an outcome.	Yes, Page 6					
	Item Janus K 1 2 3 4 5 6 7 8 9 10a 10b 11 12 13a 13b 13c 13d 13e 13f 14 15	Item Checklist item James Kitase inhibitors for Rheumatoid Arthritis: A systematic review and meta-analysis of cost-utility studies 1 Identify the report as a systematic review. 2 See the PRISMA 2020 for Abstracts checklist. 3 Describe the rationale for the review in the context of existing knowledge. 4 Provide an explicit statement of the objective(s) or question(s) the review addresses. 5 Specify the inclusion and exclusion criteria for the review and how studies were grouped for the syntheses. 6 Specify all databases, registers, websites, organisations, reference lists and other sources searched or consulted to identify studies. Specify the date when each source was last searched or consulted. 7 Present the full scarch strategies for all databases, registers and websites, including any filters and limits used. 8 Specify the methods used to decide whether a study met the inclusion criteria of the review, including how many reviewers screened each record and each report whether they worked independently, any processes for obtaining or confirming data from study investigators, and if applicable, details of automation tools used in the process. 10a List and define all outcomes for which data were sough (e.g. participant and intervention characteristics, funding sources). Describe any assumptions and about any missing or unclear information. 11 Specify the methods used to table data were sough (e.g. participant and int					

Appendices

Section and Topic	Item #	Checklist item	Location where item is reported
RESULTS			
Study selection	16a	Describe the results of the search and selection process, from the number of records identified in the search to the number of studies included in the review, ideally using a flow diagram.	Yes, Page 6, Figure 1
	16b	Cite studies that might appear to meet the inclusion criteria, but which were excluded, and explain why they were excluded.	Yes, Page 6, 7
Study characteristics	17	Cite each included study and present its characteristics.	Yes, Page 6, 7 & Table 1
Risk of bias in studies	18	Present assessments of risk of bias for each included study.	Yes, Page 8 & Supp Fig 1
Results of individual studies	19	For all outcomes, present, for each study: (a) summary statistics for each group (where appropriate) and (b) an effect estimate and its precision (e.g. confidence/credible interval), ideally using structured tables or plots.	Yes, Page 6 to 7
Results of syntheses	20a	For each synthesis, briefly summarise the characteristics and risk of bias among contributing studies.	Yes, Page 8
	20b	Present results of all statistical syntheses conducted. If meta-analysis was done, present for each the summary estimate and its precision (e.g. confidence/credible interval) and measures of statistical heterogeneity. If comparing groups, describe the direction of the effect.	Yes, Page 8 to 10 & Figure 2,3 & Supp Fig 5 to 13
	20c	Present results of all investigations of possible causes of heterogeneity among study results.	Yes, Page 8 & Supp Fig 4 to 10
	20d	Present results of all sensitivity analyses conducted to assess the robustness of the synthesized results.	Yes, Page 8 & Supp Fig 4 to 13
Reporting biases	21	Present assessments of risk of bias due to missing results (arising from reporting biases) for each synthesis assessed.	Yes, Page 8 & Supp Fig 1
Certainty of evidence	22	Present assessments of certainty (or confidence) in the body of evidence for each outcome assessed.	Yes, Page 10, & Appendix III
DISCUSSION			
Discussion	23a	Provide a general interpretation of the results in the context of other evidence.	Yes, Page 11
	23b	Discuss any limitations of the evidence included in the review.	Yes, Page 12
	23c	Discuss any limitations of the review processes used.	Yes, Page 12
	23d	Discuss implications of the results for practice, policy, and future research.	Yes, Page 12,13
OTHER INFORMATION			
Registration and protocol	24a	Provide registration information for the review, including register name and registration number, or state that the review was not registered.	Yes, Page 4
	24b	Indicate where the review protocol can be accessed, or state that a protocol was not prepared.	Yes, Page 4
	24c	Describe and explain any amendments to information provided at registration or in the protocol.	NA
Support	25	Describe sources of financial or non-financial support for the review, and the role of the funders or sponsors in the review.	Yes, Page 1
Competing interests	26	Declare any competing interests of review authors.	Yes, Page 1
Availability of data, code and other materials	27	Report which of the following are publicly available and where they can be found: template data collection forms; data extracted from included studies; data used for all analyses; analytic code; any other materials used in the review.	NA

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