HEALTH TECHNOLOGY ASSESSMENT REPORT

ON

COST-EFFECTIVENESS OF TNF-ALPHA INHIBITORS, B-CELL INHIBITORS AND JAK INHIBITORS FOR THE TREATMENT OF RHEUMATOID ARTHRITIS IN INDIA

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LIST OF ABBREVIATIONS

ACCP	Anti-Cyclic Citrullinated Peptide
ACR	American College of Rheumatology
ADA	Adalimumab
ADA40	Adalimumab 40mg
AE	Adverese Events
BARI	Baricitinib
BARI4	Baricitinib 4mg
BCDT	B Cell Depletion Therapy
bDMARDs	Biologic Disease-Modifying Antirheumatic Drugs
BMI	Body Mass Index
CAD	Coronary Artery Disease
CE	Cost Effectiveness
CEA	Cost Effectiveness Analysis
CEAC	Cost Effectiveness Acceptability Curve
CGHS	Central Government Health Scheme
CHE	Catastrophic Health Expenditure
CHEERS	Consolidated Health Economic Evaluation Reporting Standards
CI	Confidence Interval
CMCHIS	Chief Minister'S Comprehensive Health Insurance Scheme
COPCORD	Community Oriented Program For The Control Of Rheumatic Diseases
CPI	Consumer Price Index
csDMARDs	Conventional Synthetic Disease-Modifying Anti-Rheumatic Drugs
CUA	Cost Utility Analysis
CZP	Certolizumab pegol
CZP200	Certolizumab pegol 200mg
DALY	Disability-Adjusted Life Years
DAS	Disease Activity Score-28
DMARDs	Disease-Modifying Anti-Rheumatic Drugs
DMC	Direct medical costs
ECOBIAS	Economic Evaluation Bias
EMA	European Medicines Agency
EQ-5D	Euroqol 'S Five-Dimensional
ESR	Erythrocyte Sedimentation Rate
ETA	Etanercept
ETN50	Etanercept 50mg
EULAR	European League Against Rheumatism
FDA	Food And Drug Administration
FILG	Filgotinib
GDP	Gross Domestic Product
GOL	Golimumab
GOL50	Golimumab 50mg
HAD	High Disease Activity

HAQ	Health Assessment Questionnaire
HCQS400	Hydroxychloroquine 400mg
HICs	High Income Countries
HRQoL	Health-Related Quality Of Life
HTA	Health Technology Assessment
ICER	Incremental Cost-Effectiveness Ratio
IFX3	Infliximab 3mg
IMF	International Monitory Fund
INB	Incremental Net Benefit
IFX	Infliximab
INR	Indian National Rupees
IQR	Interquartile Range
IV	Intravenous
JAK-i	Janus Kinase Inhibitor
LDA	Low Disease Activity
LEF	Leflunomide
LEF20	Leflunomide 20mg
LICs	Low Income Countries
LMIC	Lower Middle-Income Countries
LY	Life Years
MDA	Moderate Disease Activity
MIC	Middle Income Countries
MTX	Methotrexate
NABH	National Accreditation Board For Hospitals
NICE	National Institute For Health And Care Excellence
NMB	Net Monetary Benefit
NNTH	Number Needed To Treat Harm
NOS	Newcastle-Ottawa Scale
OOPE	Out-Of-Pocket Expenditure
OPD	Out Patient Department
OR	Odds Ratio
OWSA	One Way Sensitivity Analysis
PGIMER	Post Graduate Institute Of Medical Education And Research
PICO	Population, Intervention, Comparator, And Outcome
PMJAY	Pradhan Mantri Jan Arogya Yojana
PPP	Purchasing Power Parity
PPPI	Purchasing Power Parity Index
PRISMA	Preferred Reporting Items For Systematic Reviews And Meta-Analyses
PRO	Patient-Reported Outcomes
PSA	Probabilistic Sensitivity Analysis
QALY	Quality-Adjusted Life Years
QoL	Quality Of Life
RA	Rheumatoid Arthritis
RBC	Red Blood Cell
RCT	Randomized Control Trial

RF	Rheumatoid Factor
RoB	Risk Of Bias
RR	Risk Ratio
RTX	Rituximab
SD	Standard Deviation
SE	Standard Error
SF-6D	Short Form -6D
SFZ	Sulfasalazine
SFZ500	Sulfasalazine 500mg
SRMA	Systematic Review And Meta-Analysis
STROBE	Strengthening The Reporting Of Observational Studies In Epidemiology
tDMARDs	Traditional Disease-Modifying Antirheumatic Drugs
TN	Tamil Nadu
TNF-a-i	Tumor Necrosis Factor Alpha Inhibitor
TOF	Tofacitinib
TOF10	Tofacitinib 10mg
TOF5	Tofacitinib 5mg
tsDMARDs	targeted synthetic DMARDs
TT	Tripple Therapy
UK	United Kingdom
UMICs	Upper-Middle Income Countries
UPA	Upadacitinib
USA	United States Of America
USD	United States Dollars
VAS	Visual Analogue Scale
WBC	White Blood Cell
WHO	World Health Organisation
WTP	Willingness To Pay

EXECUTIVE SUMMARY

Rheumatoid arthritis (RA) is an inflammatory autoimmune condition that causes pain and swelling in the wrist, small joints of the hand and feet, shoulders, and knees. RA leads to significant morbidity and mortality, affecting approximately 1% of the global population. India is one of the countries with the highest age-standardized incidence rate (22.5-25.0 per 100,000 population) and DALY rate (approximately 70 per 100,000 population) for RA globally in 2017. The condition worsens over time, causing chronic pain and often incapacitating individuals, restricting their everyday routines. Recent advancements in assessing disease activity have facilitated newer treatment strategies to prevent irreversible joint damage and disease progression. Early therapy with disease-modifying antirheumatic drugs (DMARDs) is the standard pharmacotherapy that efficiently slows disease progression and has the potential to achieve remission or low disease activity. Methotrexate (MTX), a conventional synthetic DMARD (csDMARDs), is the usual first-line treatment for RA, prescribed either as monotherapy or in combination with other csDMARDs. If MTX fails to provide adequate results, treatment with biologic synthetic DMARDs (bDMARDs) (Tumor Necrosis Factor-alpha (TNF-a-i), Interleukin-6 (IL-6), and B-cell inhibitors) and targeted synthetic DMARDs (tsDMARDs) (Janus kinase inhibitors (JAK-i)) is applied sequentially, either as monotherapy or in combination with MTX. These newer treatments aim to manage the disease effectively and improve the patient's quality of life.

Biologic or targeted therapies in combination with MTX or other csDMARDs are more efficacious than monotherapies. Though clinically effective, the higher cost of these drugs makes them less affordable. Considering the substantial economic burden that RA places on healthcare systems, it is crucial to ascertain the cost-effectiveness of these newer treatments such as TNF-a-i, B-cell, and JAK-i for implementation into the Indian health system. Therefore, we conducted a health technology assessment to evaluate the cost-effectiveness of these newer therapies compared with csDMARDs in the context of RA management.

For evidence synthesis, we conducted separate systematic reviews and meta-analyses (SRMAs) on the economic evaluation studies of TNF-a-i, B-cell, and JAK-i treatments. The SRMA on cost utility studies for JAK-i demonstrated that JAK-i are cost-effective compared to other DMARDs in high-income countries (HICs), suggesting that JAK-i offer favourable economic benefits in these settings. Based on the pooled incremental net benefit in the SRMA of cost-utility studies on Rituximab, it was found to be cost-

effective compared to other DMARDs. The results indicate that Rituximab provides a cost-effective treatment option for RA but with very-low confidence based on the GRADE assessment. In contrast, the SRMA of cost-utility analysis studies on TNF-a-i revealed that TNF-a-i are not cost-effective, even in HICs.

The assessment of health-related quality of life (HRQoL) in individuals with RA using EQ-5D revealed a significant impact of RA on patients' quality of life. The domains most affected by the condition were found to be pain and anxiety. These findings underscore the importance of interventions that address pain and anxiety management, as they are crucial in improving both the physical and psychological aspects of HRQoL for individuals with RA.

The assessment of the burden of catastrophic health expenditure (CHE) on RA patients and their households revealed that the majority of RA-related health costs are paid out-of-pocket, leading to a significant CHE burden for more than half (51.4%) of the patients. The increased expenses associated with treating RA resulted in higher out-of-pocket expenditures (OOPE) and CHE among the participants. These findings highlight the substantial financial strain faced by RA patients and their families due to the high costs of managing the condition.

To assess the cost-effectiveness of TNF-a-i, B-cell, and JAK-i in combination with MTX for patients with moderate to severe RA, we developed a time-inhomogeneous Markov model. The study findings indicate that, at the current market prices, TNF-a-i, B-cell inhibitors, and JAK-i are not cost-effective compared to csDMARDs for the treatment of moderate to severe RA in patients who failed initial MTX. The incremental costs associated with these advanced therapies outweighed the clinical gains in terms of cost-effectiveness. To ensure the robustness of our results, we conducted various sensitivity analyses, including one-way sensitivity analysis, probabilistic sensitivity analysis, and scenario analysis. The results from these analyses validated the initial findings and stability of the model's outcomes under varying assumptions and parameter values. Further the scenario analysis indicated that on reduction of costs these newer therapies by more than 75% of current prices could make then cost-effective than csDMARDs. Hence price negotiations of these newer drugs could be considered before incorporation of these drugs in the publicly funded programs.

Chapter 1 - INTRODUCTION

1.1 Background

Rheumatoid arthritis (RA) is a chronic autoimmune disease, associated with pain and swelling in wrist, elbows, knees, ankles and small joints of the hand and feet [1] [2]. RA causes substantial morbidity, mortality and affects about 1% of the global population [3]. Recent studies indicate that RA is one of the important causes attributing to the disability adjusted life years (DALY) both in developed and in developing countries [4, 5]. India is one among the countries with highest Age standardized incidence rate (22.5-25 per 100,000 population) and DALY rate (approximately 70 per 100,000 population) for RA globally in 2017 [6]. The prevalence of RA in adult Indian rural population was 0.75% as reported by a large survey in 1993 [7]. According to the Community Oriented Program for the Control of Rheumatic Diseases (COPCRD) survey conducted between 2004 to 2007, projected population prevalence of RA in North India was 0.15% and 0.4% in rural and urban areas, respectively [8].

RA is a progressive disease and often debilitating with persistent joint pains, which restricts the daily activities of the individuals [1]. In the preceding decades it is reported that RA patients gradually lose their functional ability and almost 30-50% of patients progress to severe disease requiring assistance for self-care activities within 15 years of disease onset [9]. However, with early diagnosis and newer treatment of RA in recent years, the progression of joint damage may be delayed, thereby preventing permanent impairment [10]. Recent development of novel instruments to assess the disease activity has facilitated newer treatment strategies to avert irreversible joint damage and disease progression [11] [12]. The invention of newer targeted therapies have increased the arsenal of RA pharmacotherapy [13]. Early therapy with disease modifying anti rheumatic drugs (DMARDs) is the usual pharmacotherapy of care that retards disease progression efficiently with the potential to achieve remission or a state of low disease activity [14], [15]. The list of US-FDA approved DMARDs are given in the Table 1 [16].

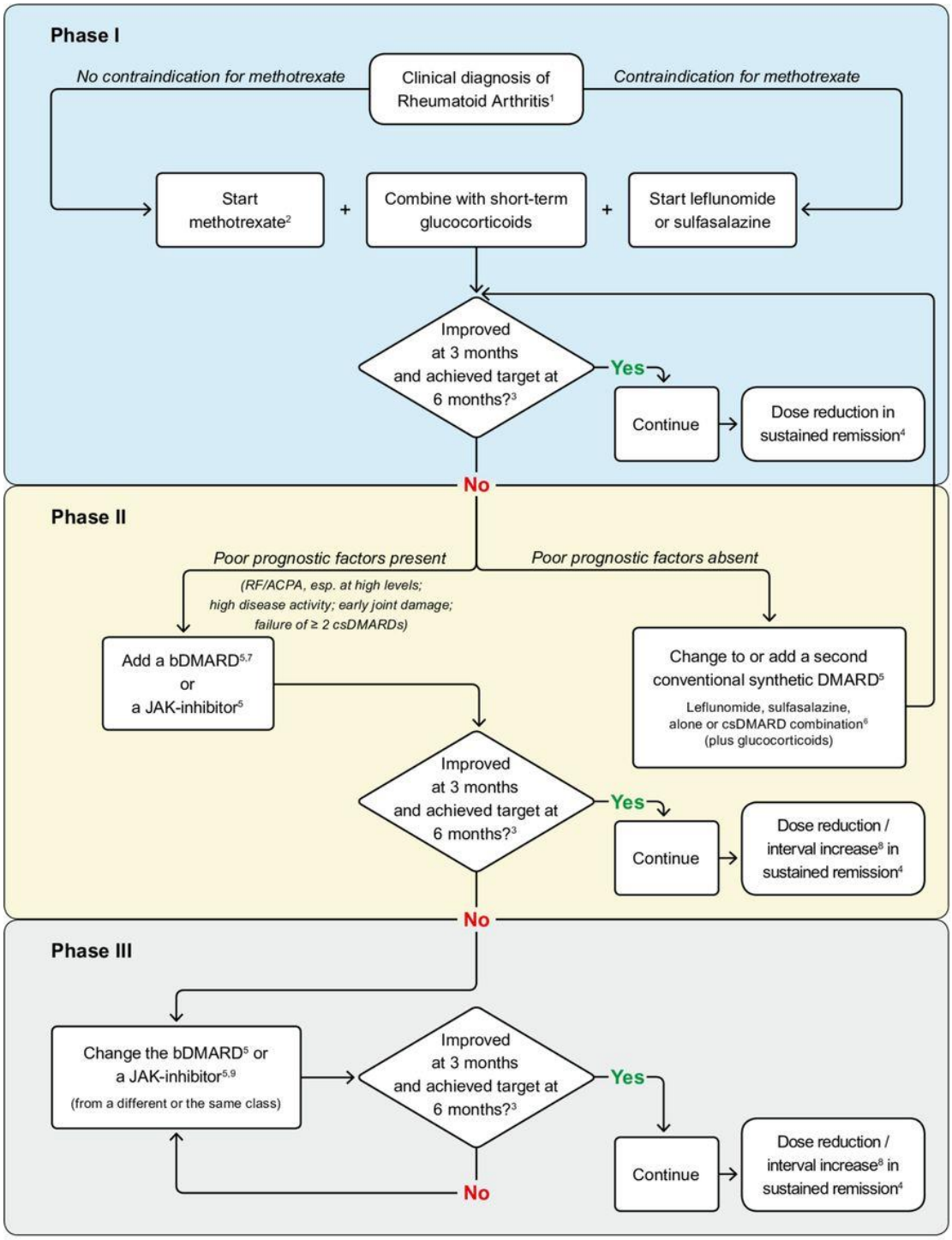
Table 1.1 List of US-FDA approved DMARDs for RA treatment

Groups	Recommended dose	Molecular Target
Conventional synthetic DMARDs (csDMARDs)		
Methotrexate	10-25 mg/week	Unknown
Sulfasalazine	2-4 g/day	Unknown
Leflunomide	20 mg/day	Dihydroorotate dehydrogenase
Hydroxychloroquine	400 mg/day	Unknown
Chloroquine	250 mg/day	Unknown
Targeted synthetic DMARDs (tsDMARDs)		
Tofacitinib	10 mg/day	JAK 1,2,3
Baricitinib	2-4 mg/day	JAK 1,2
Biologic DMARDs (bDMARDs)		
Etanercept	50 mg/week	TNF
Infliximab	3-10 mg/kg (every 8 week)	TNF
Adalimumab	40 mg (every 2 week)	TNF
Golimumab	50 mg/month	TNF
Certolizumab	200 mg (every 2 week)	TNF
Tocilizumab	162 mg/week	IL-6
Sarilumab	150-200 mg (every 2 week)	IL-6
Rituximab	1000 mg (every 6 months)	CD20 (B-cell)
Abatacept	125 mg/week	CD80/86 (co-stimulation)

Source: Aletaha, D., & Smolen, J. S. (2018). Diagnosis and Management of Rheumatoid Arthritis. JAMA, 320(13), 1360. doi:10.1001/jama.2018.13103

The first-line DMARD for RA is Methotrexate (MTX), a conventional synthetic DMARD (csDMARD), prescribed either as monotherapy or in combination with glucocorticoids where 40% to 50% of patients attain remission or low disease activity

[17]. Other csDMARDs include Sulfasalazine (3-4 g/day), Leflunomide (20 mg/day) and Hydroxychloroquine (HCQS) (400 mg/day) [18]. On failing treatment with csDMARDs, biologic synthetic DMARDs (bDMARDs) (Tumor Necrosis Factor-alpha (TNF-a), Interleukin-6 (IL-6) and B-cell inhibitors) and targeted synthetic DMARDs (tsDMARDs) (Janus kinase (JAK) inhibitors) are applied sequentially either as monotherapy or with MTX, where 75% of those patients achieve the treatment goals in time [16]. Biologic or targeted therapies in combination with MTX or other csDMARDs are more efficacious than monotherapies [19]. It has been reported that most of the bDMARDs and tsDMARDs have similar efficacy when combined with MTX [20]. The algorithm that depicts the European League Against Rheumatism (EULAR) recommendations for RA treatment is represented in Figure 1.



1. 2010 ACR-EULAR classification criteria can support early diagnosis.
2. "Methotrexate should be part of the first treatment strategy". While combination therapy of csDMARDs is not preferred by the Task Force, starting with methotrexate does not exclude its use in combination with other csDMARDs although more adverse events without added benefit are to be expected, especially if MTX is combined with glucocorticoids..
3. The treatment target is clinical remission according to ACR-EULAR definitions or, if remission is unlikely to be achievable, at least low disease activity; the target should be reached after 6 months, but therapy should be adapted or changed if insufficient improvement (less than 50% of disease activity) is seen after 3 months.
4. Sustained remission: ≥ 6 months ACR/EULAR index based or Boolean remission.
5. Consider contraindications and risks.
6. The most frequently used combination comprises methotrexate, sulfasalazine and hydroxychloroquine.
7. TNF-inhibitors (adalimumab, certolizumab, etanercept, golimumab, infliximab, including EMA/FDA approved bsDMARDs), abatacept, IL-6R inhibitors, or rituximab (under certain conditions); in patients who cannot use csDMARDs as comedication, IL6-inhibitors and tsDMARDs have some advantages.
8. Dose reduction or interval increase can be safely done with all bDMARDs and tsDMARDs with little risk of flares; stopping is associated with high flare rates; most but not all patients can recapture their good state upon re-institution of the same bDMARD/tsDMARD.
9. Efficacy and safety of bDMARDs after JAK-inhibitor failure is not fully known; also, efficacy and safety of an IL-6 pathway inhibitor after another one has failed is currently unknown. Efficacy and safety of a JAK-inhibitor after insufficient response to a previous JAK-inhibitor is unknown.

Figure 1.1 European League Against Rheumatism (EULAR) recommendations for RA treatment

1.2 Review of Literature

1.2.1 Clinical effectiveness of bDMARDs (TNF-a and B-cell inhibitors) and tsDMARDs (JAK inhibitors) versus conventional synthetic DMARDs

A systematic search was performed to retrieve the existing evidence on clinical-effectiveness of bDMARDs (TNF-a and B-cell inhibitors) and tsDMARDs (JAK inhibitors) as monotherapy or in combination with csDMARDs versus csDMARDs alone. Clinical effectiveness of RA treatments is measured primarily in terms of achieving American College of Rheumatology (ACR) 20 response and/or remission, which is based on Disease Activity Score (DAS)-28 score [21]. ACR 20, 50, or 70 responses are defined as at least a 20%, 50%, or 70% improvement, respectively, in tender and swollen joint counts [21]. DAS-28 is a measure of disease activity where 28 joints are assessed for swelling and tenderness and a composite score is derived with the swollen/tender joint count, patient's global assessment of health using a visual analog scale (VAS) and Erythrocyte sedimentation rate (ESR)/C-Reactive Protein (CRP) measurement. A DAS-28 score less than 2.6 is considered as 'remission' [22]. A systematic review reports that the first-line bDMARDs and their biosimilars were associated with a better clinical outcome relative to csDMARD alone [23]. Among the bDMARDs and its biosimilars, the considerable clinical benefits were with biosimilar etanercept, bDMARDs etanercept+, tocilizumab+ and tocilizumab monotherapy [23]. The different csDMARDs are safe and efficient to combine with advanced therapies in RA patients [24]. Although MTX seems slightly superior to other csDMARDs in combination with TNF-a inhibitors, Leflunomide might be superior to MTX in combination with rituximab [24]. The systematic review by Callhoff et al found that biologic agents were significantly effective than nonbiologic treatments in improving physical function in RA [25]. The meta-analysis of 35 studies that included 8733 treated patients with RA and 4664 controls. Over 50% of patients treated with bDMARDs experienced clinically relevant improvement [25]. Etanercept and rituximab were the most effective treatments, both in patients who had never before taken anti-rheumatic drugs and in those who had shown an inadequate response to them [25]. An evidence synthesis suggests that B-cell inhibitor, rituximab combined with MTX yielded a significantly better clinical outcomes in-terms of ACR20, ACR50, and ACR70 than MTX only treatment [26]. Another systematic review which compared the safety and efficacy of JAK inhibitors

including Tofacitinib, Baricitinib, and Upadacitinib showed to improve the clinical severity as well as quality of life in RA patients. Among the JAK inhibitors, Tofacitinib demonstrated better efficacy with the highest ACR20 response. In terms of safety, the risk for infection was highest with tofacitinib and adverse events were more frequent with Upadacitinib [27]. A post-hoc analysis of tofacitinib in the treatment of RA patients from India revealed an efficacious and safety profile which is comparable to the observations at other countries [28]. However, adverse or serious adverse events reported, seems to be comparatively low in Indian patients except for higher incidence of tuberculosis (TB) which is similar to countries posing high risk for TB [28]. Thus, with the available evidences it is prominent that the bDMARDs and tsDMARDs were efficacious when combined with csDMARDs.

1.2.2 Cost-effectiveness of bDMARDs (TNF-a and B-cell inhibitors) and tsDMARDs (JAK inhibitors) versus conventional synthetic DMARDs

Several real-world cost-effective analysis (CEAs) and economic model-based CEAs have been published in last two decades on this aspect from both developed and developing countries. Cost-effectiveness of bDMARDs (TNF-a inhibitors, IL-6 inhibitors, and B-cell inhibitors) and tsDMARDs (JAK inhibitors) as monotherapy or in combination with csDMARD (usually MTX) have been assessed in comparison to various treatment strategies including MTX alone, combination of csDMARDs (triple therapy), combination of MTX with bDMARDs. It is observed from the available evidences that bDMARDs and tsDMARDs could be a cost-effective option for moderate to severe RA patients [29, 30]. A Markov model study based on two longitudinal observational studies predicted that TNF-a inhibitors along with csDMARDs is cost-effective compared to csDMARD alone [31]. Real world CEA study of Infliximab, a TNF-a inhibitor from China has also shown that Infliximab was cost-effective to csDMARDs [32].

A CEA of various sequential treatment strategies conducted in Chinese health care setting indicates that the biologic therapy was not cost-effective option as the incremental cost-effective ratios (ICERs) were higher than 3 times the per capita gross domestic product (GDP). However, among patients living in developed regions, Infliximab-initial treatment followed by Rituximab could be a potential alternative option [33]. Among patients with early arthritis, addition of bDMARD to MTX

(infliximab) was not cost-effective [34] rather immediate triple therapy with MTX, Sulphasalazine and HCQS was cost-effective [35]. A partial primary economic evaluation study from Syngle et al from India reports that csDMARDs controls disease activity and improves disability with reasonable cost of treatment [36]. However cross-sectional nature of study including mainly drug naïve RA patients limits the evidence about lifetime costs and consequences of treatment with bDMARDs and tsDMARDs due to the chronicity of RA disease condition. In summary, the current full economic evidences are limited, context specific and inconclusive in terms of cost-effectiveness of these newer RA treatments such as bDMARDs and tsDMARDs especially in the context of developing economies.

Further the existing evidences on cost-effectiveness of bDMARDs (TNF-a and B-cell inhibitors) and tsDMARDs (JAK inhibitors) compared to csDMARDs, are predominantly from the developed countries. As the cost-effectiveness of interventions could be context specific and hence such results from developed countries may not be suitable for developing countries like India. Further, expensiveness of treatment costs for RA patients warrants the need to generate economic evidences for cost-effective treatment selection in resource-limited settings like India. Hence, we planned to synthesis the economic evidences in the literature and to conduct the full economic evaluation of newer RA pharmacotherapies to aid for evidence-based policy decision making.

1.3 Objectives

Primary:

1. To conduct systematic review and meta-analysis of cost utility evidences on the use of TNF-alpha inhibitors, B-cell inhibitors and JAK inhibitors for the treatment of RA.
2. To conduct markov model-based cost-utility analysis on the use of TNF-alpha inhibitors, B-cell inhibitors and JAK inhibitors for the treatment of RA.
3. To estimate the EuroQoL health-related quality of life (HRQoL) utility values in patients with RA.

Secondary:

1. To estimate the catastrophic health expenditure incurred to patients due to RA illness.

Chapter 2– EVIDENCE SYNTHESIS

2.1 Systematic review and meta-analysis of cost-utility studies on Tumor Necrosis Factor-alpha inhibitors for RA

2.1.1 Introduction

TNF-a-i alone or in combination with csDMARDs is clinically effective [37-41]. However, due to the higher costs of biological inhibitors [33, 34, 38, 42-45], cost-effectiveness analysis is essential to determine the efficient treatment. TNF-a-i has been reported to be cost-effective [38, 40, 46] and not cost-effective [39, 41, 45, 47, 48] in the literature. While the clinical effectiveness of TNF-a-i is apparent from the literature [37-41], the studies on cost-effectiveness have yielded inconsistent evidence. While several studies have reported the cost-effectiveness of TNF-a-i for RA treatment, no systematic review of an economic evaluation study is available. To generate synthesised consistent evidence, we systematically reviewed all the cost-utility studies of TNF-a-i compared to other DMARDs from the available literature and estimated the pooled incremental net benefit (INB).

2.1.2 Methods

The study adhered to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines [49], and the protocol was pre-registered with PROSPERO (CRD 42021222541) [50]. This study is part of a more extensive cost-utility analysis (CUAs) of RA treatments.

2.1.2.1 Data sources and eligibility

We searched PubMed, Embase, Scopus, and the Tufts Medical Centers' cost-effective

analysis (CEA) registry [51] from inception to 5th May 2022. The search terms were constructed using the Population, Intervention, Comparator, Outcome (PICO) approach. We included studies reporting economic outcomes in incremental cost-effectiveness ratios (ICER) per quality-adjusted life years (QALYs) or INBs with no language restrictions. All published CUA studies of TNF-a-i in the treatment of adult RA patients were included and studies with effectiveness measured other than in QALYs, reviews, letters, editorials, abstracts, books, reports, grey literature, and methodological articles were excluded. The detailed search strategy is reported in Appendix 1.

2.1.2.2 Study selection

We identified 4,640 studies and exported the identified studies into Rayyan-web application [52] for manual duplicate removal and screening. The listed studies were screened independently for titles and abstracts by SK and BSB. Reviewers independently reviewed the full text of the finalised 86 studies after the title and abstract screening. The independent assessors' (SK and BSB) mutual agreement produced the final list of studies meeting the inclusion and exclusion criteria (n=27), and data were extracted from the selected studies. The PRISMA flow chart of the screening process is appended in Figure 2.1.1.

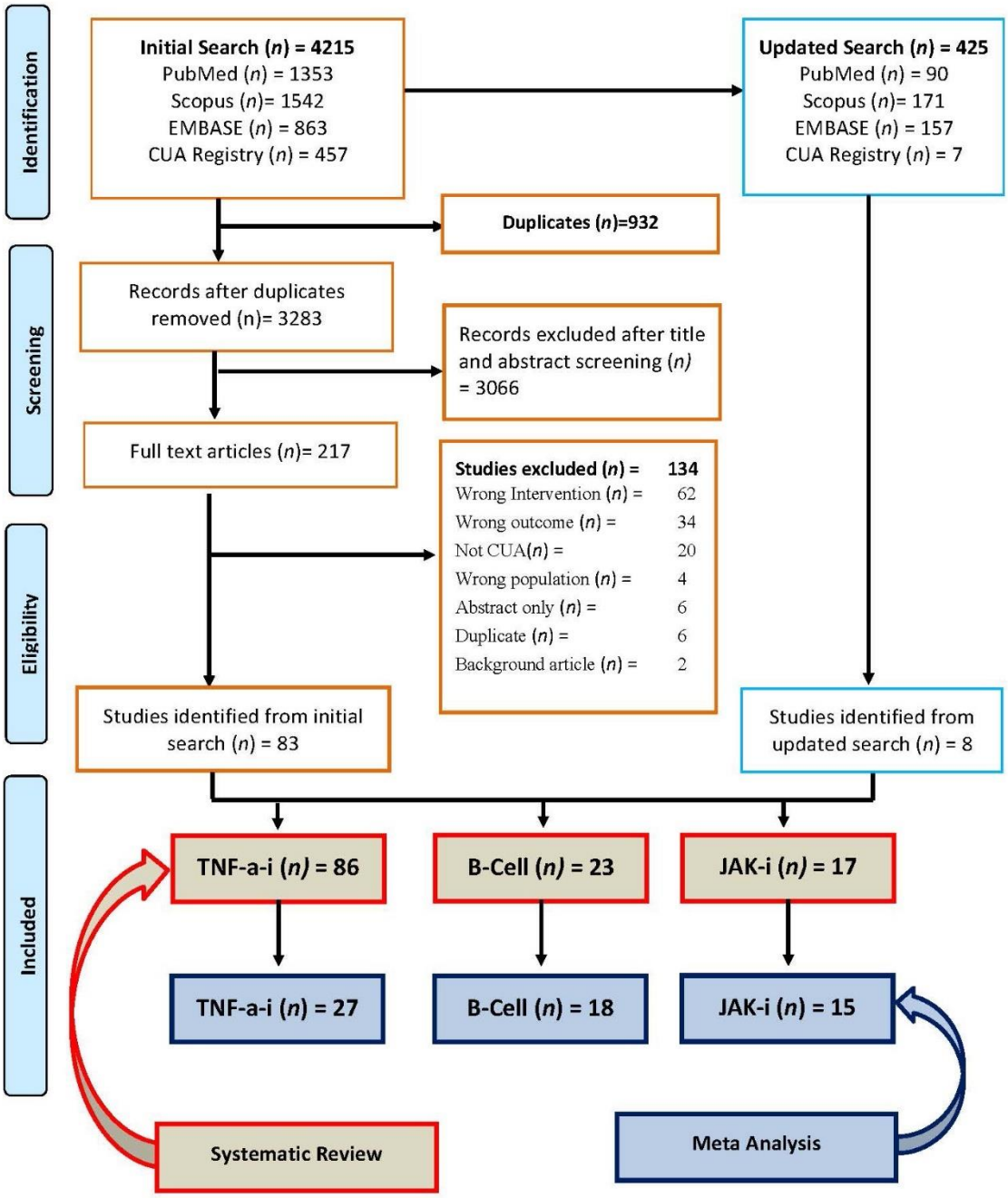


Figure 2.1.1 PRISMA FLOW CHART

2.1.2.3 Data extraction

For each included study, we extracted the following data using a predesigned data extraction form: author, year, country of setting, intervention, comparator, patient characteristics, line of treatment, and the general characterisation of the model, which

included model type, perspective, time horizons, discount rate, and currency year. Further, we extracted economic parameters such as costs (C), incremental costs (ΔC), clinical effectiveness (E), its incremental effectiveness (ΔE), ICERs, INB values, and their measures of dispersion [i.e., standard deviation (SD), standard error (SE), or 95% confidence interval (CI), willingness to pay (WTP), and threshold (K). For studies which didn't report ΔC and ΔE but provided a cost-effective (CE) plane graph, we extracted ΔC and ΔE values using Web-Plot-Digitaliser [53] from the graph. The INB estimates the incremental cost and benefit gained by TNF-a-i compared to other DMARDs.

In our study, we employed adjustment factors, namely the Consumer Price Index (CPI) and Purchasing Power Parity (PPP) values, to normalize the willingness-to-pay levels across different countries. This enabled us to convert all threshold values to a unified currency, specifically USD in the year 2021, for subsequent calculations. By applying these adjustment factors, we ensured consistency and comparability of different threshold values in our analysis (Appendix II).

2.1.2.4 The outcome of interest

We estimated the pooled INB with a 95 per cent confidence interval, defined as pooled INB = K*ΔE–ΔC, where K was the WTP threshold, ΔC= incremental cost and ΔE= incremental effectiveness. A positive INB indicates a cost-effective intervention, whereas a negative INB favours the comparator, indicating a non-cost-effective intervention. If both the upper and lower limit CI values are positive or negative, the results are significant. A non-significant result shows that the lower limit value is in the negative quadrant and the upper limit is in the positive quadrant. Due to ICER's inherent limitations and ambiguous interpretation, INB is preferred as an outcome measure over ICER. [54-56].

2.1.2.5 Data preparation and statistical analysis

For data preparation and analysis, we have used the methods reported by Bagepally et al. [57]. Pooled INB calculation requires mean values along with dispersions of ΔC and ΔE and ICER. Depending on the availability of reported data in the primary study (i.e., INB, ICER, cost, effectiveness, incremental cost, incremental effectiveness, and its dispersion measures) we designed five scenarios (Table 2.1.1).

Table 2.1.1 Details of five Scenarios used to obtain variance

Scenario	Estimates available from the study	Calculation method
One	Study reports all point estimates and its variance	Direct use
Two	Means and 95% CIs of every parameter and ICER reported	Calculate using formula
Three	Means and 95% CI of costs/outcomes, or ΔC and ΔE available	Monte Carlo simulation for ΔC and ΔE to estimate covariance.
Four	Studies do not report any dispersion but provides the Cost effectiveness plane (CE plane) graphs.	Data directly extracted from the CE Plane using Web-Plot Digitizer software.
Five	The study reports only the means of costs, outcomes, and ICER, not reported any dispersion	The measures of dispersions can be used from another similar study if they fulfil the following criteria: 1) Same stratum of country income level, perspective, intervention, comparator, time period, country region, model type, and inputs (i.e., discounting, time horizon). 2) Their ICERs are not much different.

Using the data reported in the primary study and following the approach detailed in Bagepally et al.[57] and reported elsewhere [54, 58-64], we calculated the INB and its variances for each intervention comparator combination. If there is inadequate data to calculate pooled INB, we used Monte-Carlo simulations to estimate covariance from the extracted costs and effectiveness values.

Included studies reported costs in different currencies from different reference years.

To convert all monetary units into a single point common currency (US dollar for the year 2021), we used the consumer price index (CPI) and purchasing power parities (PPP) index, as detailed in Appendix II. Further, countries were stratified by income classification as low-income (LIC), lower-middle (LMIC), upper-middle (UMIC), and high-income (HIC) countries as per the World Bank classification [65].

Meta-analysis was applied to pool the INBs using a random-effects model based on the DerSimonian and Laird method. I^2 statistics were used to assess heterogeneity, $I^2 > 50\%$ was considered substantial heterogeneity, or Cochrane Q p-value < 0.05 was taken as a cut-off for significant heterogeneity. Further, we did a subgroup analysis to explore the source of heterogeneity. Funnel's pot, Eggers' test and Galbraith plot were used to assess the publication bias. All data were prepared using Microsoft Excel version 2019 [66] and analysed using Stata software version 17 [67].

2.1.2.6 Risk of bias assessment and quality assessment

The modified economic evaluation bias (ECOBIAS) checklist [68] was used to report the quality of the included studies. ECOBIAS considers overall biases (11 items) and model-specific biases, including structure (4 items), data (6 items), and internal consistency (1 item) of the study. A five-point rating was applied to each item (applicable, partially applicable, unclear, no, not applicable).

Grading of Recommendation, Assessment, Development, and Evaluation (GRADE) was used to assess the quality of synthesised evidence [69, 70]. We graded the evidence for the cost-effectiveness of TNF-a-i compared to other DMARDs. The grading assessment will consider the risk of bias, inconsistency, indirectness, imprecision, and publication bias and classify the final evidence as high, moderate, low, or very low quality [69, 70].

2.1.3 Results

2.1.3.1 Characteristics of included studies

We included 86 [29, 32-34, 37-48, 71-140] potentially pertinent articles for systematic review, of which 27[33, 34, 39, 46, 48, 71, 75-78, 84, 91-93, 96, 100, 103, 105, 111-113, 115, 121, 122, 125, 129, 136] studies qualified with adequate data for meta-analysis (Figure 2.1.1). The remaining (n=59) studies were included in the systematic review but were excluded from the meta-analysis due to insufficient data. Table 2.1.2 provides a summary of the general characteristics of the included studies.

Majority of the studies (n = 71) were conducted in HICs [29, 34, 37, 38, 40, 42-44, 46, 48, 71-73, 75-81, 83-86, 88-123, 125-131, 134, 136, 139, 140], followed by 12 studies in UMICs [32, 33, 41, 45, 47, 74, 82, 124, 132, 133, 137, 138] and three in LMICs [39, 87, 135]. Forty studies conducted from country-specific settings [29, 33, 42, 43, 46, 48, 73, 75-77, 80, 81, 83, 85, 88, 90-92, 101, 106, 107, 109-113, 116-118, 121, 122, 125-128, 130, 131, 134, 136, 138], risk group setting [34, 37-41, 45, 47, 71, 72, 74, 78, 79, 82, 84, 86, 87, 89, 94-100, 103-105, 108, 114, 115, 119, 120, 123, 124, 129, 132, 133, 135, 137, 139, 140] for n=42 studies and from state level for the remaining four studies [32, 44, 93, 102]. Most of the studies followed model based analytic approach (n=70) [29, 33, 37, 39-44, 46-48, 72, 73, 75, 77-82, 85-91, 93-95, 97-121, 123, 124, 126-128, 130-132, 134, 136-140]and the remaining sixteen were primary economic evaluations[32, 34, 38, 45, 71, 74, 76, 83, 84, 92, 96, 122, 125, 129, 133, 135]. Nearly 61 per cent (n=53) of studies analysed a lifetime horizon [29, 32, 33, 37, 39-41, 46-48, 71, 72, 75, 77-82, 85, 86, 88-91, 93, 95, 101-104, 106-109, 111, 113, 115-120, 123, 124, 127, 130-132, 134, 135, 137, 138] followed by 17 studies with zero to five-year time frame [34, 38, 45, 73, 76, 83, 84, 92, 96, 98, 99, 110, 122, 125, 128, 129, 133] and fourteen studies with a three to ten-year horizon[42-44, 87, 94, 97, 100, 112, 114, 121, 126, 136, 139, 140]. The remaining studies (n=2) did not mention time horizon [74, 105].

Nearly 40 per cent of studies (n=35) chose a national health system perspective [29, 32, 45, 47, 72-76, 78, 79, 82-84, 88, 92, 93, 95, 99, 100, 104-106, 109-111, 117, 118, 124, 131, 132, 134, 136-138], societal

perspective [33, 34, 37, 38, 40-42, 44, 46, 71, 86, 89-91, 96-98, 101, 102, 112, 114, 115, 119-123, 125, 126, 129, 133, 135, 139, 140] by another set of thirty-four studies and individual payer perspective by the remaining (n=17) studies [39, 43, 48, 77, 80, 81, 85, 87, 94, 103, 107, 108, 113, 116, 127, 128, 130]. All the studies reported using the country-specific willingness to pay threshold (n=67) [29, 34, 37, 38, 40-44, 46, 48, 71-73, 75-81, 83-86, 88, 90-100, 102-109, 111-123, 125-129, 131, 134, 139, 140] except seventeen (n=19) used a GDP based threshold [32, 33, 39, 45, 47, 74, 82, 87, 89, 101, 110, 124, 130, 132, 133, 135-138]. Based on the delineated outcome measures, fifty-two studies were categorised as scenario 5 [32, 37, 38, 40-42, 44, 45, 47, 72-74, 79, 80, 82, 83, 86-90, 94, 95, 97, 98, 101, 102, 104, 107-110, 114, 116-120, 123, 124, 127, 128, 130-135, 137-140], followed by eighteen studies in scenario 4 [29, 33, 39, 43, 46, 48, 75-77, 81, 84, 85, 93, 100, 103, 111, 113, 136], nine studies in scenario 3 [34, 92, 99, 106, 112, 115, 121, 126, 129], four studies in scenario 2[71, 78, 105, 125], and three studies in scenario 1 [91, 96, 122].

Table 2.1.2 General characteristics of the studies identified for systematic review and meta-analysis

Author_Year	Country	Income classification	Setting	Study perspective	Analytic approach	Time Horizon	Intervention	Comparator	Remarks
Alemao_2017[48]*	UK	HIC	Country	Payer	Model	Lifetime	Adali	Abata	Not cost effective
Bansback_2005[29]	Sweden	HIC	Country	Health System	Model	Lifetime	Adali + MTX	csDMARDs	Not cost effective
Bansback_2017[71]*	Canada	HIC	Risk Group	Societal	Primary study	Lifetime	Eta + MTX	csDMARDs	Not cost effective
Barbieri_2005[72]	UK	HIC	Risk Group	Health System	Model	Lifetime	Infli + MTX	MTX	cost effective
Barreto_2020[82]	Brazil	UMIC	Risk Group	Health System	Model	5 Year	Goli	Eta	Dominant
Benucci_2011[73]	Italy	HIC	Country	Health System	Primary study	1 Year	TNFi	Ritu + MTX	Not cost effective
Bin wu_2012[33]	China	UMIC	Country	Societal	Model	Lifetime	Eta	csDMARDs	Not cost effective
Boyadzieva_2018[74]	Bulgaria	UMIC	Risk Group	Health System	Primary study	Not Clear	Adali	Cert	Not cost effective
Brennan_2004[46] *	UK	HIC	Country	Societal	Model	Lifetime	Eta + csDMARDs	csDMARDs	cost effective
Brennan_2007[75] *	UK	HIC	Country	Health System	Model	Lifetime	Infli- Eta – Adali	csDMARDs	cost effective
Brown_2018[76] *	UK	HIC	Country	Health System	Primary study	48 weeks	Eta - Adali - Infli - Certo – Goli	Ritu	cost effective
Carlson_2015[127]	USA	HIC	Country	Payer	Model	Lifetime	Adali	Tocili	Not cost effective
Chen_2006[78] *	UK	HIC	Risk Group	Health System	Model	Lifetime	Adali	csDMARDs	cost effective
Chen_2019[77] *	Taiwan	HIC	Country	Payer	Model	Lifetime	Adali + MTX	Tofa+MTX	cost effective
Claxton_2018[79]	USA	HIC	Risk Group	Health System	Model	Lifetime	MTX - Tofa- Adali- Abat -Toci- Ritu	MTX - Eta- Adali- Abat- Toci- Ritu	Not cost effective
Davies_2009[80]	USA	HIC	Country	Payer	Model	Lifetime	Infli + MTX - MTX	MTX - MTX+ HCQs	dominant
Diamantopoulos_2012[81]	Italy	HIC	Country	Payer	Model	Lifetime	Eta- Adali- Ritu- Abat	Tozil- Adali- Ritu- Abat	dominated
Erikson_2014[34] *	Sweden	HIC	Risk Group	Societal	Primary study	9 months	Infli + MTX	csDMARDs	Not cost effective
Fang Chiou_2004[141]	USA	HIC	Country	Payer	Model	1 Year	Eta	Ana	cost effective
Farahani_2006[84] *	Canada	HIC	Risk Group	Health System	Primary study	1 Year	Eta + csDMARDs	csDMARDs	Not cost effective
Fatemi_2020[39] *	Iran	LMIC	Risk Group	Payer	Model	Lifetime	Eta + MTX	Tofa + MTX	Not cost effective
Fournier_2019[43]	USA	HIC	Country	Payer	Model	10 Year	Adali - csDMARDs	Sari - csDMARDs	Dominant
Ghabri_2020[85]	France	HIC	Country	Payer	Model	40 Year	Eta_BS - Abat – Infli	Eta - Abat - Infli	Not cost effective
Gholami_2021[135]	Iran	LMIC	Risk Group	Societal	Primary study	Lifetime	Eta	Infli	Not cost effective
Gissel_2016[38]	Germany	HIC	Risk Group	Societal	Primary study	6 months	Adali + MTX	csDMARDs	cost effective
Hallinen_2010[86]	Finland	HIC	Risk Group	Societal	Model	Lifetime	Adali - Abat -Eta	Ritu + MTX	Not cost effective
Hirose_2022[136] *	Japan	HIC	Country	Health System	Model	10 Year	Eta	MTX	cost effective
Houponen_2019[89]	Finland	HIC	Risk Group	Societal	Model	Lifetime	TNFi	Ritu	Dominant
Incerti_2020[90]	USA	HIC	Country	Societal	Model	Lifetime	Adali + MTX	Eta + MTX	Not cost effective
Jalal_2016[42]	USA	HIC	Country	Societal	Model	5 Year	Eta	csDMARDs	Not cost effective
Jansen_2017[91] *	USA	HIC	Country	Societal	Model	Lifetime	Eta- Adali- Abat- Tocili- Tofa- Ritu- csDMARDs	csDMARDs	cost effective

Author_Year	Country	Income classification	Setting	Study perspective	Analytic approach	Time Horizon	Intervention	Comparator	Remarks
Jingyang_2016[32]	China	UMIC	State	Health System	Primary study	Lifetime	Infli	csDMARDs	cost effective
Joensuu_2016[92] *	Finland	HIC	Country	Health System	Primary study	1 Year	TNFi	csDMARDs	Not cost effective
Kaczor_2007[93] *	Poland	HIC	State	Health System	Model	Lifetime	Eta + csDMARDs	csDMARDs	cost effective
Kielhorn_2008[95]	UK	HIC	Risk Group	Health System	Model	Lifetime	Ritu+MTX- Adali+MTX- Infli+MTX– Leflu	Adali + MTX- Infli + MTX – Lefl	cost effective
Kievit_2016[96] *	Netherland	HIC	Risk Group	Societal	Primary study	18 months	Adali – Eta	csDMARDs	cost effective
Kobelt_2003[97]	Sweden	HIC	Risk Group	Societal	Model	10 Year	Infli + MTX	MTX	cost effective
Kobelt_2005[139]	Sweden	HIC	Risk Group	Societal	Model	1 Year	Eta	MTX	Not cost effective
Kobelt_2011[98]	Sweden	HIC	Risk Group	Societal	Model	10 Year	Eta + MTX	MTX	cost effective
Kobelt_2014[140]	Swedan	HIC	Risk Group	Societal	Model	10 years	Etanercept	MTX	cost effective
Koops_2009[142]	Germany	HIC	Risk Group	Societal	Model	Not Clear	Eta + MTX	MTX	cost effective
Krieckaert_2015[99]	Netherland	HIC	Risk Group	Health System	Model	3 Year	Adali	Adali -Eta	dominant
Kuwana_2022[134]	Japan	HIC	Country	Health System	Model	Lifetime	Infli + MTX	tDMARD + MTX	cost effective
Kvarmme_2015[100] *	Norway	HIC	Risk Group	Health System	Model	10 Year	TNFi - csDMARDs	csDMARDs	cost effective
Lekander_2010[102]	Sweden	HIC	State	Societal	Model	Lifetime	Infli	csDMARDs	cost effective
Lekander_2012[37]	Sweden	HIC	Risk Group	Societal	Model	20 years	TNFi + MTX	csDMARDs	Not cost effective
Lindgren_2009[44]	Sweden	HIC	State	Societal	Model	Not Clear	Ritu + TNFi	TNFi	Dominant
Lopatina_2020[103] *	Canada	HIC	Risk Group	Payer	Model	6 Year	Adali	Ritu	Dominated
Lyseng_2004[104]	UK	HIC	Risk Group	Health System	Model	Lifetime	Eta + csDMARDs	csDMARDs	cost effective
Malottki_2011[105] *	UK	HIC	Risk Group	Health System	Model	Not Clear	Adali	csDMARDs	Not cost effective
Manders_2015[143]	Netherland	HIC	Country	Health System	Primary study	1 Year	TNFi	Ritu	Dominated
Matusevich_2021[94]	USA	HIC	Risk group	Payer	Model	10 Year	Adali - Abat – Tocili	Aba - Toci - Ritu	Not cost effective
Mercado_2013[144]	Colombia	UMIC	Risk Group	Societal	Model	Lifetime	Eta - Adali - Infli - Certo – Goli	MTX	Not cost effective
Merkesdal_2010[145]	Germany	HIC	Country	Health System	Model	Lifetime	Ritu+ MTX- Adali+ MTX- Infli+ MTX	Adali + MTX - Infli + MTX	cost effective
Meshkini_2016[146]	Iran	LMIC	Risk Group	Payer	Model	5 Year	Infli	Tocili	cost effective
Mulligen_2020[122] *	Netherland	HIC	Country	Societal	Primary study	2 Year	TNFi	csDMARDs	Not cost effective
Muszbek_2019[107]	USA	HIC	Risk Group	Payer	Model	Not Clear	TNFi + MTX	Sari + MTX	Dominated
Muszsbek_2019[108]	USA	HIC	Country	Payer	Model	Lifetime	Adali + MTX	Sari + MTX	Dominated
Navarro_2020[109]	Spain	HIC	Country	Health System	Model	Lifetime	Adali - Ritu- Tocili- Eta – Certo	Tofa- Ritu - Toci - Eta – Cert	Dominant
Nguyen_2012[147]	USA	HIC	Country	Health System	Model	5 Year	Eta + MTX	MTX	Dominant
Park_2016[111] *	South Korea	HIC	Country	Health System	Model	Lifetime	Eta	Lefl – Eta	cost effective
Patel_2020[129] *	UK	HIC	Risk Group	Societal	Primary study	1 Year	TNFi	csDMARDs	Not cost effective
Schipper_2011[112] *	Netherland	HIC	Country	Societal	Model	5 Year	TNFi+MTX	MTX	Not cost effective
Schleuter_2019[113] *	Spain	HIC	Country	Payer	Model	Lifetime	Adali	Bari	Dominant
Shi_2020[45]	China	UMIC	Risk Group	Health System	Primary study	1 Year	Eta + MTX	csDMARDs	Not cost effective

Author_Year	Country	Income classification	Setting	Study perspective	Analytic approach	Time Horizon	Intervention	Comparator	Remarks
SiNi Li_2021[137]	China	UMIC	Risk Group	Health System	Model	Lifetime	Adali + MTX	Baricitinib + MTX	Not cost effective
SiNi Li_2021[47]	China	UMIC	Risk Group	Health System	Model	Lifetime	Eta - Abat – Tofa	TT- Ritu - Tofa	Not cost effective
Soini_2012[115] *	Finland	HIC	Risk Group	Societal	Model	Lifetime	Eta + MTX	MTX	Not cost effective
Soini_2017[126]	Finland	HIC	Country	Societal	Model	5 Year	Certolizumab	Abat - Adali - Certoli - Eta - Goli	Dominant
Spalding_2006[116]	USA	HIC	Country	Payer	Model	Lifetime	Adali	MTX	cost effective
Stephens_2015[117]	UK	HIC	Country	Health System	Model	30 Year	Adali + MTX	MTX	cost effective
Stevenson_2016[118]	UK	HIC	Country	Health System	Model	Lifetime	Adali	csDMARDs	Not cost effective
Tan_2021[138]	China	UMIC	Country	Health System	Model	Lifetime	Tofa - Eta - Ritu – Tocili	Eta - Ritu – Tocili	cost effective
Tan_2021[132]	China	UMIC	Risk Group	Health System	Model	Lifetime	Eta - Tofa - Ritu – Tocili	MTX	Not cost effective
Tanaka_2016[148]	Japan	HIC	Risk Group	Societal	Model	Not Clear	Adali - Eta - Infli – Tocili	MTX	cost effective
Tanno_2006[120]	Japan	HIC	Risk Group	Societal	Model	Lifetime	Eta	MTX + Sulf	cost effective
Tian_2021[133]	China	UMIC	Risk Group	Societal	Primary study	1 Year	Eta_BS + MTX	csDMARDs	cost effective
Tran-Duy_2018[125] *	Netherland	HIC	Country	Societal	Primary study	1 Year	TNFi	csDMARDs	cost effective
Tzanetakos_2017[149]	Greece	HIC	Country	Payer	Model	Lifetime	Certo + MTX	Goli + MTX	Dominant
Van De Laar_2020[121] *	Netherland	HIC	Country	Societal	Model	5 Year	csDMARDs Mono- csDMARDs Combi - Adali – bDMARDs	csDMARD Mono- csDMARD Combi - Bari - bDMARDs	Not cost effective
Vega_2015[88]	Spain	HIC	Country	Health System	Model	Lifetime	Certo	Adali	Cost effective
Wailoo_2008[131]	USA	HIC	Country	Health System	Model	Lifetime	Infli	Eta	Not cost effective
Whittington_2019[150]	USA	HIC	Risk Group	Societal	Model	Lifetime	Adali	Sari	Dominated
Wong_2002[151]	USA	HIC	Risk Group	Societal	Model	Lifetime	Infli	MTX	cost effective
Wu_2015[124] *	China	UMIC	Risk Group	Health System	Model	Lifetime	Eta_BS - Ritu + csDMARDs	csDMARDs	cost effective
Young lee_2015[101]	South Korea	HIC	Country	Societal	Model	Lifetime	Tofa + MTX - Adali + MTX + Eta + MTX – csDMARDs	Adali + MTX + Eta + MTX - csDMARDs	cost effective

*meta-analysis, HIC– High-income country, UMIC– Upper middle-income country, LMIC– Lower middle-income country, MTX– Methotrexate, Aba– Abatacept, Ritu– Rituximab, Ada– Adalimumab, Toci– Tocilizumab, Goli– Golimumab, Eta– Etanercept, TT– Tripple therapy, Tofa– Tofacitinib, Bari- Baricitinib, Certo- Certolizumab, Sari- Sarilumumab, Lefl– Leflunomide, csdmards– conventional synthetic disease-modifying anti rheumatic drugs

2.1.3.2 Risk of bias assessment

To assess the risk of bias in the selected studies, we used a modified ECOBIAS checklist [68]. The overall ECOBIAS checklist analysis reveals that the studies are more likely to be biased. Only one-third of the research adopted a societal perspective, and most of the remaining studies failed to articulate why they chose another perspective, indicating a high perspective bias. Similarly, treatment effect bias is high due to improper extrapolation and synthesis of relative treatment effects. More than two-thirds of the research did not explore the four uncertainty principles in sufficient detail, resulting in limited sensitivity and restricted scope bias. However, the bias associated with internal consistency in terms of mathematical logic is unknown (Figure 2.1.2, 2.1.3).

Figure 2.1.2 ECOBIAS graph

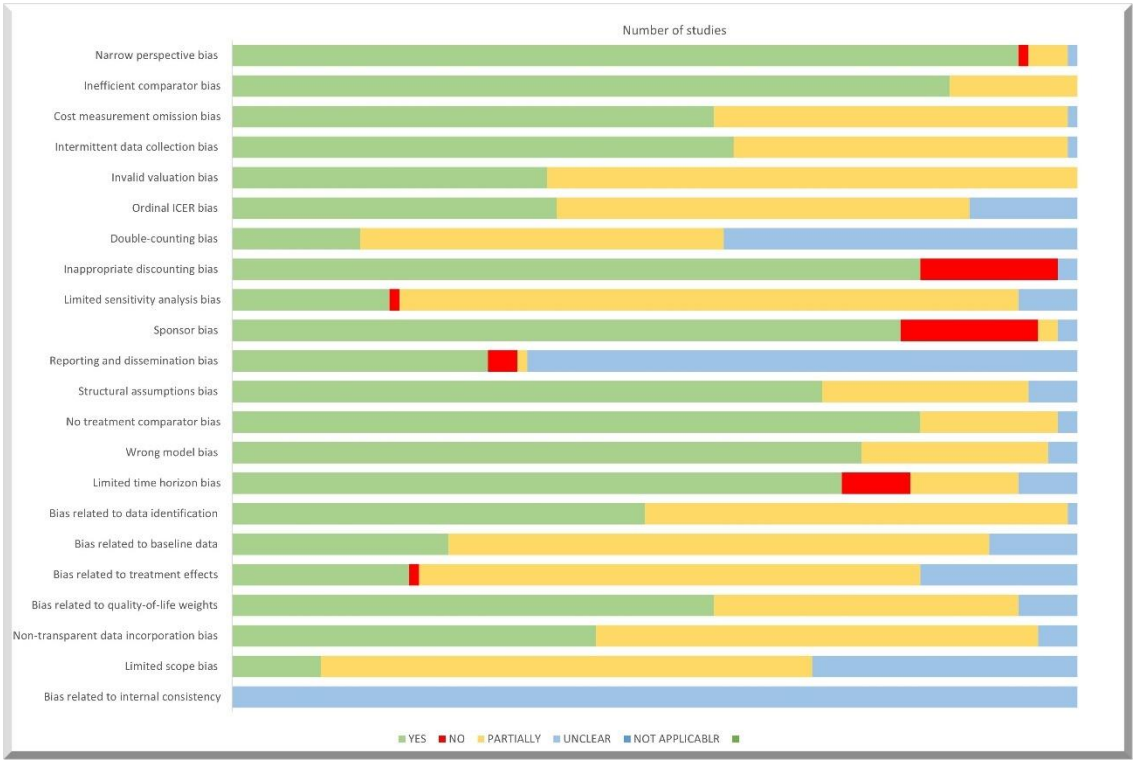


Figure 2.1.3 Assessment of Risk of Bias using ECOBIAS Checklist

Author_Year	Narrow perspective bias	Inefficient comparator bias	Cost measurement omission bias	Intermittent data collection bias	Invalid valuation bias	Ordinal ICER bias	Double counting bias	Inappropriate discounting bias	Limited sensitivity analysis bias	Sponsor bias	Reporting and Dissemination bias	Structural Assumptions bias	No treatment Comparator bias	Wrong model bias	Limited time horizon bias	Bias related to data identification	Bias related to baseline data	Bias related to treatment effects	Bias related to quality-of-life weights	Non-transparent data incorporation bias	Limited scope bias	Bias related to Internal consistency
Bansback_2005(1)	P	Y	Y	Y	P	Y	P	Y	P	P	U	U	Y	U	Y	Y	Y	Y	Y	P	P	U
Fang_2004	P	P	U	P	Y	Y	P	U	N	U	U	Y	P	Y	N	P	U	N	Y	P	P	U
Fournier_2019	P	Y	P	Y	P	Y	P	Y	U	Y	U	Y	Y	Y	P	P	Y	P	P	P	U	U
Jalal_2016	Y	Y	Y	Y	P	Y	P	Y	P	Y	U	Y	Y	Y	P	Y	Y	Y	Y	P	P	U
Davies_2009	Y	Y	Y	Y	P	Y	P	Y	P	P	P	Y	Y	Y	Y	Y	Y	Y	Y	P	P	U
Chen_2019 (2)	Y	Y	Y	Y	Y	Y	P	Y	P	Y	U	Y	Y	Y	Y	Y	Y	Y	Y	Y	P	U
Carlson_2015	Y	Y	Y	Y	Y	Y	P	Y	P	N	U	Y	Y	Y	Y	Y	Y	P	Y	Y	P	U
Boyadziena_2018	Y	Y	Y	Y	P	P	P	Y	P	Y	Y	P	Y	P	Y	Y	P	P	Y	Y	P	U
Brennan_2007(2)	N	Y	Y	Y	Y	Y	P	Y	P	Y	U	Y	Y	Y	Y	Y	Y	P	Y	Y	P	U
Manders_2015	Y	Y	P	P	P	U	U	N	P	Y	Y	P	Y	Y	N	P	P	U	P	P	U	U
Diamantopoulos_2012	P	Y	Y	Y	Y	Y	P	Y	P	Y	U	Y	Y	Y	Y	Y	Y	P	Y	Y	Y	U
Navarro_2020	Y	Y	P	P	P	P	U	Y	P	Y	U	Y	Y	Y	Y	P	P	P	P	P	P	U
Malottki_2011	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	U	Y	Y	Y	Y	Y	P	U
Schipper_2011	Y	Y	Y	Y	Y	P	P	N	P	Y	Y	Y	Y	Y	N	Y	P	U	Y	Y	U	U
Spalding_2006	Y	Y	P	P	P	P	U	Y	P	Y	U	P	Y	P	Y	P	P	P	P	P	P	U
Tran-Duy_2018	Y	P	Y	Y	Y	Y	U	N	P	Y	Y	Y	P	P	P	Y	Y	P	Y	Y	P	U
Bin wu_2012	Y	Y	P	P	P	P	U	Y	P	Y	U	P	Y	P	Y	P	P	U	P	P	P	U
Van De Laar_2020	Y	Y	P	P	P	U	U	Y	U	Y	U	Y	Y	Y	Y	P	P	U	P	P	P	U
Kobelt_2005 (2)	Y	Y	Y	P	Y	Y	P	Y	P	N	U	Y	Y	P	Y	P	P	P	P	P	U	U
Muszsbek_2019(1)	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	U
Barbieri_2005	Y	Y	P	P	P	P	U	Y	P	Y	U	Y	Y	Y	Y	Y	P	P	P	P	P	U
Incerti_2020	Y	Y	Y	Y	P	Y	Y	Y	P	Y	Y	Y	P	P	U	Y	U	Y	Y	U	P	U
Gissel_2016	Y	Y	Y	Y	Y	P	Y	Y	P	N	U	Y	Y	Y	N	Y	U	U	Y	Y	U	U
Erikson_2014	Y	Y	Y	Y	P	P	P	N	P	Y	Y	Y	Y	P	U	Y	P	U	Y	Y	U	U
Bansback_2017(2)	Y	Y	P	U	P	U	U	Y	P	Y	U	P	Y	Y	Y	P	U	U	U	P	U	U
Lekander_2010(1)	Y	Y	Y	Y	Y	P	U	Y	P	Y	U	Y	Y	Y	Y	Y	U	U	Y	Y	U	U
Joensuu_2016	Y	Y	P	P	Y	P	U	N	P	N	N	P	U	P	Y	P	P	P	P	U	U	U
Jessica_2020	Y	Y	P	Y	P	P	U	Y	P	Y	U	Y	Y	Y	Y	P	U	U	Y	U	U	U

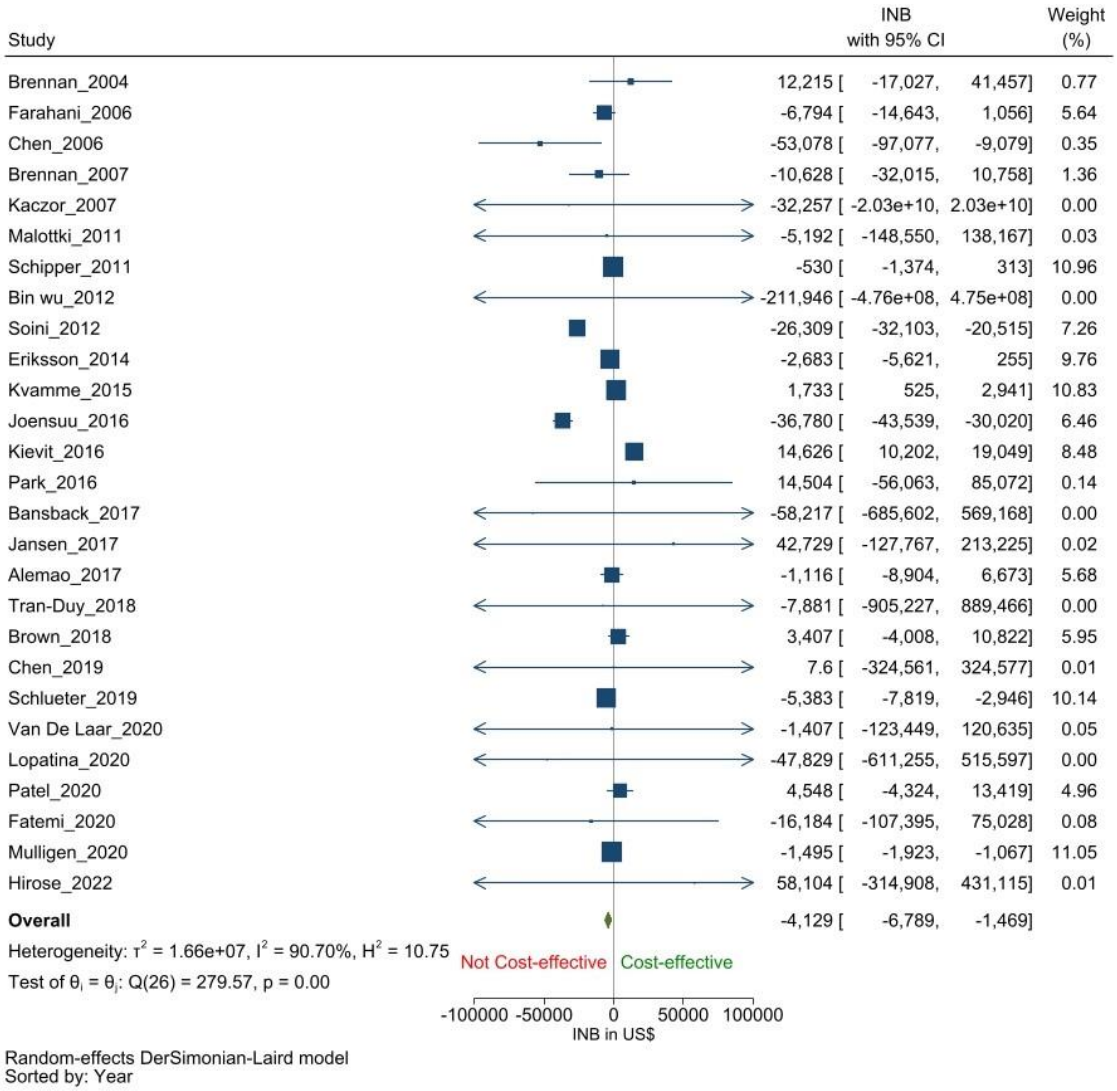
Author_Year	Narrow perspective bias	Inefficient comparator bias	Cost measurement omission bias	Intermittent data collection bias	Invalid valuation bias	Ordinal ICER bias	Double counting bias	Inappropriate discounting bias	Limited sensitivity analysis bias	Sponsor bias	Reporting and Dissemination bias	Structural Assumptions bias	No treatment Comparator bias	Wrong model bias	Limited time horizon bias	Bias related to data identification	Bias related to baseline data	Bias related to treatment effects	Bias related to quality-of-life weights	Non-transparent data incorporation bias	Limited scope bias	Bias related to Internal consistency
Merkesdal_2010	Y	Y	Y	Y	P	P	U	Y	Y	N	U	Y	Y	Y	P	P	U	U	Y	P	U	U
Young lee_2015	Y	Y	Y	Y	Y	Y	P	Y	U	Y	U	Y	Y	Y	Y	U	U	P	U	Y	P	U
Lopatina_2020	Y	Y	Y	P	Y	P	U	Y	P	Y	Y	Y	Y	Y	Y	P	P	Y	Y	Y	P	U
Meshkini_2016	Y	P	Y	P	P	P	Y	Y	P	Y	U	P	P	P	P	P	P	P	P	P	P	U
Kievit_2016	Y	P	Y	Y	P	Y	P	N	P	Y	Y	Y	P	Y	N	Y	Y	P	Y	Y	P	U
Kielhorn_2008	Y	P	P	P	P	U	U	Y	P	Y	U	Y	Y	Y	Y	P	P	P	Y	P	U	U
Ghabri_2020	Y	Y	P	P	P	P	U	Y	P	N	Y	Y	Y	Y	Y	P	P	P	Y	P	P	U
Kobelt_2011 (3)	Y	Y	Y	Y	P	Y	P	Y	P	Y	U	Y	Y	Y	Y	Y	Y	P	P	P	P	U
Houponen_2019	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	P	P	Y	Y	U	U
Patel_2020	Y	P	P	Y	P	P	U	N	P	Y	Y	P	P	Y	P	P	P	P	P	P	U	U
Stevenson_2016	Y	Y	Y	Y	Y	Y	Y	Y	P	Y	Y	Y	Y	Y	Y	Y	P	Y	Y	Y	P	U
Krieckaert_2015	Y	P	P	P	P	P	P	Y	P	Y	U	P	P	P	P	P	P	P	P	P	P	U
Kvamme_2015	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	U	Y	Y	Y	Y	Y	P	Y	Y	Y	P	U
Lekander_2012(2)	Y	Y	Y	Y	Y	Y	P	Y	P	Y	U	Y	Y	Y	Y	Y	P	Y	Y	Y	P	U
Schleuter_2019	Y	Y	Y	P	P	P	P	Y	P	Y	Y	Y	Y	Y	Y	P	P	P	Y	Y	P	U
Whittington_2019	Y	Y	Y	Y	P	P	U	Y	P	Y	U	Y	Y	Y	Y	P	P	P	P	P	U	U
Vega_2015	Y	Y	Y	Y	Y	P	P	Y	P	Y	U	Y	Y	Y	Y	Y	Y	P	P	P	U	U
Park_2016	Y	Y	Y	P	Y	P	U	Y	P	Y	Y	Y	Y	Y	Y	P	P	Y	Y	Y	P	U
Matusevich_2021	Y	Y	Y	Y	Y	P	U	Y	P	Y	U	Y	Y	Y	Y	Y	Y	P	Y	Y	P	U
Jansen_2017	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	P	Y	Y	Y	Y	U
Brown_2018	Y	Y	Y	Y	Y	Y	P	N	P	Y	Y	Y	Y	Y	P	Y	Y	P	Y	Y	P	U
Kobelt_2014 (4)	Y	P	P	Y	P	P	P	Y	P	Y	U	Y	P	Y	Y	P	P	U	P	P	U	U
Kobelt_2003 (1)	Y	Y	Y	Y	P	P	P	Y	P	N	U	Y	Y	P	Y	P	Y	P	Y	Y	P	U
Lindgren_2009	Y	Y	P	Y	P	P	P	Y	P	Y	U	Y	Y	P	N	P	P	P	Y	P	P	U
Mercado_2013	Y	P	P	Y	P	P	U	Y	Y	N	U	Y	P	Y	Y	Y	P	P	Y	P	P	U
Muszbek_2019(2)	Y	Y	P	Y	P	P	P	Y	P	Y	Y	Y	Y	Y	Y	P	P	P	Y	P	P	U
Shi_2020	Y	Y	P	P	P	P	P	N	P	Y	U	Y	Y	Y	N	P	P	P	P	P	U	U
Soini_2012 (1)	Y	Y	P	P	P	P	P	Y	P	Y	U	Y	Y	Y	Y	P	P	P	P	P	P	U
Tanaka_2016	Y	P	P	P	P	P	P	Y	P	Y	U	Y	P	P	U	P	P	P	P	P	P	U

Author_Year	Narrow perspective bias	Inefficient comparator bias	Cost measurement omission bias	Intermittent data collection bias	Invalid valuation bias	Ordinal ICER bias	Double counting bias	Inappropriate discounting bias	Limited sensitivity analysis bias	Sponsor bias	Reporting and Dissemination bias	Structural Assumptions bias	No treatment Comparator bias	Wrong model bias	Limited time horizon bias	Bias related to data identification	Bias related to baseline data	Bias related to treatment effects	Bias related to quality-of-life weights	Non-transparent data incorporation bias	Limited scope bias	Bias related to Internal consistency
Tanno_2006	Y	Y	Y	P	P	P	P	Y	Y	Y	U	Y	Y	P	Y	Y	P	P	Y	P	P	U
Claxton_2018	Y	Y	Y	Y	P	P	P	Y	P	Y	Y	Y	Y	Y	Y	P	P	P	Y	Y	Y	U
Kaczor_2007	Y	Y	P	P	P	Y	P	Y	P	N	U	P	Y	Y	Y	P	P	P	P	P	P	U
Farahani_2006	Y	P	P	P	P	U	U	N	P	Y	U	P	P	P	Y	P	P	P	P	P	P	U
Fatemi_2020	Y	Y	Y	Y	Y	Y	P	Y	Y	Y	U	Y	Y	Y	Y	Y	P	P	Y	Y	Y	U
Lyseng_2004	Y	Y	P	P	P	P	U	Y	Y	N	U	P	Y	U	Y	P	P	P	U	P	P	U
Tzanetakos_2017	Y	Y	Y	Y	P	P	P	Y	Y	Y	U	Y	Y	Y	Y	Y	P	Y	Y	P	U	U
Wailoo_2008	Y	Y	P	P	P	P	U	Y	P	Y	U	U	Y	Y	Y	P	P	U	U	P	U	U
Alemao_2017	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	U	Y	Y	Y	Y	Y	Y	P	Y	Y	Y	U
Benucci_2011	U	P	P	P	P	U	U	N	P	N	U	P	P	P	Y	P	P	U	P	P	U	U
Nguyen_2012	Y	Y	Y	Y	P	Y	U	Y	P	Y	U	P	Y	Y	Y	P	P	P	Y	Y	Y	U
Soini_2017 (2)	Y	Y	P	P	P	U	U	Y	P	Y	U	Y	Y	Y	Y	P	P	P	Y	P	P	U
Stephens_2015	Y	Y	P	P	P	U	U	Y	P	Y	U	P	Y	P	Y	P	P	P	P	P	P	U
Koops_2009	Y	Y	P	P	P	P	P	N	U	Y	U	U	Y	Y	U	P	P	P	P	P	P	U
Wong_2002	Y	Y	P	P	P	U	U	Y	P	Y	U	U	Y	Y	P	Y	P	U	U	P	U	U
Brennan_2004 (1)	Y	Y	Y	Y	Y	Y	P	Y	Y	U	U	Y	Y	Y	Y	Y	Y	Y	Y	Y	P	U
Chen_2006 (1)	Y	Y	Y	Y	P	Y	P	Y	U	Y	U	Y	Y	Y	P	Y	Y	P	Y	Y	U	U
Hallinen_2010	Y	Y	P	P	P	U	U	Y	P	Y	U	P	Y	Y	Y	P	P	U	P	Y	P	U
Wu_2015	Y	Y	P	Y	P	P	U	Y	Y	Y	U	Y	Y	Y	Y	Y	P	P	Y	Y	P	U
Mulligan_2020	Y	P	P	Y	P	P	U	N	P	Y	Y	U	P	U	Y	P	P	U	P	P	P	U
Jingyang_2016	Y	Y	P	Y	Y	P	U	U	P	N	N	P	U	P	Y	P	P	P	P	U	U	U
Tan_2021(1)	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	P	Y	Y	Y	Y	P	P	Y	P	U	U
Gholami_2021	Y	Y	Y	P	P	Y	P	Y	P	N	U	P	Y	Y	U	P	P	P	U	P	P	U
Tan_2021(2)	Y	Y	Y	Y	Y	U	Y	Y	P	Y	Y	P	Y	Y	Y	Y	P	Y	Y	Y	Y	U
Hirose_2022	Y	Y	Y	P	Y	Y	Y	Y	U	Y	U	Y	Y	Y	P	Y	Y	P	P	Y	Y	U
SiniLI_2021 (1)	Y	Y	Y	Y	P	P	U	Y	Y	Y	Y	Y	Y	Y	Y	Y	P	Y	P	Y	P	U
Tian_2021	Y	Y	P	P	P	P	U	N	P	N	N	P	P	P	Y	P	P	P	P	P	U	U
SiniLI_2021 (2)	Y	Y	Y	Y	Y	Y	U	Y	P	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	P	U
Kuwana_2022	Y	Y	P	P	P	P	U	Y	P	Y	Y	Y	Y	Y	Y	Y	U	P	P	P	U	U

2.1.3.3 TNF-a-i compared with other DMARDs

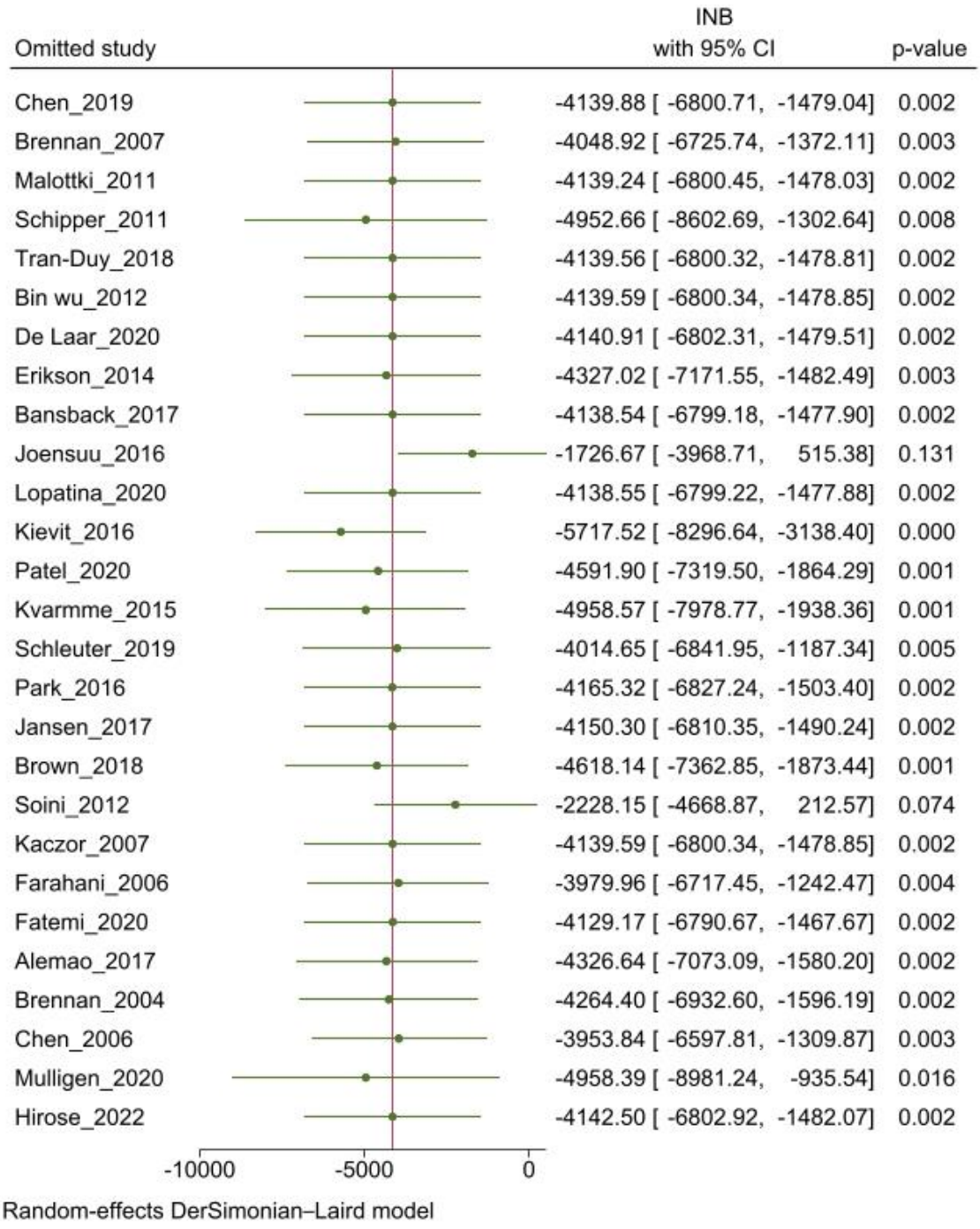
The pooled INB is $ -4,129 with 95% CI (-6,789 to -1,469), revealing that TNF-a-i is significantly not cost-effective than other DMARDs but with considerable heterogeneity (I^2 =90.70) between the studies (Figure 2.1.4).

Figure 2.1.4 TNF-a-i compared with other DMARDs



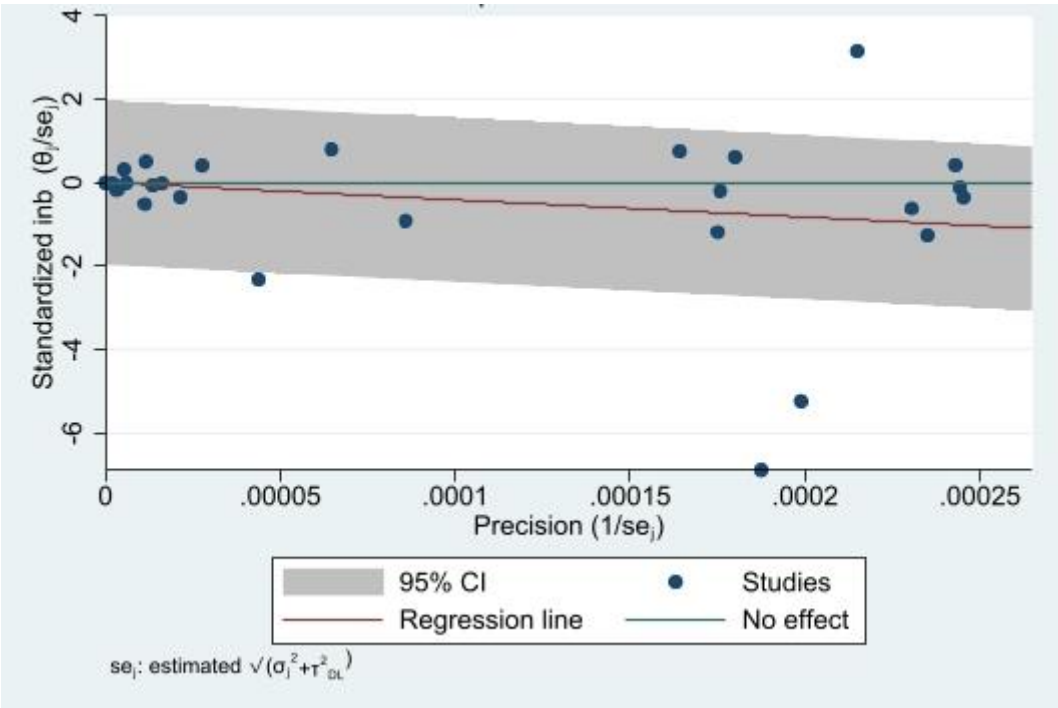
The leave-one-out analysis (Figure 2.1.5) revealed that three studies, Soini, Joensuu and Kievit [92, 96, 115], appear to have a greater influence on the estimation of the overall INB when compared to other studies.

Figure 2.1.5 Leave-one-analysis for pooled INBs for TNF-a-i compared to other DMARDs



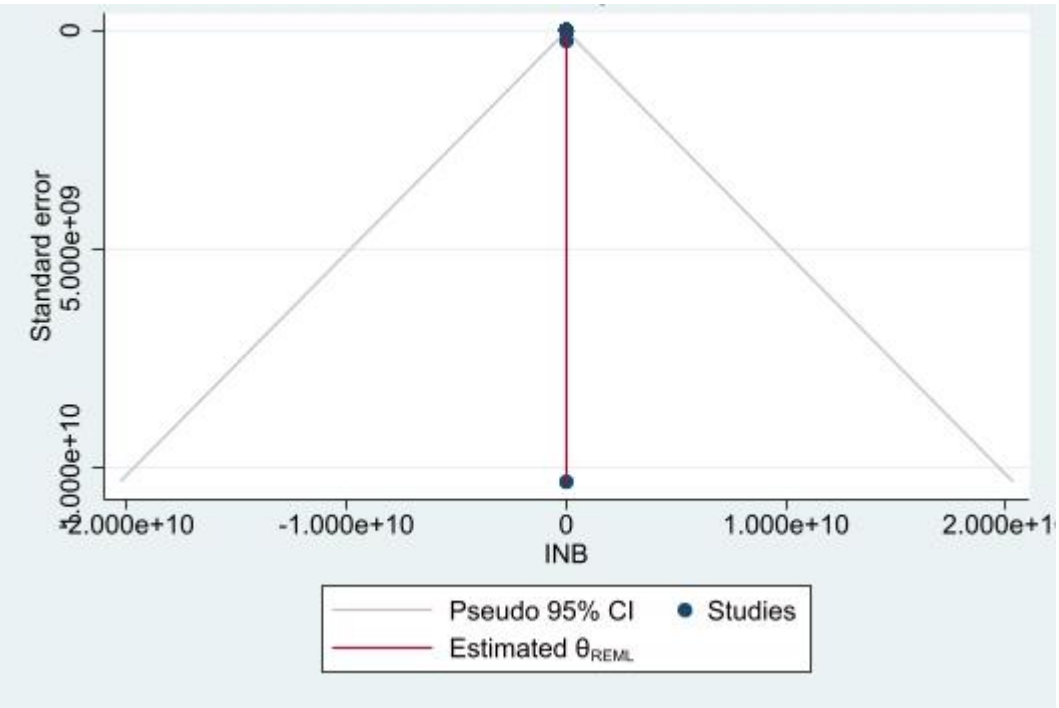
The overall result, however, remains unchanged. The Galbraith plot (Figure 2.1.6) also revealed that, except for three studies, all are within the 95% confidence interval, indicating the consistency among studies and the variations in findings are compatible with homogeneity.

Figure 2.1.6 Galbraith plot



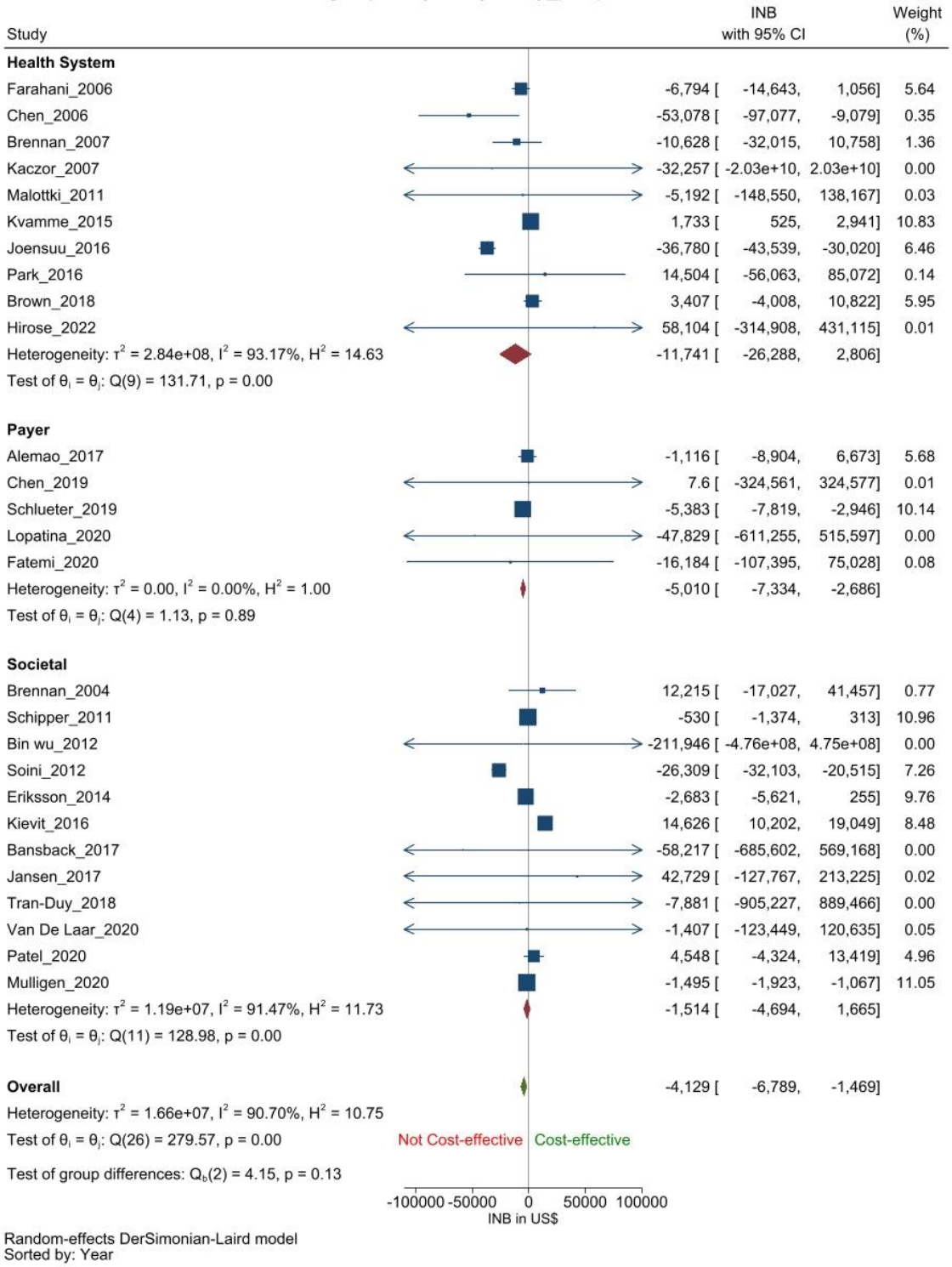
Publication bias: Due to high heterogeneity between the studies, the visual assessment of the funnel plot was insufficient to determine publication bias, but studies with larger standard errors reported larger effect sizes than the precise studies. (Figure 2.1.7). However, Egger's test reported a higher p-value (p = 0.447), indicating no publication bias.

Figure 2.1.7 Funnel plot for publication bias



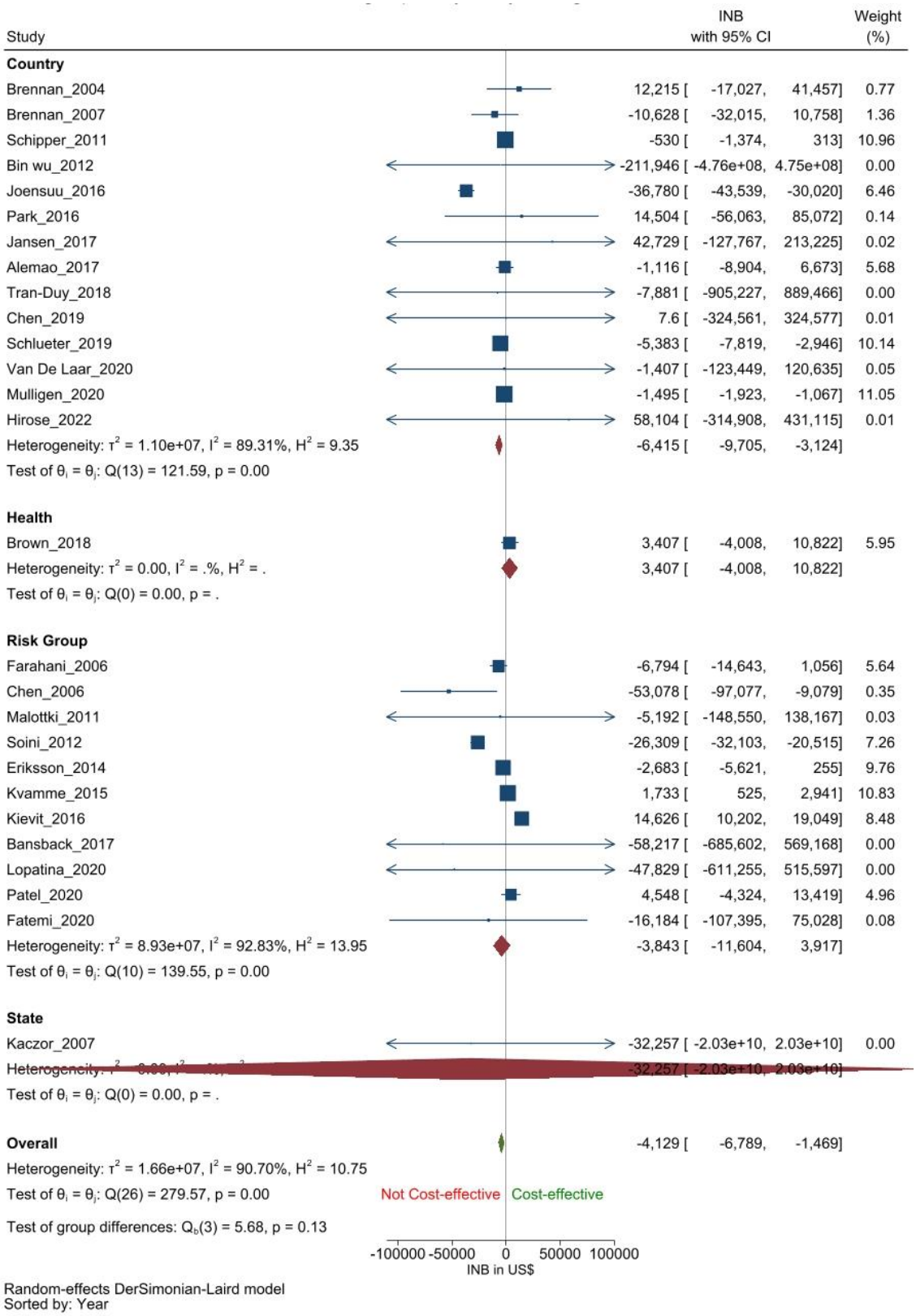
Subgroup analysis: Subgroup analyses were performed to investigate the differences in pooled INBs and study heterogeneity between studies. Subgroup based on the study perspective found that the TNF-a-i is not cost-effective than other DMARDs neither in the health system perspective [75, 76, 78, 84, 92, 93, 100, 105, 111, 136] with an INBp of $ -11,741 (-26,288 to 2,806), or societal perspective [33, 34, 46, 71, 91, 96, 112, 115, 121, 122, 125, 129] [$ -1,514 (-4,694 to 1,665)]. However, the result in payer perspective is statistically significant [39, 48, 77, 103, 113] [$ -5,010 (-7,334 to -2,686)] with no heterogeneity (I^2=0.0%) (Figure 2.1.8).

Figure 2.1.8 Subgroup analysis of pooled INBs based on study perspectives



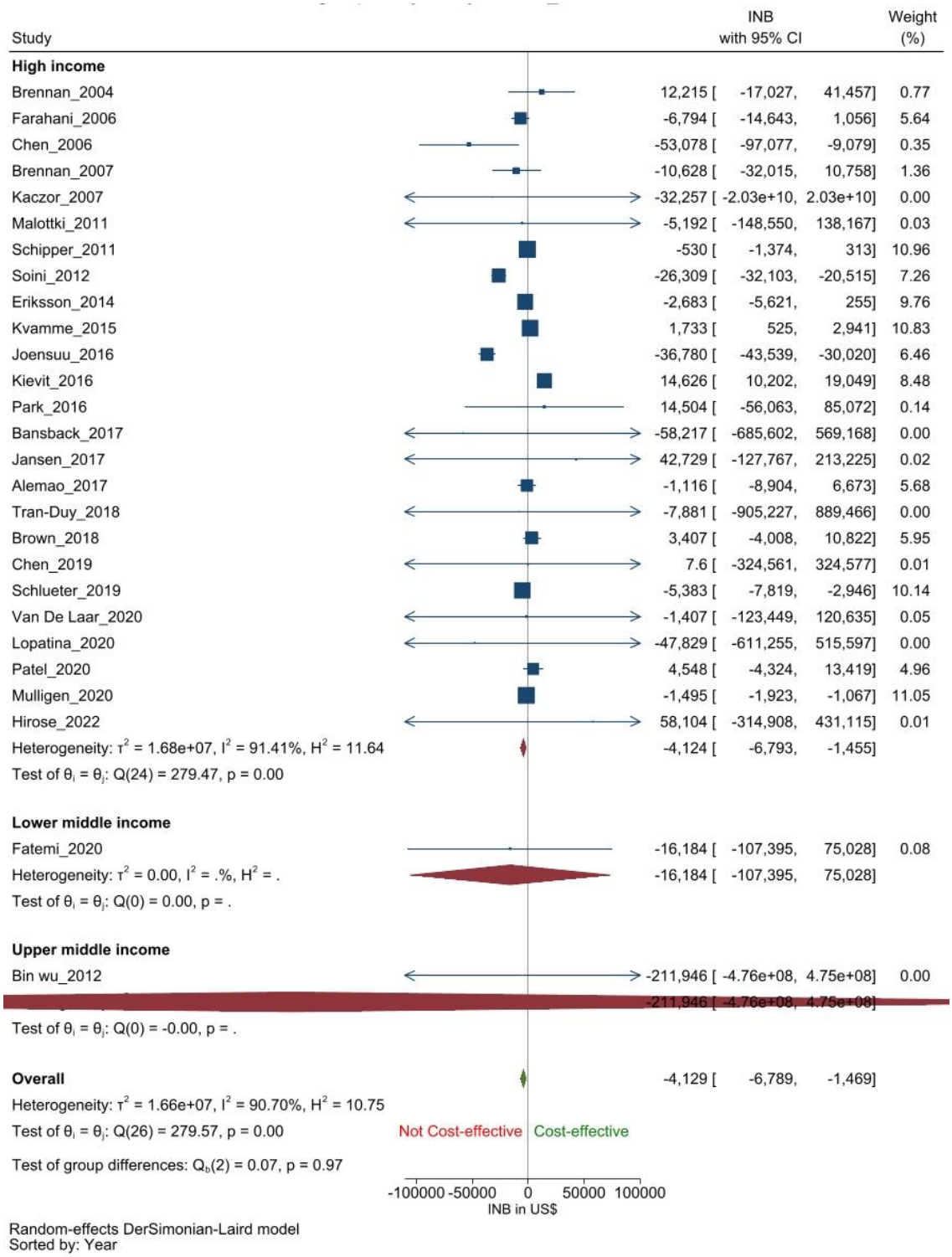
Similarly, the TNF-a-i is not cost-effective in a risk group setting [34, 39, 71, 78, 84, 96, 100, 103, 105, 115, 129], INBp $ -3,843 (-11,604 to 3,917) and country setting [33, 46, 48, 75, 77, 91, 92, 111-113, 121, 122, 125, 136] [$ -6,415 (-9,705 to -3,124)] with high heterogeneity (Figure 2.1.9).

Figure 2.1.9 Subgroup analysis of pooled INBs based on study setting



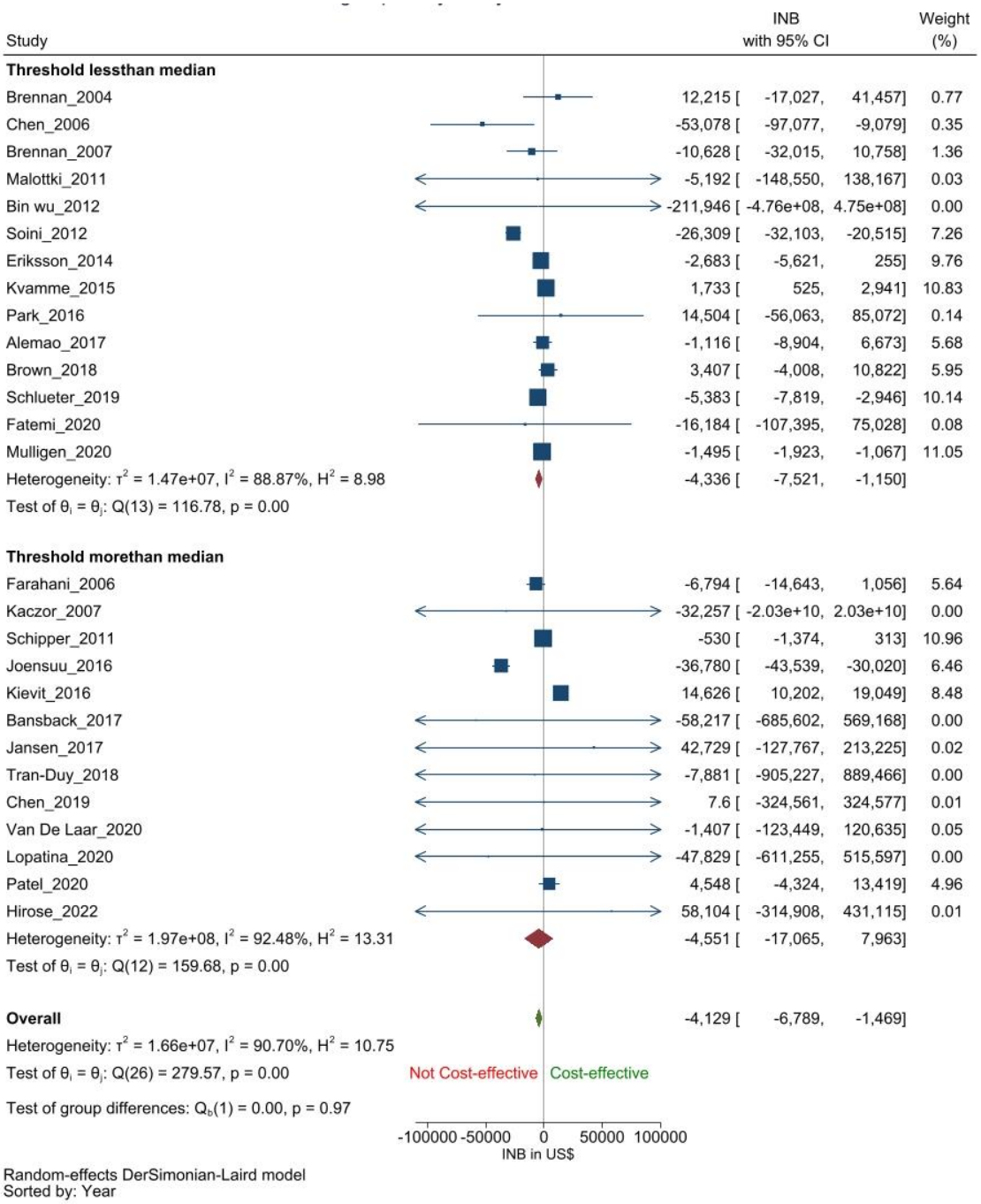
On subgroup analysis based on income classification, TNF-a-i is not cost-effective in HICs [34, 46, 48, 71, 75-78, 84, 91-93, 96, 100, 103, 105, 111-113, 115, 121, 122, 125, 129, 136] with a pooled INB of $ -4,124 (-6,793 to -1,455) with considerable heterogeneity (Figure 2.1.10).

Figure 2.1.10 Subgroup analysis of pooled INBs based on income classification



The median threshold value of all the studies included in the analysis was $ 63,938 and a subgroup analysis based on the WTP threshold revealed that TNF-a-i is not cost-effective for both thresholds, less than the median [33, 34, 39, 46, 48, 75, 76, 78, 100, 105, 111, 113, 115, 122] with an INBp of $ -4,336 (-7,521 to -1,150) and threshold more than median [$ -4,551(-17,065 to 7,963)] [71, 77, 84, 91-93, 96, 103, 112, 121, 125, 129, 136] (Figure 2.1.11).

Figure 2.1.11 Subgroup analysis of pooled INBs based on median Threshold



Scenario-wise subgroups also revealed a similar result for TNF-a-i compared to other DMARDs. The intervention is not cost-effective neither in scenario one [91, 96, 122] with an INBp of $ 6,709 (-8,902 to 22,314), scenario two [71, 78, 105, 125] [$ -48,907 (-90,830 to -6,985)], scenario three [34, 92, 112, 115, 121, 129] [$ -12,185 (-22,811 to -,1558)] or in scenario four [33, 39, 46, 48, 75-77, 84, 93, 100, 103, 111, 113, 136] with an INBp of $ -1,576 (-5,500 to 2,348) (Figure 2.1.12).

Subgroup analysis based on the analytic approach revealed that both model-based studies [INBp=-5,639 (-9,797 to -1,482)] and primary economic evaluations [INBp= -3,459 (-10,738 to 3,820)] found TNF-a-i treatments to be not cost-effective compared to other DMARDs (Figure 2.1.13).

Figure 2.1.12 Subgroup analysis of pooled INBs based on Scenario

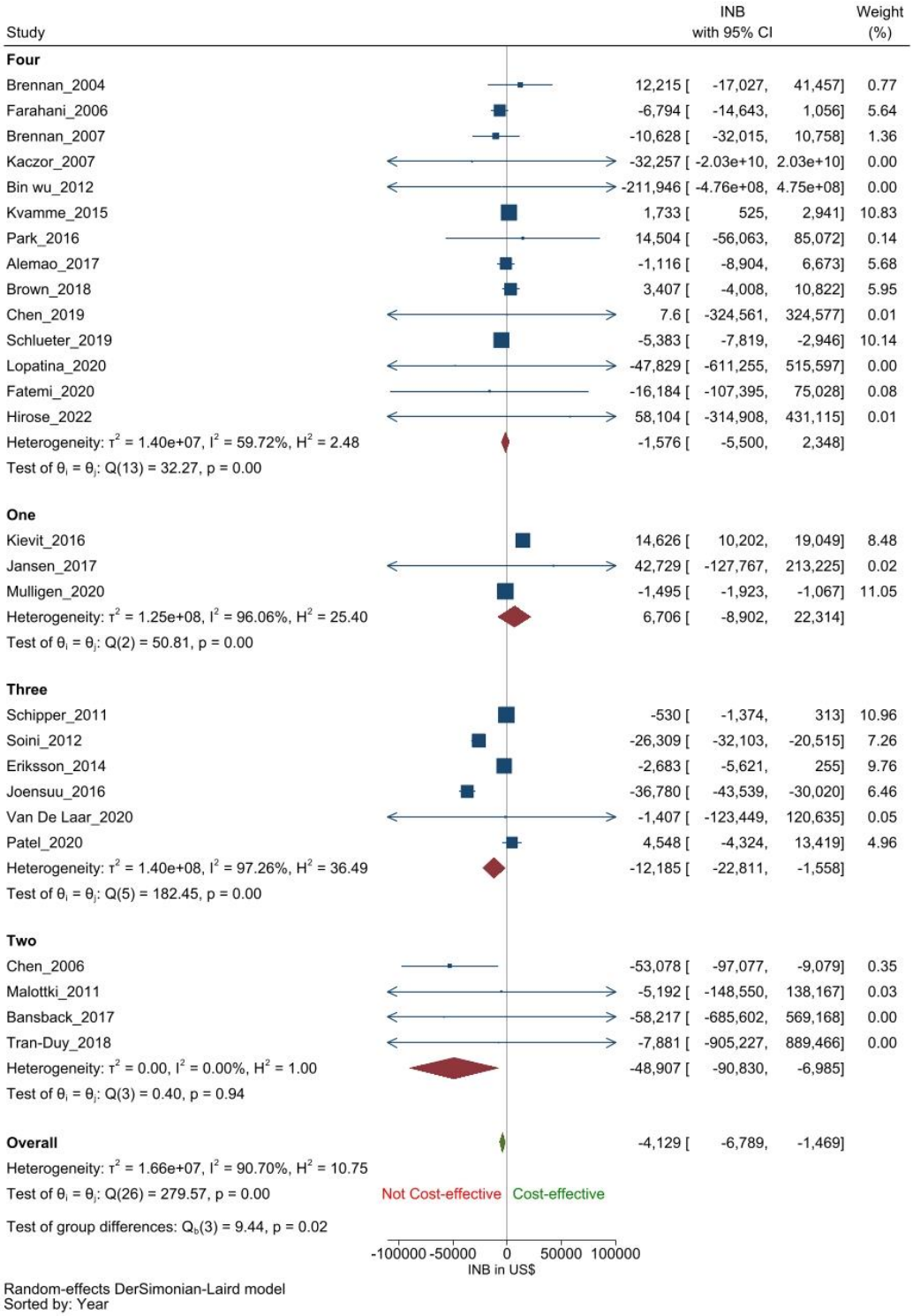
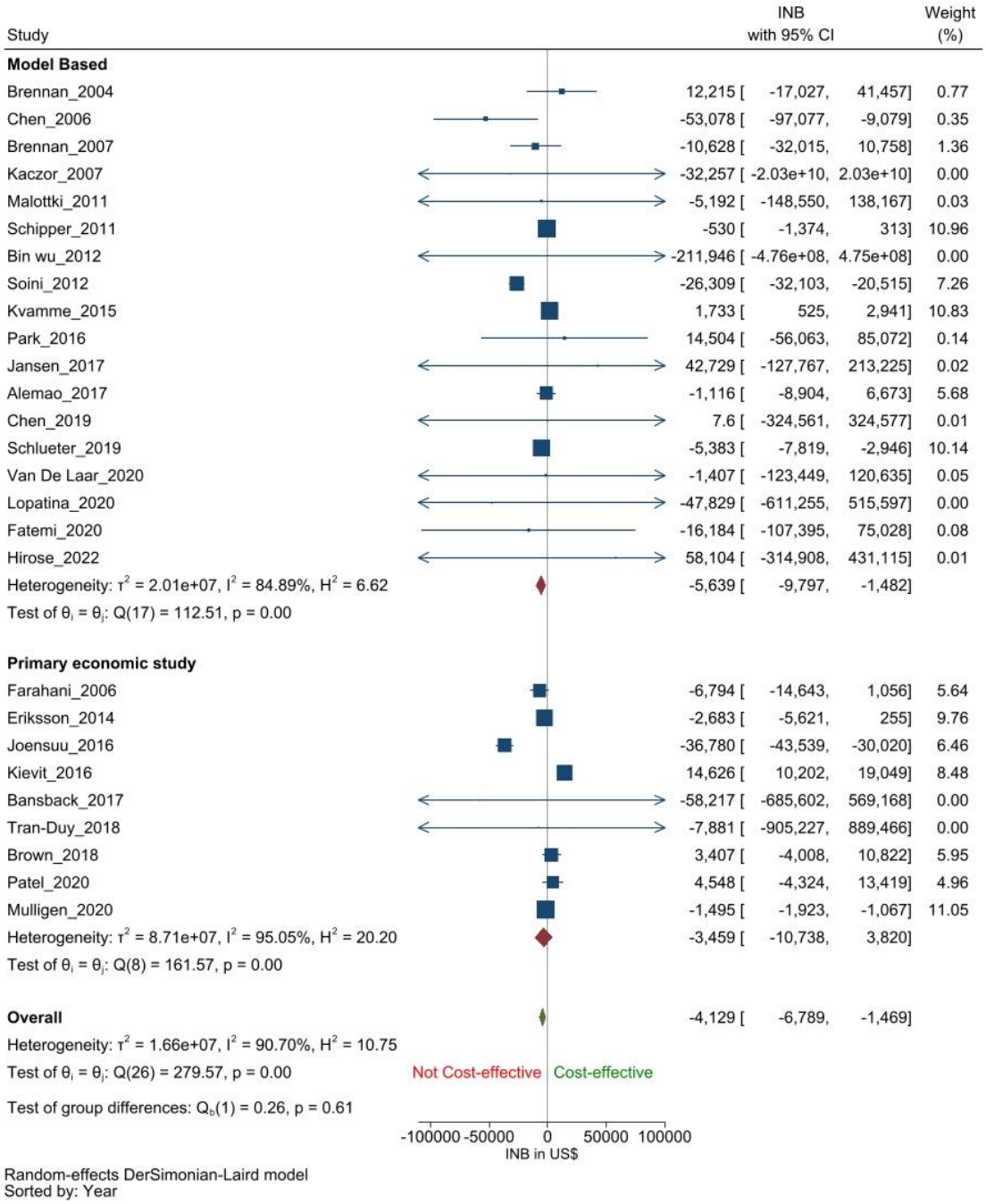
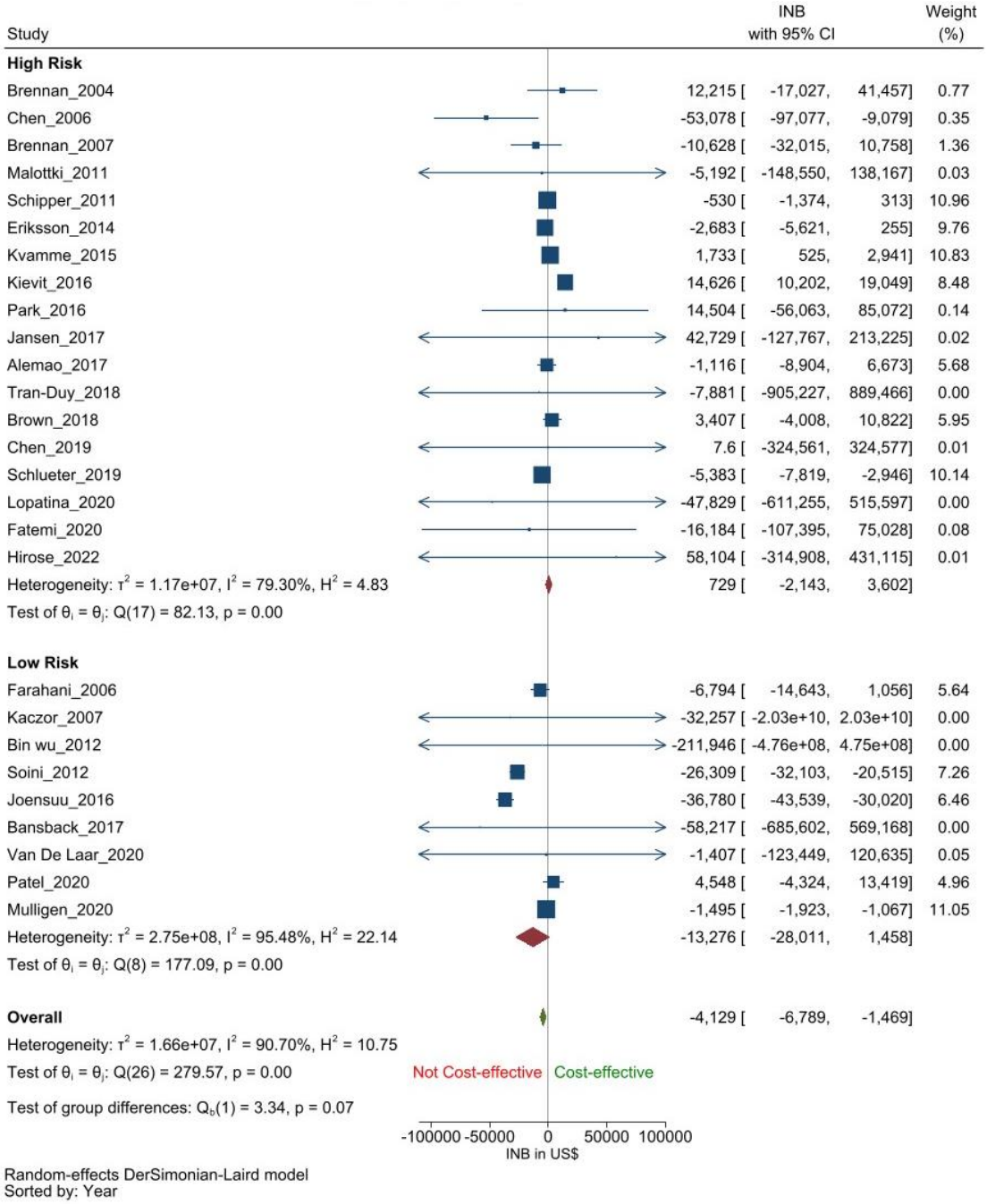


Figure 2.1.13 Subgroup analysis of pooled INBs based on analytic appraoch



Furthermore, a subgroup analysis based on the ECOBIAS checklist found that TNF-a-i is not cost effective in both low risks of bias studies [INBp=-13,276 (-28,011 to 1,458)] and studies with a high risk of bias [INBp=729 (-2,143 to 3,602) (Figure 2.1.14).

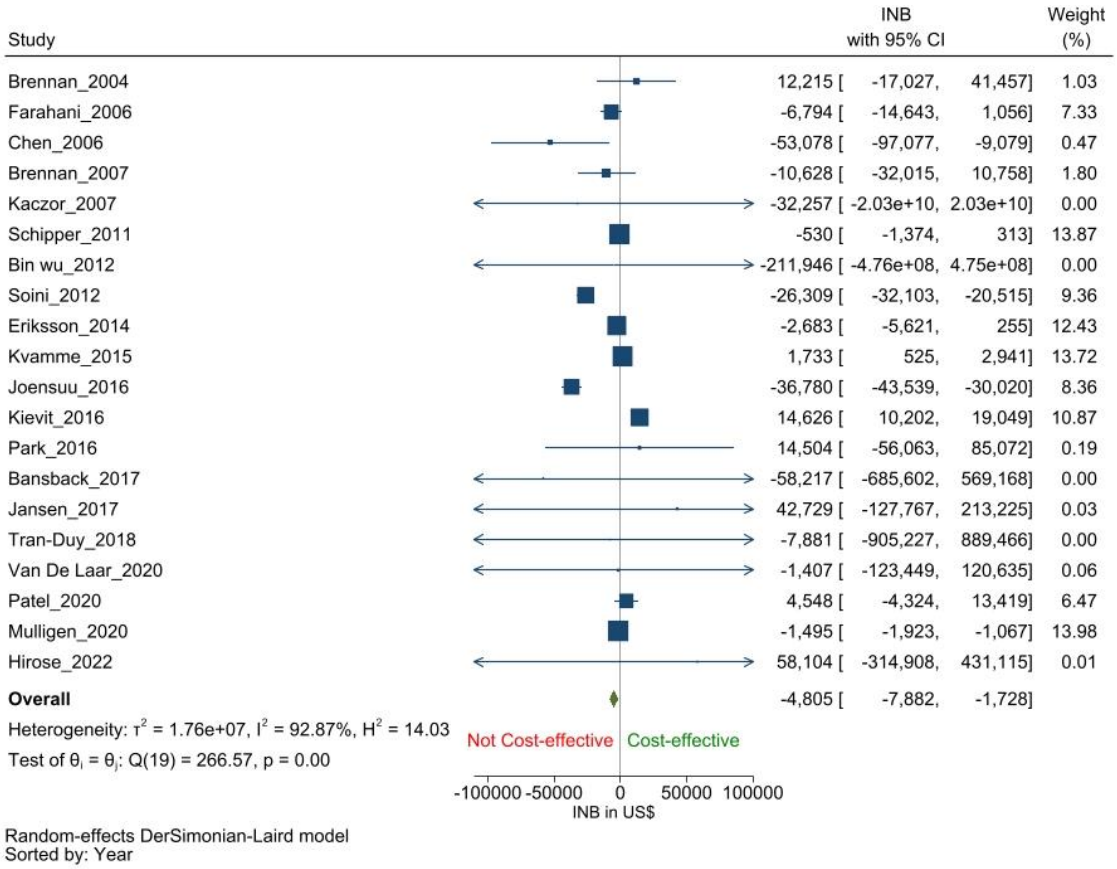
Figure 2.1.14 Subgroup analysis of pooled INBs based on ECOBIAS result



2.1.3.4 Separate analysis for the cost-effectiveness of TNF-a-i versus csDMARDs

Twenty studies assessed the cost-effectiveness of TNF-a-i compared to csDMARDs [33, 34, 46, 71, 75, 78, 84, 91-93, 96, 100, 111, 112, 115, 121, 122, 125, 129, 136]. The pooled INB from these studies was $ -4,805 (-7,882 to -1,728) with considerable heterogeneity (I^2=92.87%), showing that TNF-a-i is not cost-effective compared to csDMARDs for RA patients (Figure 2.1.15).

Figure 2.1.15 Separate analysis for TNF-a-i compared with csDMARDs

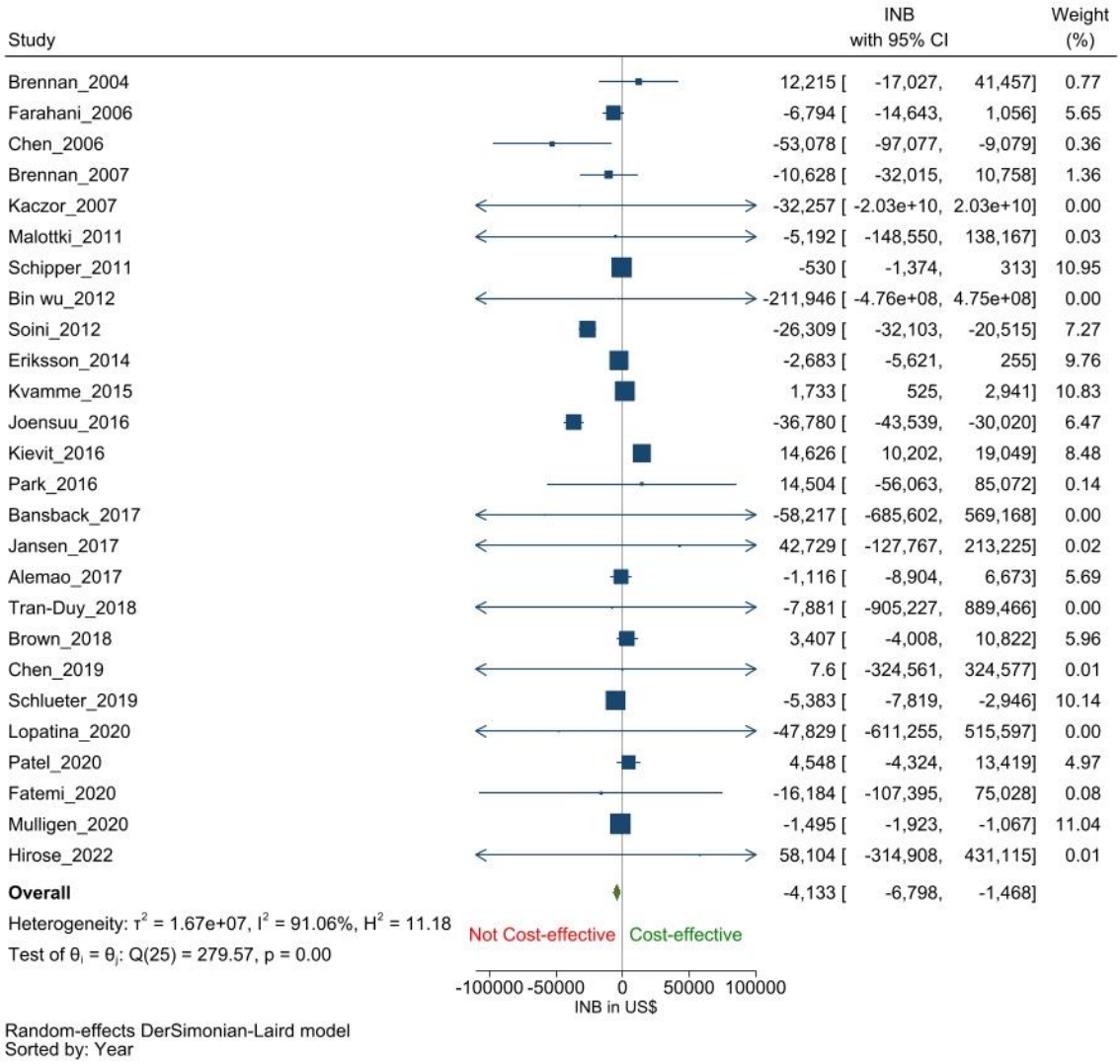


2.1.3.5 Separate analysis for the cost-effectiveness of TNF-a-i as a second-line treatment versus other DMARDs

All the studies except Van De Laar [121] compared the cost-effectiveness of TNF-a-i as a second-line treatment (n=26) [33, 34, 39, 46, 48, 71, 75-78, 84, 91-93, 96, 100, 103, 105, 111-113, 115, 122, 125, 129, 136] and the pooled analysis found that TNF-a-i as second-line treatment is not cost-

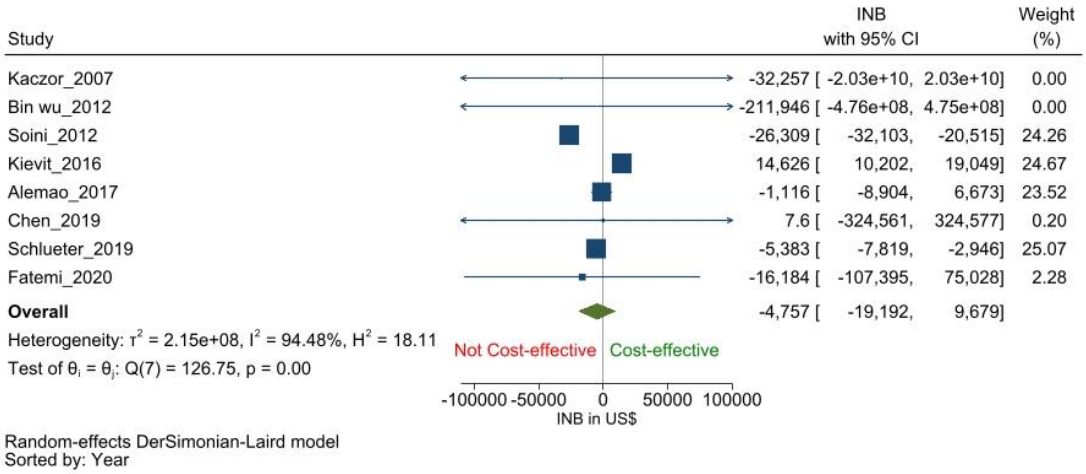
effective compared to other DMARDs [$ -4,133 (-6,798 to -1,468)] (Figure 2.1.16).

Figure 2.1.16 Separate analysis for TNF-a-i as a second line treatment compared with other DMARDs



Separate analysis for adalimumab as a second-line treatment (n=7) [33, 39, 48, 77, 93, 96, 113, 115] also found that intervention is not cost-effective compared to other DMARDs with high heterogeneity (I^2=94.48%) (Figure 2.1.17).

Figure 2.1.17 Separate analysis for Adalimumab as a second line treatment compared with other DMARDs



Similarly, Etanercept as second-line treatment (n=6) is also not cost-effective compared to other DMARDs with an INBp of $ -861 (-6,146 to 4,424) (Figure 2.1.18). [46, 71, 76, 84, 111, 136] Likewise, Infliximab is also not cost-effective as a second line (n=5) compared to other DMARDs with a pooled INB of $-9,075 (-22,851 to 4,700) but with low heterogeneity (I^2=27.72%). [34, 75, 78, 103, 105] (Figure 2.1.19).

Figure 2.1.18 Separate analysis for Etanercept as a second line treatment compared with other DMARDs

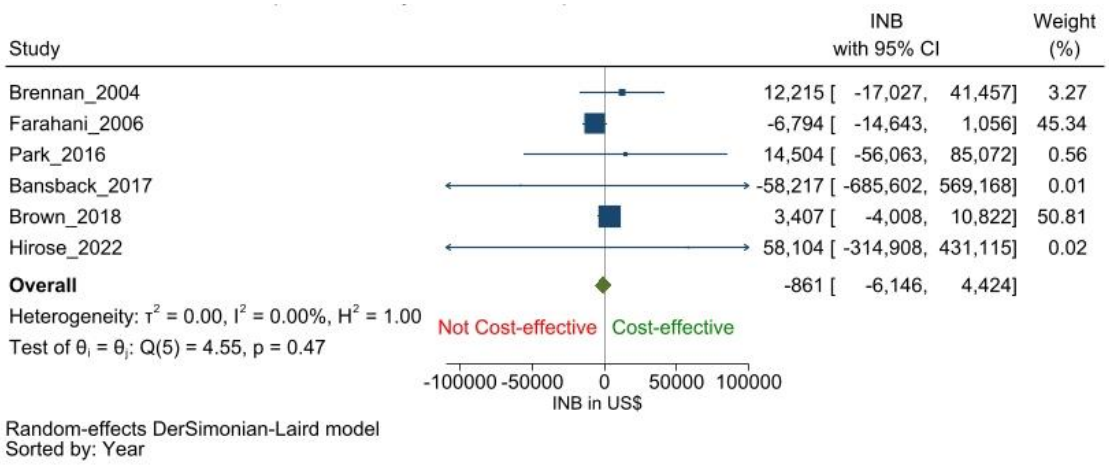
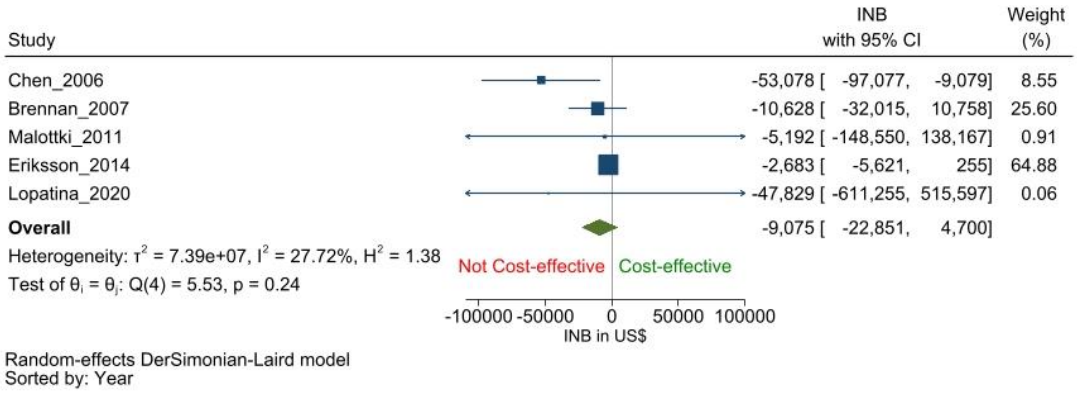


Figure 2.1.19 Separate analysis for Infliximab as a second line treatment compared with other DMARDs



2.1.3.6 Certainty of evidence

The GRADE quality assessment indicated a very low confidence in the overall pooled evidence regarding the cost-effectiveness of TNF-a-i compared to other DMARDs for RA patients. Similarly for the results of HICs and societal perspectives the confidence was very low confidence. Also, the confidence of results for TNF-a-i as a second-line treatment and TNF-a-i compared with csDMARDs is also very low. The findings of the GRADE assessment are detailed in Table 2.1.3.

Table 2.1.3 Findings of GRADE Assessment

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

P: Adult subjects with rheumatoid arthritis

I: TNF-a-inhibitors (Adalimumab, Infliximab, Etanercept, Golimumab, Certolizumab)

C: Any other DMARDs

O: incremental cost-effectiveness ratio (ICER), incremental net benefit (INB)

Quality assessment						Summary of findings			Comments
No of studies	**Risk of Bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Publication Bias**	**INB ($)**	**95%CI**	**Certainty/Quality**	
Cost-effectiveness of TNF-a-i when compared to other DMARDs (Assessed with meta-analysis)									
27	not serious	serious[a,c]	serious[d]	serious[b]	unlikely but high between-study heterogeneity.	-4,129	-6,789 to -1,469	Å• • • Very Low	Unexplained high heterogeneity. Less studies from lower middle and upper middle-income countries. No studies from low-income countries. High inconsistency, imprecision, and indirectness in intervention.
Cost-effectiveness of TNF-a-i when compared to csDMARDs (Assessed with meta-analysis)									
20	not serious	serious[a,c]	serious[d]	serious[b]	unlikely but high between-study heterogeneity.	-4,805	-7,882 to -1,728	Å• • • Very Low	Unexplained high heterogeneity. Wider confidence interval, inconsistency, and indirectness.
Cost-effectiveness of TNF-a-i when compared to other DMARDs from societal perspective (Assessed with meta-analysis)									
12	not serious	serious[a,]	serious[d]	serious[b]	unlikely	-1,514	-4,694 to 1,665	Å• • • Very Low	Unexplained high heterogeneity. Wider confidence interval, inconsistency, and indirectness.
Cost-effectiveness of TNF-a-i when compared to other DMARDs for higher income countries (Assessed with meta-analysis)									
25	not serious	serious[a,]	serious[d]	serious[b]	unlikely but high between-study heterogeneity.	-4,124	-6,793 to -1,455	Å• • • Very Low	Unexplained high heterogeneity. Wider confidence interval, inconsistency, and indirectness.
Cost-effectiveness of TNF-a-i as second line treatment compared to other DMARDs (Assessed with meta-analysis)									
26	not serious	serious[a,c]	serious[d]	serious[b]	unlikely but high between-study heterogeneity.	-4,133	-6,798 to -1,468	Å• • • Very Low	Unexplained high heterogeneity. Less studies from lower middle and upper middle-income countries. No studies from low-income countries. High inconsistency, imprecision, and indirectness in intervention.

[a] inconsistency $I^2 \approx 100\%$ [b] studies included have reported a wide confidence intervals [c] high heterogeneity [d] Lack of generalisability

GRADE Working Group grades of evidence

High certainty: we are very confident that the true effect lies close to that of the estimate of the effect.

Moderate certainty: we are moderately confident in the effect estimate; the true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different.

Low certainty: our confidence in the effect estimate is limited; the true effect may be substantially different from the estimate of the effect.

Very low certainty: we have very little confidence in the effect estimate; the true effect is likely to be substantially different from the estimate of effect

2.1.4 Discussion

We synthesised the cost-effectiveness of TNF-a-i compared to other DMARDs using a systematic review and meta-analysis of cost-utility studies. The pooled INBs from the meta-analysis show that TNF-a-i is significantly not cost-effective than other DMARDs, such as csDMARDs/other bDMARDs. Despite the high heterogeneity, only two studies [92, 115] greatly influence the pooled INBs, and excluding them does not affect the overall directionality result. The subgroup analysis used to identify the source of heterogeneity in the overall results supported the findings that TNF-a-i is not cost-effective from a societal, payer, or healthcare perspective. Similarly, TNAF-a-i intervention is not cost-effective for HICs, LMICs, or UMICs; however, the number of studies from UMICs and LMICs is limited. It is worth noting that TNF-a-i is not cost-effective when compared to other DMARDs in both subgroups, irrespective of lower and higher median willingness to pay thresholds. The increased pharmacological costs, high indirect costs, adverse events and the WTP threshold all contribute to the intervention's inefficiency in the aggregated outcome. [33, 34, 38, 42-46, 74, 97, 121, 129]

Further, the subgroup analysis also revealed that TNF-a-i is not cost-effective than csDMARDs as a second-line treatment, which is consistent with other studies. [34, 42, 129]

The separate analysis also found that TNF-a-i as a second-line treatment for RA patients is not cost-effective when compared to other DMARDs. Similarly, the presence of adalimumab, Etanercept, and Infliximab as second-line therapies that were not cost-effective supported the robustness of our findings. [47, 78, 113, 115]

Previous studies [43, 105, 108] have found that TNF-a-i is not cost-effective when compared to other DMARDs [verses B-Cell [44, 74, 105], JAK-i [113, 121, 137], and csDMARDs [34, 42, 47, 118, 129]. However, the study population may differ between early, moderate, and severe RA patients. Chen et al. suggest that TNF-a-i as the last active therapy for early RA

patients after csDMARDs failure [78], and discontinuing TNF-a-i for patients with low disease activity will be cost-saving. [125]

Considering various differences in economic parameters, income level of countries, perspectives, timings etc., it is challenging to pool the results of cost-effectiveness studies quantitatively. Further, the market prices of drugs and willingness to pay thresholds could play a significant role in deciding the cost-effectiveness of RA treatment. Since most of the cost-effectiveness studies are context-specific, the observed differences in outcomes and the considerable heterogeneity between the studies may be due to changes in the prices of medicines or methods of cost estimations with variable perspectives considered across the studies. Similarly, considering the lower cost of biosimilars compared to the originator drug, the use of more biosimilars may exhibit better cost-effectiveness outcomes for RA patients and future research in this area to be considered. Furthermore, a sizable majority of the studies fell into scenario five. This is because these studies either neglected or failed to disclose measures of dispersion or precision estimates for the ICER point estimates. As a result, we decided to leave these studies from the meta-analysis but include them in the systematic review (SR) section of our study. By focusing primarily on studies that offered enough data for precise estimations of the INB, we hoped to maintain the robustness of our meta-analysis. However, we attempted to address these issues by standardizing the data extraction and preprocessing from published cost-utility analyses to provide the pooled INB estimate and its precision measure.

The study has a few limitations. The comprehensiveness of these cost-effectiveness results is debatable because most of the data is from HICs, and the majority of studies did not include indirect costs, thereby missing a significant source of costs in the form of caregiver time and costs, as well as out-of-pocket expenditure. The drug price and

WTP threshold significantly impact the cost-effectiveness of RA treatment. The observed discrepancies in reported outcomes, as well as the substantial heterogeneity assessed across studies, could be attributed to changes in drug prices or cost estimations under different study perspectives. Moreover, some models used sequential therapy data to estimate cost-effectiveness, while others used either combination or monotherapy. Despite the abundance of literature, there is a scarcity of high-quality evidence directly comparing the cost-effectiveness of the five TNF-a-i against each other, as well as other biologics and DMARDs. Similarly, considering intervention as a sequential treatment for RA patients makes it difficult to separate the cost and effectiveness of TNF-a-i alone. Though subgroups are made to address heterogeneity, we agree that as a meta-analysis of published research, it is quite difficult to manage all of the assumptions. As a result, extrapolating the findings to other healthcare and treatment contexts should be done with caution.

2.1.5 Conclusion

TNF-a-i is not a cost-effective option for treating RA compared to other DMARDs. However, the high heterogeneity and low confidence in the results based on the GRADE quality assessment preclude the results from being generalizable. Extensive primary studies assessing the cost-effectiveness of TNF-a-i, particularly in LIC and LMIC settings, are required to bridge the quality gap in the available literature.

2.2 Systematic review and meta-analysis of cost-utility studies on Rituximab therapy for Rheumatoid Arthritis

2.2.1 Introduction

The efficacy and good safety profile of Rituximab is accompanied by the concern of an increase in healthcare costs[152]. Further, the cost-effectiveness evidence of Rituximab is also varying, as some studies report it as not cost-effective for RA compared to other DMARDs[33, 153-155]. Hence, a systematic review of the Rituximab cost-utility studies for the treatment of RA was conducted to provide a synthesized quantitative metric, incremental net benefit (INB).

2.2.2 Methods

The SRMA conducted on Rituximab compared to other pharmacotherapies for RA is a component of a broader SRMA. The methods employed for this specific section are consistent with those outlined in Section 2.2.1 and Figure 2.1.1 (PROSPERO Id: CRD 42021222541).

2.2.3 Results

2.2.3.1 Characteristics of included studies

We identified and included twenty-three [33, 47, 73, 74, 76, 79, 81, 86, 95, 103, 106, 109, 153-163] relevant articles for systematic review, and eighteen studies with Rituximab as an intervention were included for the meta-analysis [33, 73, 74, 76, 86, 95, 103, 106, 153, 155-163] (Figure 2.1.1). The features of included studies in SRMA are summarised in Table 2.2.1.

Included studies compare Rituximab with other bDMARDs (n=11)[73, 74, 76, 81, 86, 103, 154, 157, 159, 160, 163], with csDMARDs (n=7) [33, 153, 155, 156, 158, 161, 162] and with combination of bDMARDs and csDMARDs (n=4)[79, 95, 106, 109]. Most of the studies were set in HICs

(n=17), four based on UMICs[33, 74, 154, 161] and one from LMIC[153]. Seventeen studies reported from a health system perspective[73, 74, 76, 79, 81, 95, 103, 106, 109, 153-156, 159-162] and the remaining five from a societal perspective[33, 86, 157, 158, 163]. All studies except four primary economic study[73, 74, 76, 160] used models based analytic approach (n=19)[33, 79, 81, 86, 95, 103, 106, 109, 153-159, 161-163]. Life time horizon was most commonly used time horizon (n=12) [33, 79, 81, 86, 95, 106, 109, 154, 155, 157, 158, 161] followed by zero to five year (n=4)[73, 76, 156, 160] and five to ten year (n=2)[103, 159] time horizon. The country-specific willingness to pay threshold (WTP) was used in all the studies [73, 76, 79, 81, 86, 95, 103, 106, 109, 155, 156, 158-160, 162, 163] except for six studies that used GDP–based WTP[33, 74, 153, 154, 157, 161]. Twelve studies[33, 79, 81, 86, 109, 154, 155, 157-159, 161, 163] discounted cost at 3 per cent per annum rate followed by four studies[95, 106, 156, 162] at 3.5 per cent. Lopatina et al. [103] used a 1.5 per cent per annum growth rate, and the remaining five studies[73, 74, 76, 153, 160] did not perform cost discounting. Nearly 60 per cent (n=13)[73, 74, 79, 86, 95, 109, 153, 154, 156, 159-161, 163] studies were scenario five followed by five studies in the scenario four[33, 76, 81, 103, 157] category, two studies under scenario two [155, 162] and one each under scenario one[158] and three[106]. In the meta-analysis, for calculating INB variance for studies in scenario five, we have used the INB variance from the most comparable studies. The INB variances of Wu, B et al. were used for two studies[153, 161], Brown, S et al. were used for four studies[73, 74, 156, 163], and Merkesdel et al. was used for three studies[95, 109, 159].

2.2.3.2 Quality Appraisal

Risk of Bias Assessment: We have used ECOBIAS checklist to analyse the risk of bias among the identified studies[68]. The ECOBIAS checklist shows that 82 per cent of the studies either chose a societal perspective or justified the reason for a different perspective, hence having a narrow perspective bias. More than 52 per cent of the studies failed to report all the cost data in a detailed manner triggering high valuation

bias. However, the treatment comparator bias was low as there is an adequate comparator in 89 per cent of studies. Limited scope bias is observed in most of the studies (82 per cent); also, internal consistency was not evaluated properly (Figure 2.2.1).

Figure 2.2.1 Assessment of Risk of Bias using ECOBIAS Checklist

Issue addressed / Author_Year	Ahmadiani 2016	Boyadzieva 2018	Manders_2015	Diamantopoulos 2012	Navarro_2020	Malothi_2011	Bin wu_2012	Youn yuan 2010	Merkesdal 2010	Lopatina_2020	Kielhorn_2008	Hoiponen 2019	Matusevich 2021	Jansen_2017	Sarah Brown 2018	Lindgren_2009	Claxton_2018	Bagust_2009	Benucci_2011	Hallinen_2010	Tan_2021(1)	Tan_2021(2)	SinLI_2021 (2)
Narrow perspective bias	P	Y	Y	P	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	P	P	Y	Y	Y	Y
Inefficient comparator bias	P	Y	Y	Y	Y	Y	Y	Y	Y	Y	P	Y	Y	Y	Y	Y	Y	P	P	Y	Y	Y	Y
Cost measurement omission bias	N	Y	P	Y	P	Y	P	Y	Y	Y	P	Y	Y	Y	Y	P	Y	P	P	P	Y	Y	Y
Intermittent data collection bias	N	Y	P	Y	P	Y	P	Y	Y	P	P	Y	Y	Y	Y	Y	Y	P	P	P	Y	Y	Y
Invalid valuation bias	P	P	P	Y	P	Y	P	Y	P	Y	P	Y	Y	Y	Y	P	P	P	P	P	Y	Y	Y
Ordinal ICER bias	Y	P	U	Y	P	Y	P	P	P	P	U	Y	P	Y	Y	P	P	P	U	U	Y	U	Y
Double-counting bias	U	P	U	P	U	Y	U	Y	U	U	U	Y	U	Y	P	P	P	P	U	U	Y	Y	U
Inappropriate discounting bias	N	Y	N	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	N	Y	Y	Y	N	Y	Y	Y	Y
Limited sensitivity analysis bias	N	P	P	P	P	Y	P	P	Y	P	P	Y	P	Y	P	P	P	P	P	P	Y	P	P
Sponsor bias	U	Y	Y	Y	Y	Y	Y	P	N	Y	Y	Y	Y	Y	Y	Y	Y	Y	N	Y	Y	Y	Y
Reporting and dissemination bias	U	Y	Y	U	U	Y	U	Y	U	Y	U	Y	U	Y	Y	U	Y	Y	U	U	Y	Y	Y
Structural assumptions bias	N	P	P	Y	Y	Y	P	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	U	P	P	P	P	Y
No treatment comparator bias	P	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	P	P	Y	Y	Y	Y
Wrong model bias	N	P	Y	Y	Y	Y	P	Y	Y	Y	Y	Y	Y	Y	Y	P	Y	U	P	Y	Y	Y	Y
Limited time horizon bias	N	Y	N	Y	Y	U	Y	P	P	Y	Y	Y	Y	Y	P	N	Y	N	Y	Y	Y	Y	Y
Bias related to data identification	N	Y	P	Y	P	Y	P	P	P	P	P	Y	Y	Y	Y	P	P	P	P	P	Y	Y	Y
Bias related to baseline data	Y	P	P	Y	P	Y	P	Y	U	P	P	P	Y	P	Y	P	P	P	P	P	P	P	Y
Bias related to treatment effects	Y	P	U	P	P	Y	U	P	U	Y	P	P	P	Y	P	P	P	P	U	U	P	Y	Y
Bias related to quality-of-life weights	P	Y	P	Y	P	Y	P	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	P	P	P	Y	Y	Y
Non-transparent data incorporation bias	P	Y	P	Y	P	Y	P	Y	P	Y	P	Y	Y	Y	Y	P	Y	P	P	Y	P	Y	Y
Limited scope bias	N	P	U	Y	P	P	P	P	U	P	U	U	P	Y	P	P	Y	U	U	P	U	Y	P
Bias related to internal consistency	U	U	U	U	U	U	U	U	U	U	U	U	U	U	U	U	U	U	U	U	U	U	U

Y- Yes, N-No, P-Partly, U-Unclear, NA- Not Applicable. Source:http://dx.doi.org/10.1586/14737167.2015.1103185

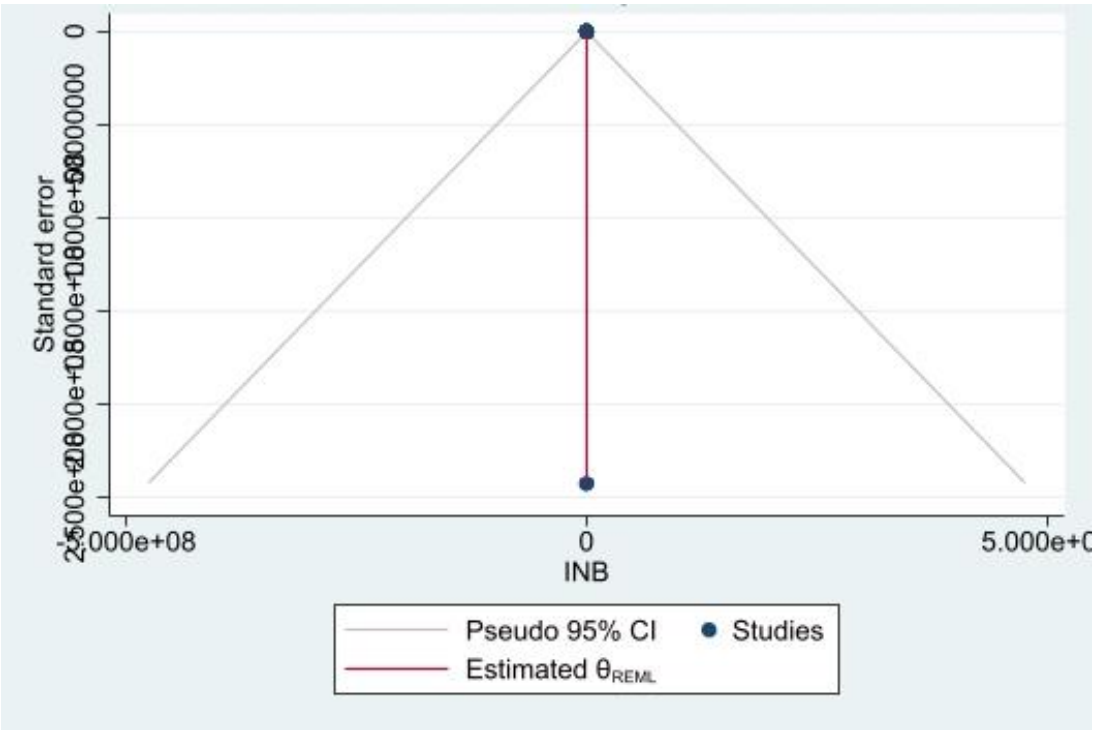
Table 2.2.1– General characteristics of the included studies in systematic review and meta-analysis

Author_ year	Country	Income class	Perspective	Target population-RA	Time Horizon (Years)	Discount Rate (%)	Reference year	Intervention	Comparator	Remarks
Ahmadiani_2016 [153]	Iran	LMIC	Health System	Refractory	NR	NR	2012	Ritu	csdmards	Not Cost-effective
Bagust_2009 [156]	UK	HIC	Health System	Severe	0 – 5	3.5	2007	Ritu	MTX	Cost-effective
Benucci_2011 [73]	Italy	HIC	Health System	Moderate to severe	0 – 5	NR	2007	Ritu+ MTX	TNFi	Cost-effective
Bin wu_2012 [33]	China	UMIC	Societal	Moderate to severe	Lifetime	3.0	2011	Eta + Ritu	csdmards	Not Cost-effective
Boyadzieva_2018 [74]	Bulgaria	UMIC	Health System	Biologic Naive	NR	NR	2016	Ritu	Toci	Cost-effective
Brown_2018 [76]	UK	HIC	Health System	MTX resistant	0 – 5	NR	2015	Ritu	Eta– Ada– Infl – Cert – Goli	TNFi cost-effective
Claxton_2018* [79]	USA	HIC	Health System	Moderate to severe	Lifetime	3.0	2015	MTX–Tofa– Ada– Aba– Toci–Ritu	MTX –Eta– Ada – Aba – Toci – Ritu	Dominant
Diamantopoulos_2012* 81	Italy	HIC	Health System	Moderate to severe	Lifetime	3.0	2009	Eta–Ada– Ritu– Aba	Toci–Ada–Ritu– Aba	Dominates
Hallinen_2010 [86]	Finland	HIC	Societal	TNF failed	Lifetime	3.0	2008	Ritu+ MTX	Ada– Aba –Eta	Cost-effective
Houponen_2019 [157]	Finland	HIC	Societal	Moderate to severe	Lifetime	3.0	2017	Ritu	Aba	Dominated
Jansen_2017 [158]	USA	HIC	Societal	Moderate to severe	Lifetime	3.0	2016	Eta – Ada– Aba –Tozi – Tofa – Ritu –csdmards	csdmards	Cost-effective
Kielhorn_2008 [95]	UK	HIC	Health System	Biologic Naive	Lifetime	3.5	2007	Ritu+MTX – Ada+MTX– Infl+ MTX – Lefl	Ada+ MTX– Infl+ MTX – Lefl	Cost-effective
Lindgren_2009 [163]	Sweden	HIC	Societal	Biologic Naive	NR	3.0	2008	Ritu+ TNFi	TNFi	Dominant
Lopatina_2020 [103]	Canada	HIC	Health System	TNF failed	5 –10	1.5	2020	Ritu	Adali	Dominant
Malottki_2011 [162]	UK	HIC	Health System	Biologic Naive	NR	3.5	2007	Ritu	csdmards	Cost-effective
Manders_2015 [160]	Netherland	HIC	Health System	Moderate	0– 5	NR	2013	Ritu	Aba	Cost-effective
Matusevich_2021 [159]	USA	HIC	Health System	Biologic Naive	5 – 10	3.0	2016	Abat– Toci – Ritu	Ada – Aba – Toci	Cost-effective
Merkesdal_2010 [106]	Germany	HIC	Health System	MTX resistant	Lifetime	3.5	2008	Ritu+MTX – Ada+ MTX – Infl+ MTX	Ada+ MTX – Infl + MTX	Cost-effective
Navarro_2020*[109]	Spain	HIC	Health System	Moderate to severe	Lifetime	3.0	2018	Tof+ MTX– Ritu+ MTX– Toci+MTX– Eta+ MTX – Cert+ MTX	Ada+ MTX– Ritu+ MTX– Toci+ MTX– Eta + MTX– Cert+ MTX	Dominant
SiNi Li_2021* [47]	China	UMIC	Health System	Moderate to severe	Lifetime	3.0	2019	Eta– Ritu– Tofa	TT– Aba– Tofa	Cost-effective
Tan_2021(1) *[154]	China	UMIC	Health System	Moderate to severe	Lifetime	3.0	2019	Tofa– Eta– Ritu– Toci	Eta– Ritu– Toci	Dominant
Tan_2021(2)[161]	China	UMIC	Health System	Moderate to severe	Lifetime	3.0	2019	Eta– Tofa– Ritu– Toci	MTX	Not cost-effective
Youn yuan_2010 [155]	USA	HIC	Health System	Moderate to severe	Lifetime	3.0	2007	Ritu+ MTX	MTX	Not cost-effective

*Systematic review, HIC– High income country, UMIC– Upper middle income country, LMIC– Lower middle income country, NR- not reported, RA– Rheumatoid Arthritis, MTX– Methotrexate, Aba– Abatacept, Ritu– Rituximab, Ada– Adalimumab, Toci– Tocilizumab, Goli– Golimumab, Eta– Etanercept, TT– Tripple therapy, Tofa– Tofacitinib, Lefl– Leflunomide, csdmards– conventional synthetic disease modifying anti rhematic drugs, Seq– Sequential, TNFi– Tuber necrosis factor inhibitors.

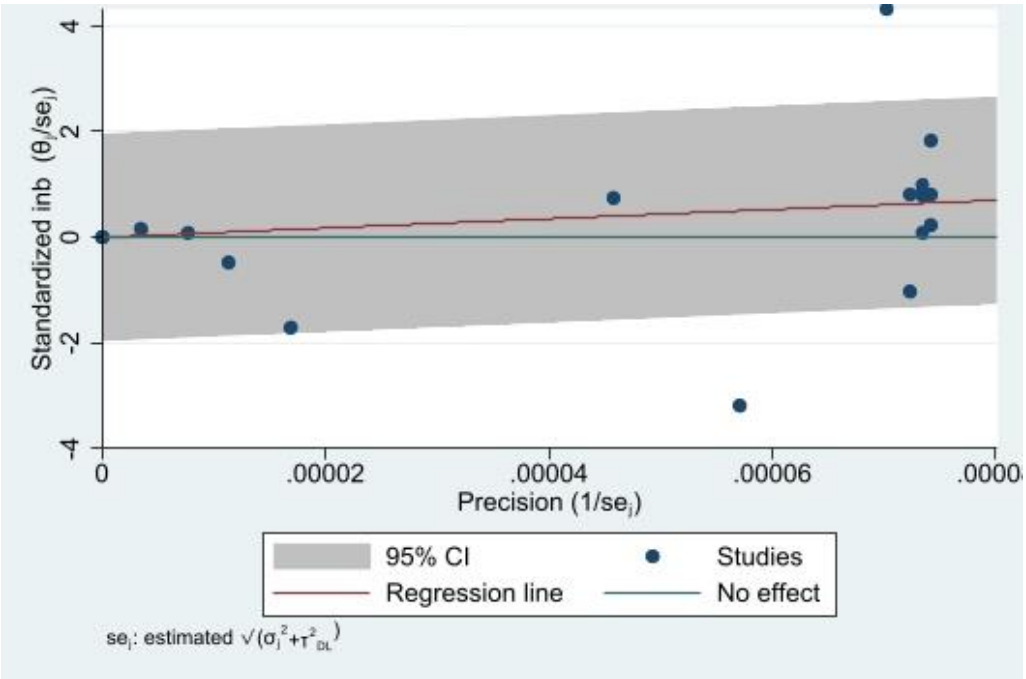
Publication Bias For the comparison between Rituximab with other DMARDs, the visual assessment of the funnel plot was inadequate to determine whether funnel plot asymmetry or publication bias was present but showed studies with larger standard errors reporting larger effect sizes than the precise studies (Figure 2.2.2). Hence, a formal statistical test of asymmetry, the Egger's test, was performed, which reported a higher p-value (p = 0.678), indicating no publication bias.

Figure 2.2.2 Funnel plot



We attempted to explore the heterogeneity among the effect sizes and detect potential outliers using a Galbraith plot. It revealed that, apart from two studies, all are within the 95% confidence interval, indicating that the studies are consistent and that variations in findings are compatible with homogeneity (Figure 2.2.3). To further quantify the impact of the potential outliers on the estimation of the overall INB, we used leave–one–out–meta-analysis.

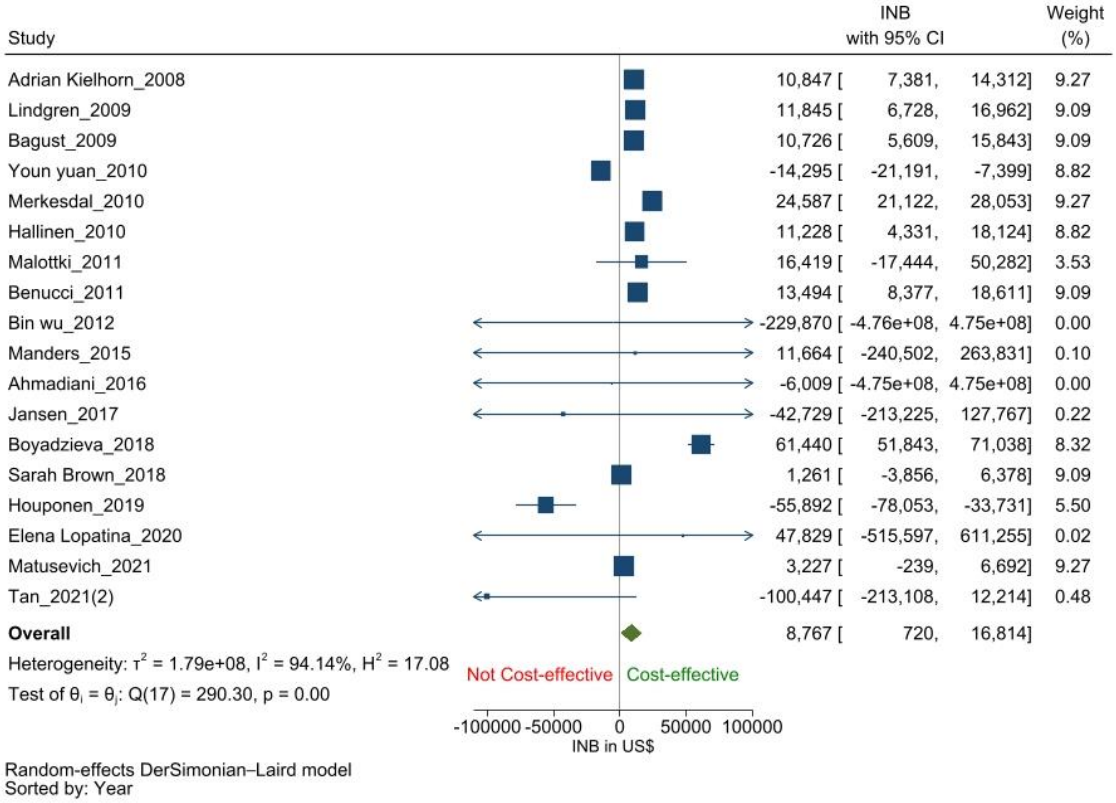
Figure 2.2.3 Galbraith plot



2.2.3.3 Rituximab, compared with other DMARDs

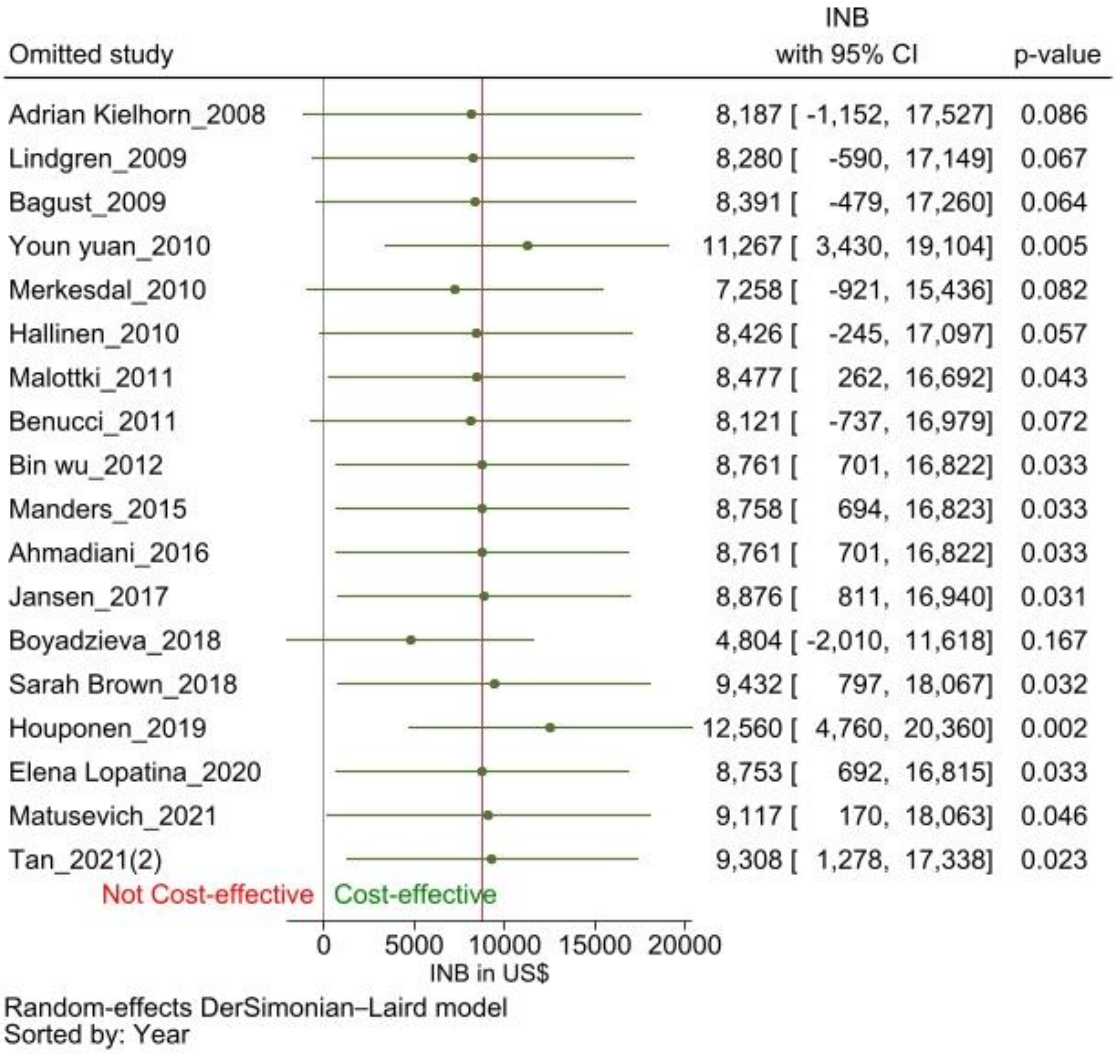
The pooled INB (INBp) of Rituximab as compared to other DMARDs was $ 8,767 (720 to 16,814) with a considerable heterogeneity (I^2 = 94.14%) (Figure 2.2.4). These results indicate that Rituximab is significantly cost-effective compared with other DMARDs.

Figure 2.2.4 Rituximab as compared to other DMARDs



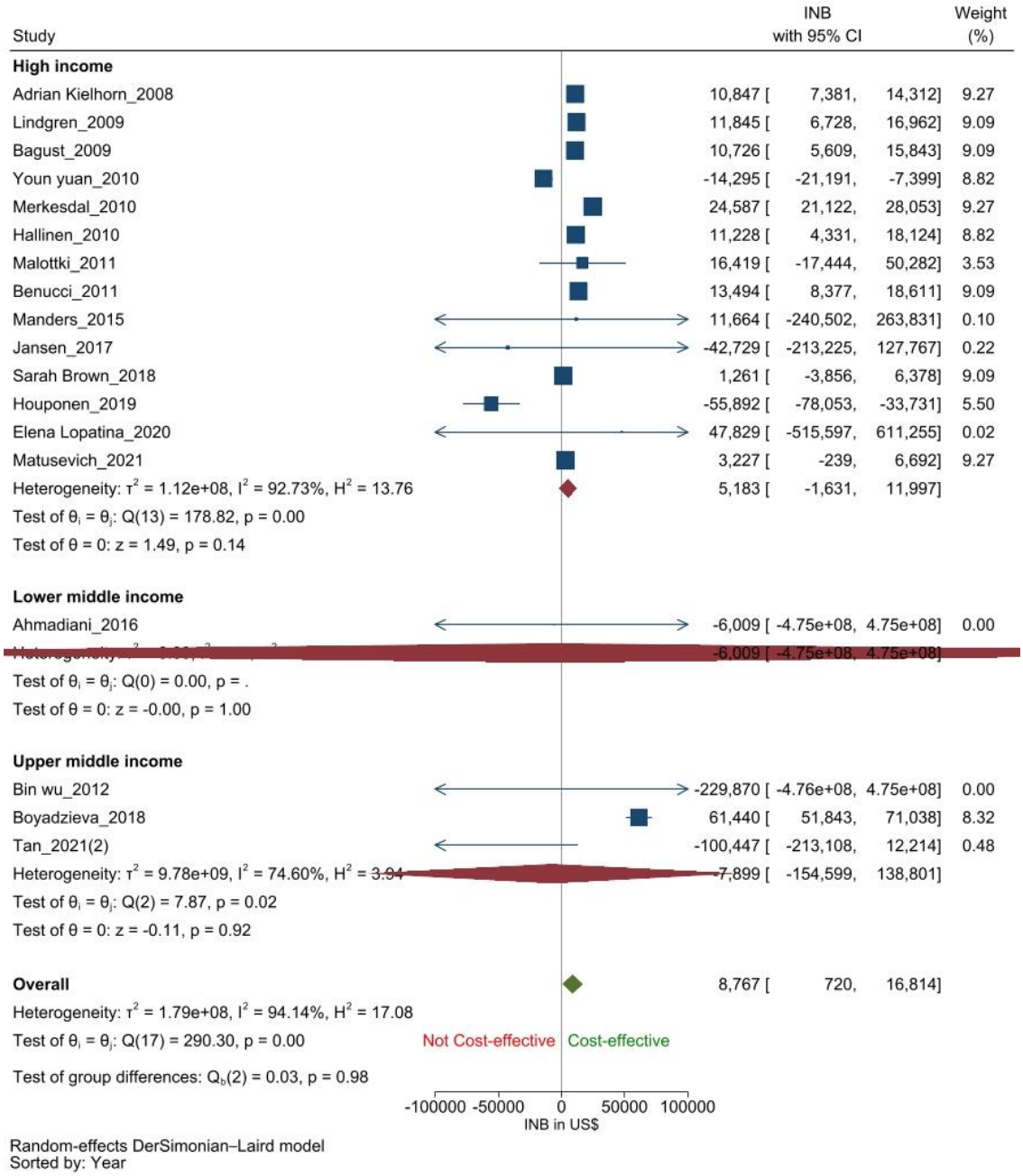
The leave-one-out forest plot revealed that the omission (each at a time) of four individual studies[74, 106, 155, 157] affected the overall pooled estimate, i.e., INBp (Figure 2.2.5). Houponen et al.[157] and Boyadzieva et al.[74] seem to have a larger influence when compared to other studies on the estimation of the INBp. The omission of Boyadzieva et al. causes the INBp to decrease by roughly $ 3,963, whereas omitting Houponen et al. causes the INBp to increase by roughly $ 3,793, making Rituximab significantly cost-effective compared with other DMARDs.

Figure 2.2.5 Leave one out analysis for pooled INBs for Rituximab compared to other DMARDs



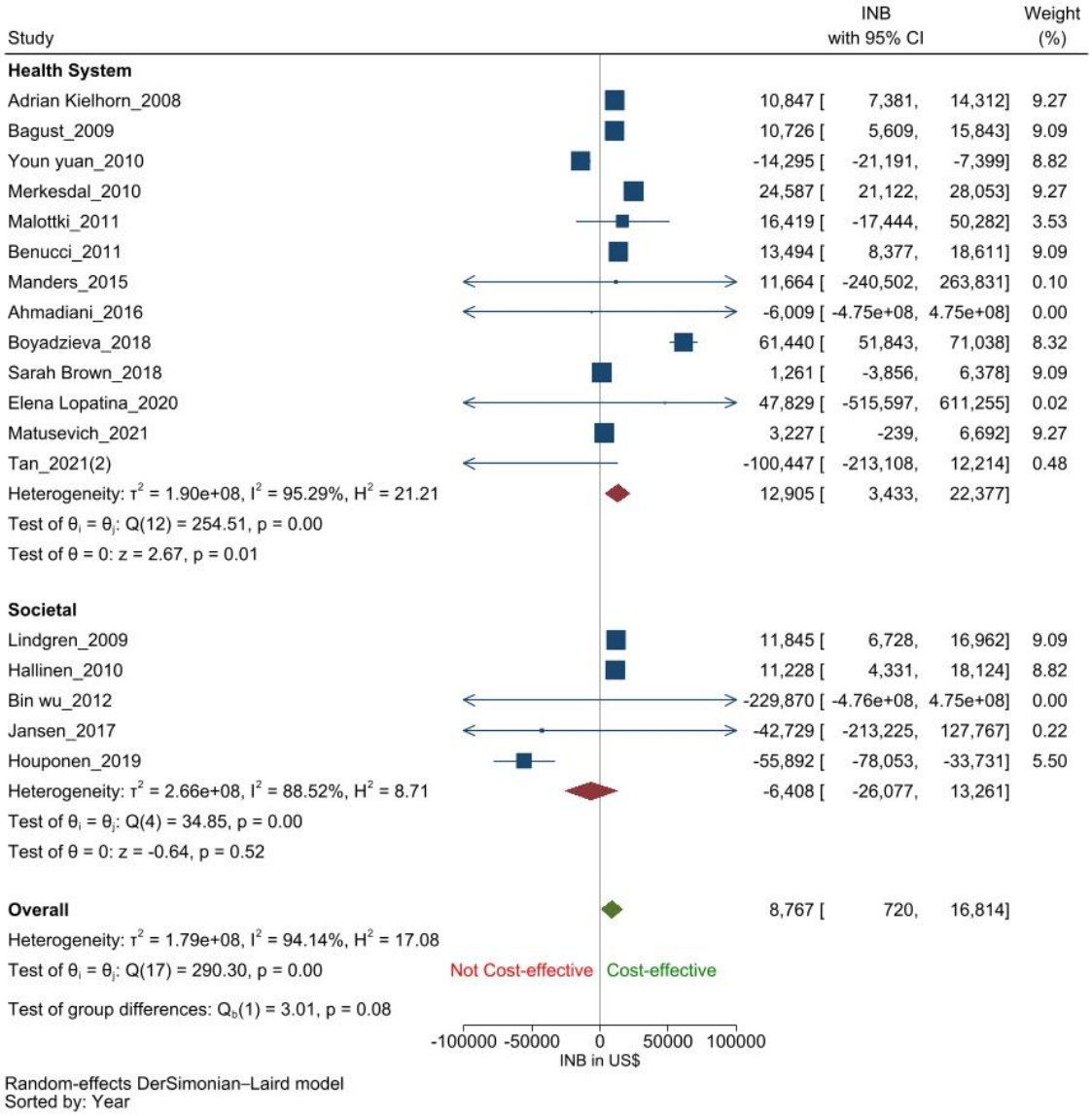
Subgroup analyses were conducted to explore the difference in INBps and heterogeneity between the studies. Subgroup analysis based on the income classification revealed that rituximab is neither cost-effective in high income (HIC)[73, 76, 86, 95, 103, 106, 155-160, 162, 163] nor in upper-middle income (UMIC)[33, 74, 161] countries with no statistical significance and considerable heterogeneity in both subgroups, I^2 = 92.74% and 79.60% respectively (Figure 2.2.6).

Figure 2.2.6 Subgroup analysis of pooled INBs based on income classifications



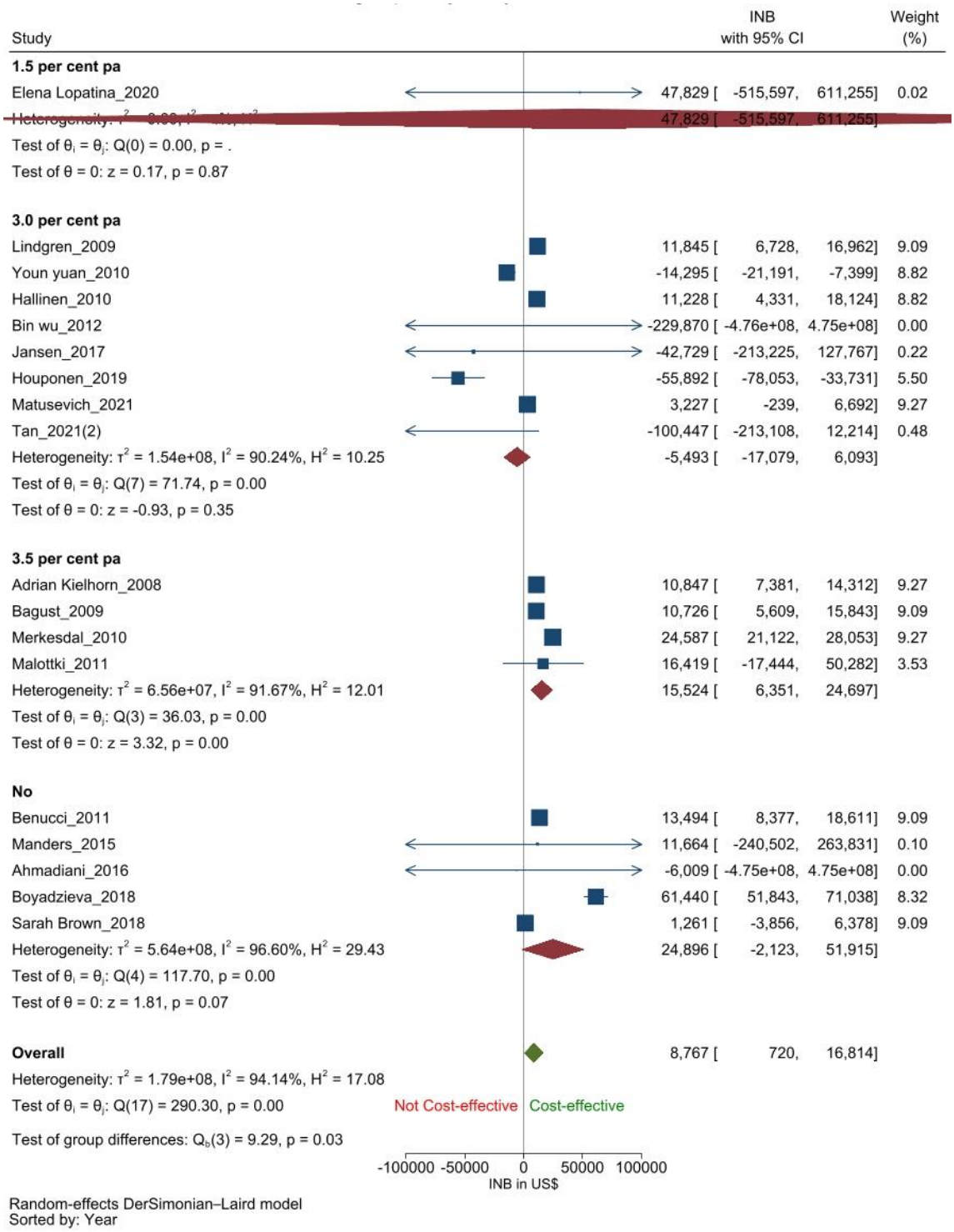
Subgroup analysis by the study perspective revealed that from the health system perspective, rituximab is cost-effective compared to other DMARDs (n=13)[73, 74, 76, 95, 103, 106, 153, 155, 156, 159-162] with an INBp of $ 12,832 (3,392 to 22,272) but not cost-effective from the societal perspective (n = 5)[33, 86, 157, 158, 163] with INBp $ -5,627 (-37,648 to 26,394) with considerable heterogeneity in both subgroups, I^2 = 94.89% and 88.50 (Figure 2.2.7).

Figure 2.2.7 Subgroup analysis of pooled INBs based on Perspective



On subgroup analysis based on discount rate, INBp for studies which used a 3.5 per cent discount rate (n=4) [95, 106, 156, 162] showed that Rituximab is cost-effective compared with other DMARDs, INBp of $ 15,468 (5,973 to 24,963) with considerable heterogeneity (I^2 = 91.67%) , however for studies which used a 3 per cent discount rate [33, 86, 155, 157-159, 161, 163], Rituximab is not cost-effective with INBp of $ -5,493 (-17,079 to 6,093) and considerable heterogeneity (I^2 = 90.24%) (Figure 2.2.8).

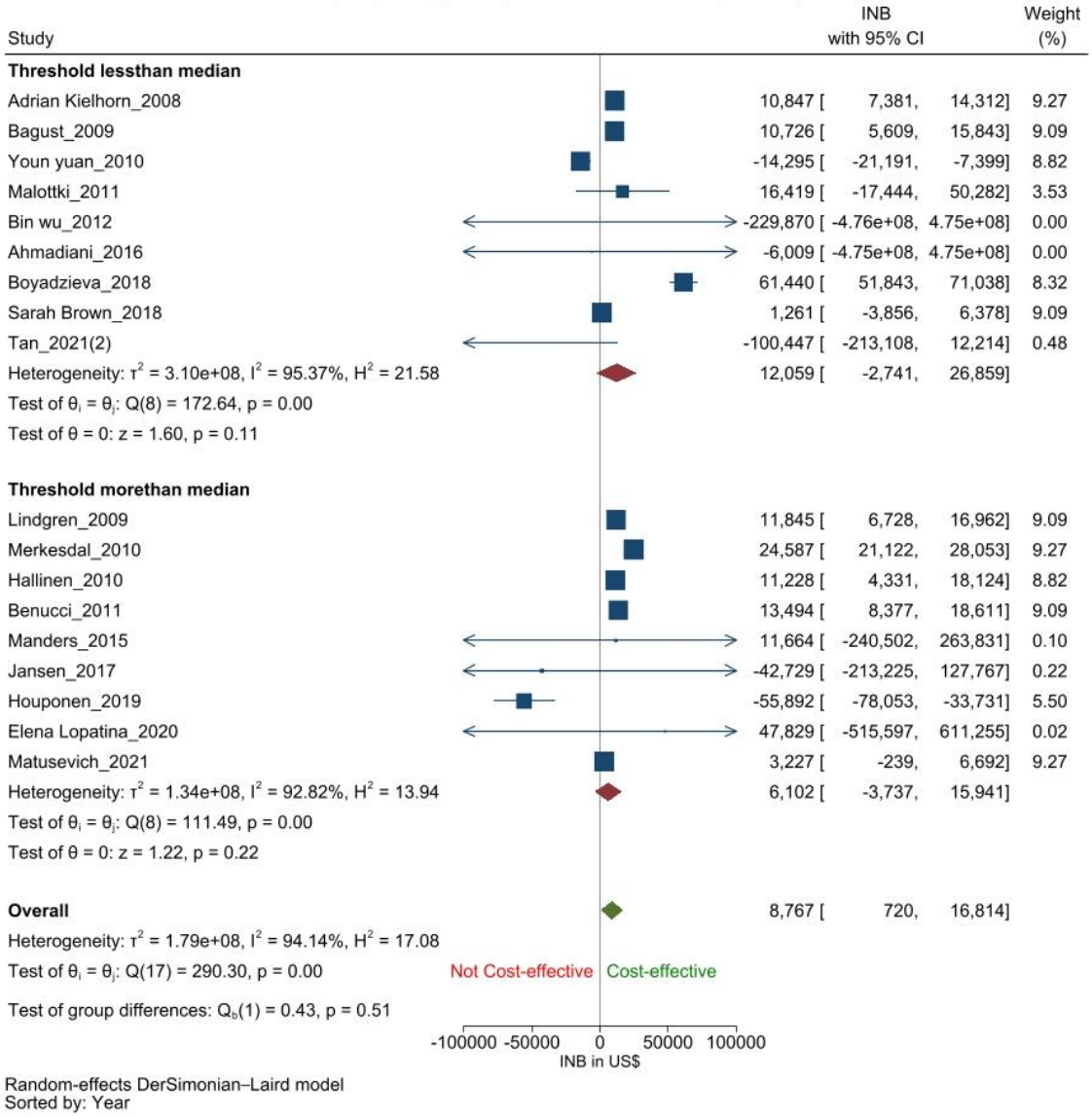
Figure 2.2.8 Subgroup analysis of pooled INBs based on Discount rate



The subgroup analysis based on the WTP, while considering the median threshold value of $ 50,342, showed that Rituximab is not cost-effective when threshold is more[73, 86, 103, 106, 158-160, 163] or less[33, 74, 76, 95, 153, 155-157, 161, 162] than the median, with INBp of $ 6,102 (-3,737 to 15,941) and $ 12,059 (-2,741 to 26,859) with considerable heterogeneity in

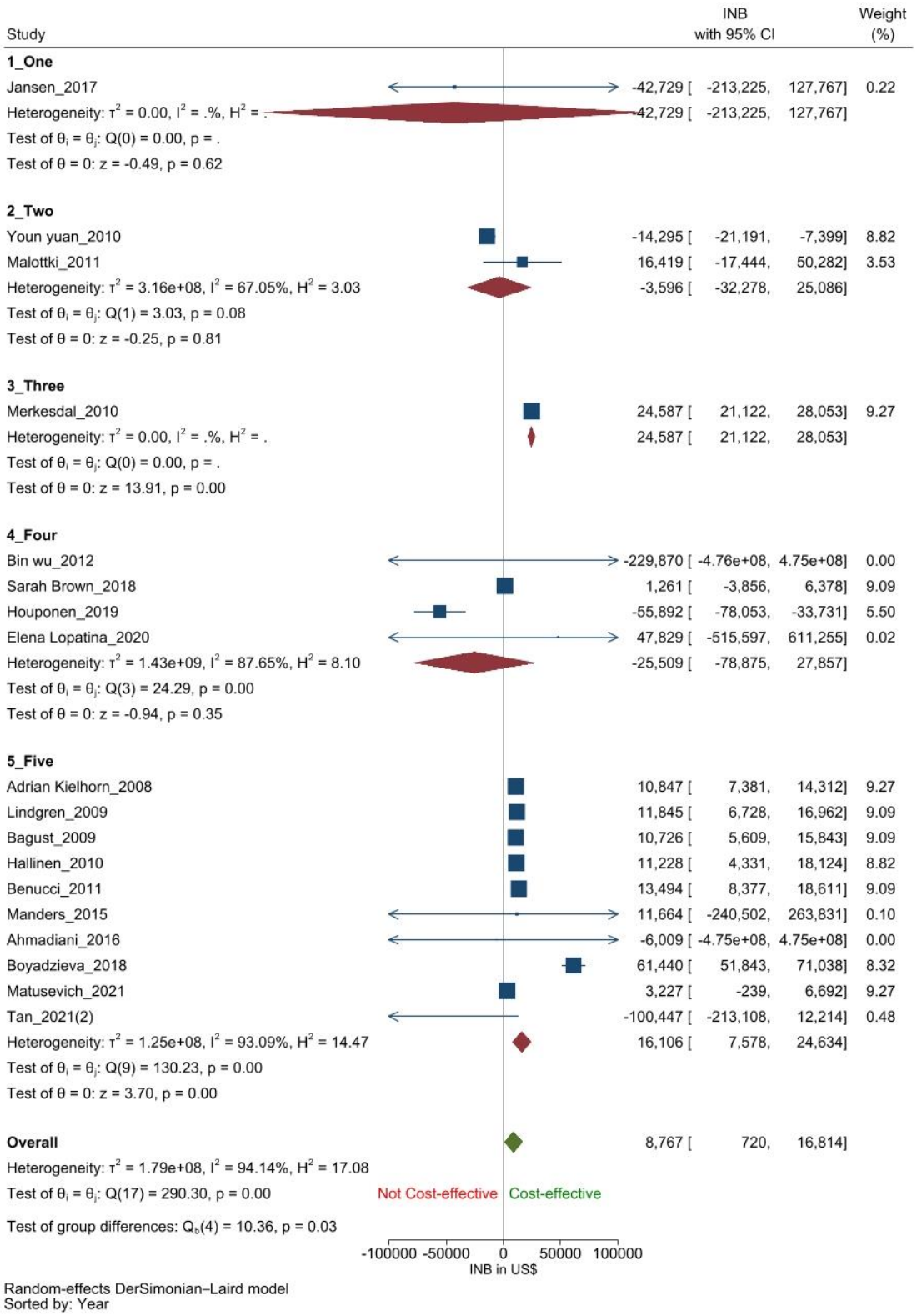
both subgroups (I^2 = 92.82% and 95.37%) respectively (Figure 2.2.9).

Figure 2.2.9 Subgroup analysis of pooled INBs based on Threshold



On Scenario based subgroup analysis Rituximab is cost-effective for studies under scenario three [106] with an INBp of $ 24,587 (21,122 to 28,053) and for scenario five[73, 74, 86, 95, 153, 156, 159-161, 163] with a INBp of $ 16,106 (7,578 to 24,634). However, INBp for studies under scenarios one[158], two [155, 162] and four[33, 76, 103, 157] showed that Rituximab is not cost-effective in comparison to other DMARDs (Figure 2.2.10).

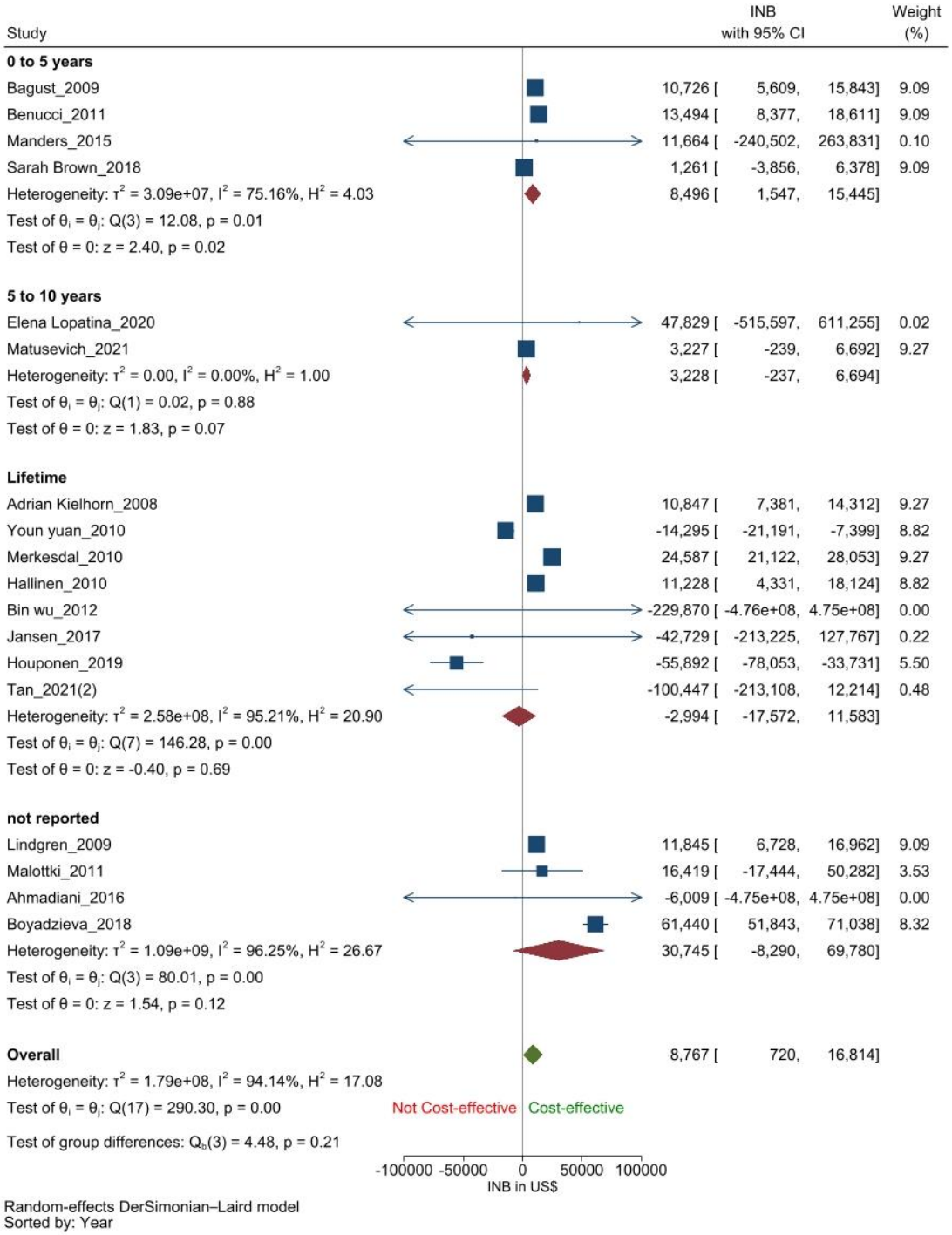
Figure 2.2.10 Subgroup analysis of pooled INBs based on Scenario



Subgroup analysis conducted for studies with different time horizons revealed that Rituximab is cost-effective while considering a shorter time horizon (less than five years)[73, 76, 156, 160] with an INBp $ 8,496 (1,547 to 15,445) but with substantial heterogeneity (I^2 = 75.16%). While considering a five-to-ten-year time horizon[103, 159],

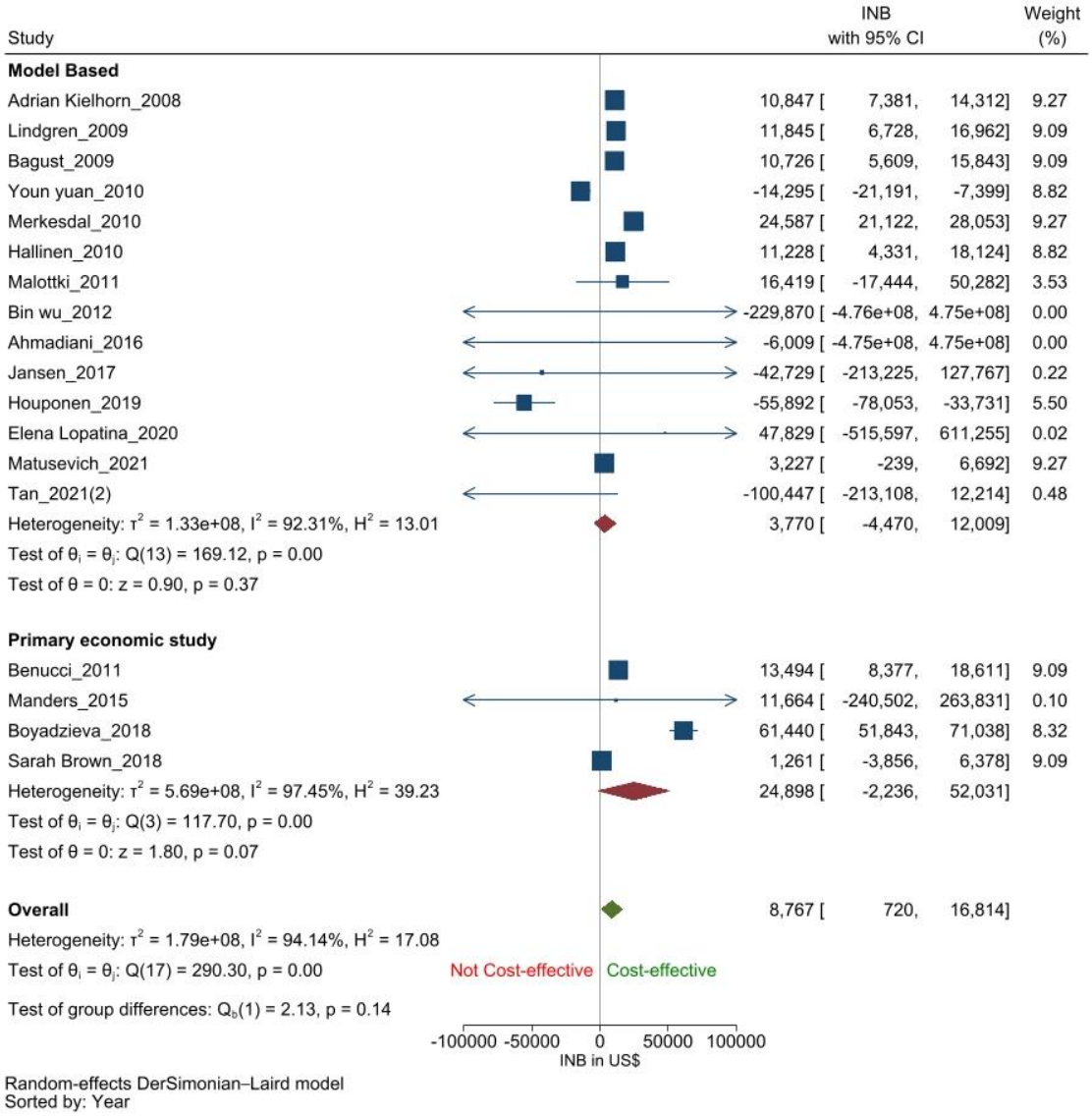
Rituximab is not cost-effective with an INBp of $ 3,228 (-237 to 6,694) with no heterogeneity (I^2 = 0.00%) but with no statistical significance. For studies using a lifetime horizon [33, 86, 95, 106, 155, 157, 158, 161], Rituximab is not cost-effective compared to other DMARDs, INBp of $ -2,994 (-17,572 to 11,583) and considerable heterogeneity (I^2 = 95.21%). (Figure 2.2.11).

Figure 2.2.11 Subgroup analysis of pooled INBs based on Time horizon



On subgroup analysis based on the analytical approach Rituximab is not cost-effective in neither model based approach[33, 86, 95, 103, 106, 153, 155-159, 161-163] nor in primary economic studies [73, 74, 76, 160], INBp $ 3,770 (-4,470 to 12,009) and INBp $ 24,898 (-2,236 to 52,031) with considerable heterogeneity (I^2 = 92.31% and 97.45%) respectively (Figure 2.2.12).

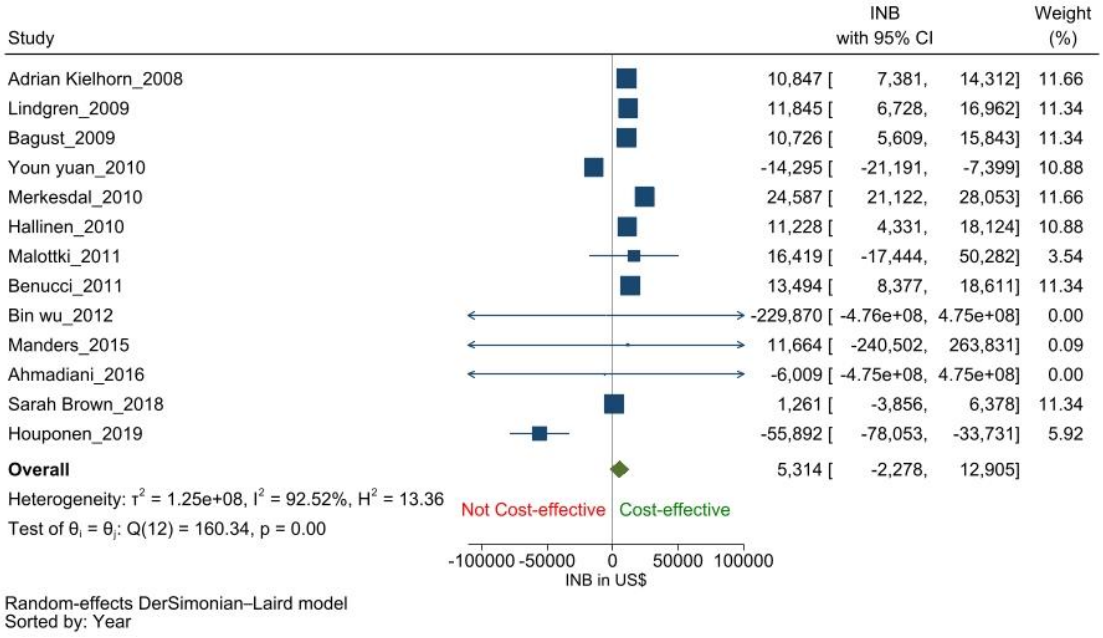
Figure 2.2.12 Subgroup analysis of pooled INBs based on Analytical approach



2.2.3.4 Rituximab compared with other DMARDs in bDMARDs failure

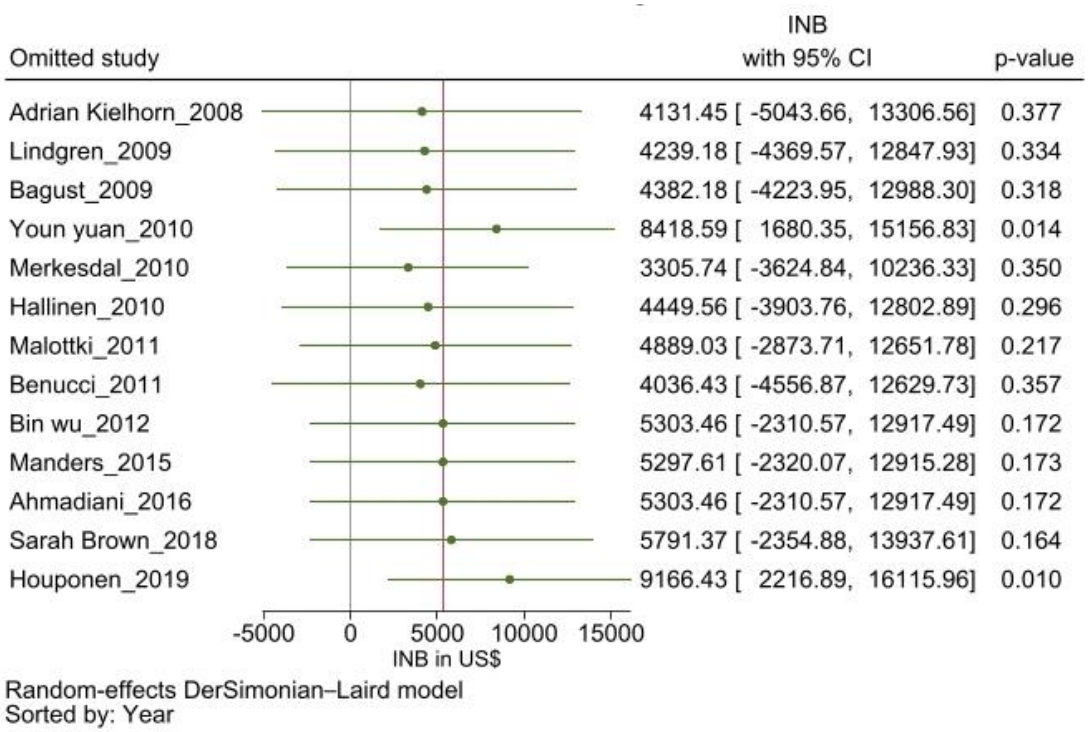
The pooled INB (INBp) with 95% CI, $5,314 (-2,278 to 12,905) showed that Rituximab is not cost-effective compared with other DMARDs after biologics' failure (n=13) [33, 73, 76, 86, 95, 106, 153, 155-157, 160, 162, 163], with considerable heterogeneity (I^2 = 92.52%) (Figure 2.2.13).

Figure 2.2.13 Rituximab compared with other DMARDs after biologics' failure



The leave-one-out forest plot revealed that Houponen et al.[157] study has a larger influence than other studies on estimating the overall INB. The omission of Houponen et al. causes the overall INB to increase by roughly $ 3,852, making Rituximab significantly cost-effective compared with other DMARDs after biologics' failure (Figure 2.2.14).

Figure 2.2.14 Leave one out analysis for pooled INBs Rituximab compared to other DMARDs in Biologics failure



Subgroup analyses conducted to explore the difference in pooled INBs and heterogeneity between studies revealed that Rituximab is not cost-effective compared with csDMARDs after biologics' failure (n=6) INBp with 95% CI is $ 814 (-13,360 to 14,989) [33, 86, 153, 155, 156, 162], or TNFi after biologics' failure (n=8) INBp with 95% CI is $ 1,348 (-10,959 to 13,654) [73, 76, 95, 106, 157, 160, 162, 163], with considerable heterogeneity, I^2 = 87.15% and 97.72% respectively (Figure 2.2.15, 2.2.16) supp 15

Figure 2.2.15 Subgroup analysis of pooled INBs for Rituximab compared to csDMARDs in Biologics failure

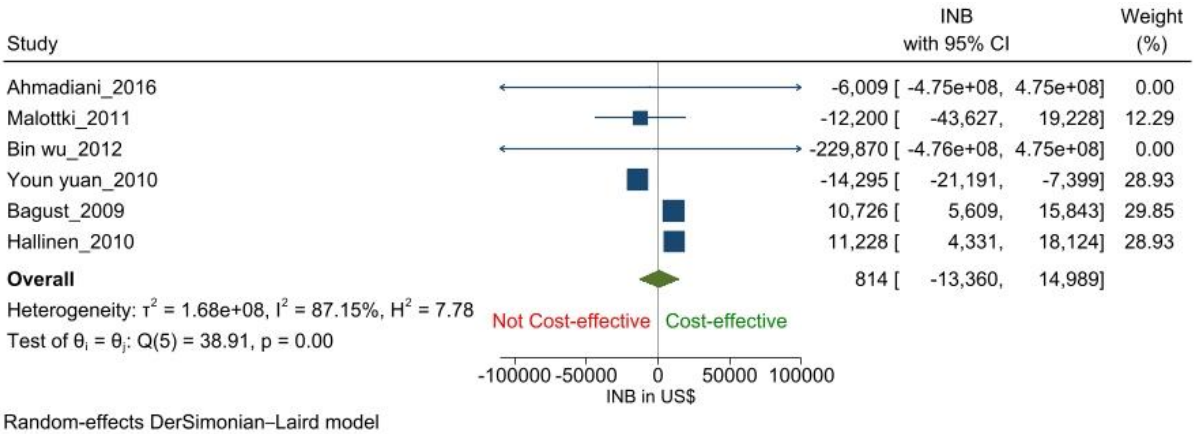
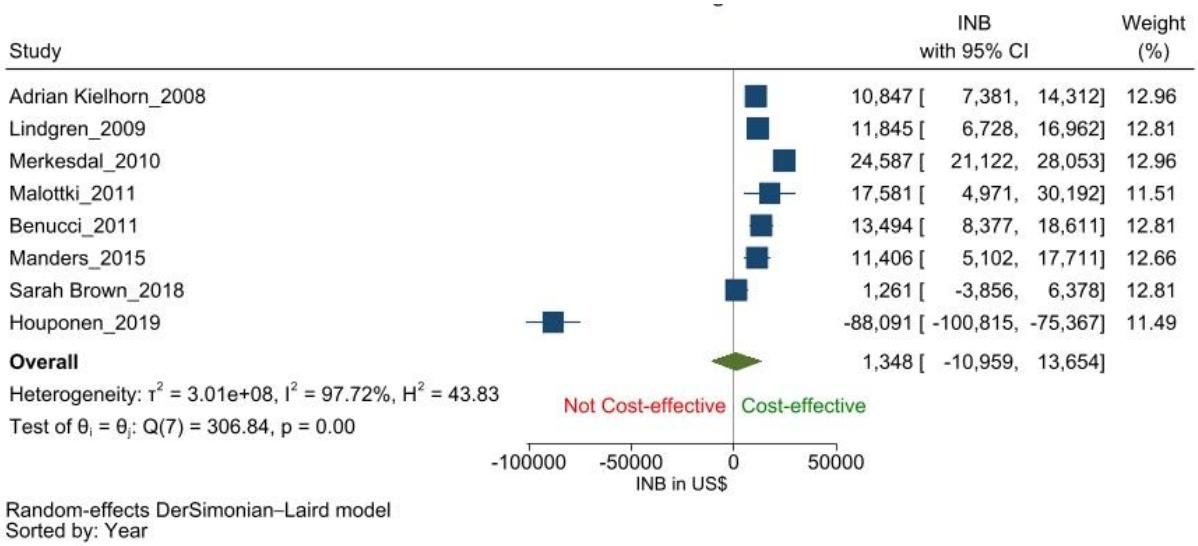


Figure 2.2.16 Subgroup analysis of pooled INBs for Rituximab compared to TNFi in Biologics failure



The leave-one-out forest plot revealed that Houponen et al. have a larger influence compared to other studies on estimating the overall INB. The omission of Houponen et al. causes the overall INB to increase by roughly $ 11,517, making Rituximab significantly cost-effective compared with TNFi after biologics' failure (Figure 2.2.17, Figure 2.2.18).

Figure 2.2.17 Leave one out analysis for pooled INBs Rituximab compared to TNFi in Biologics failure

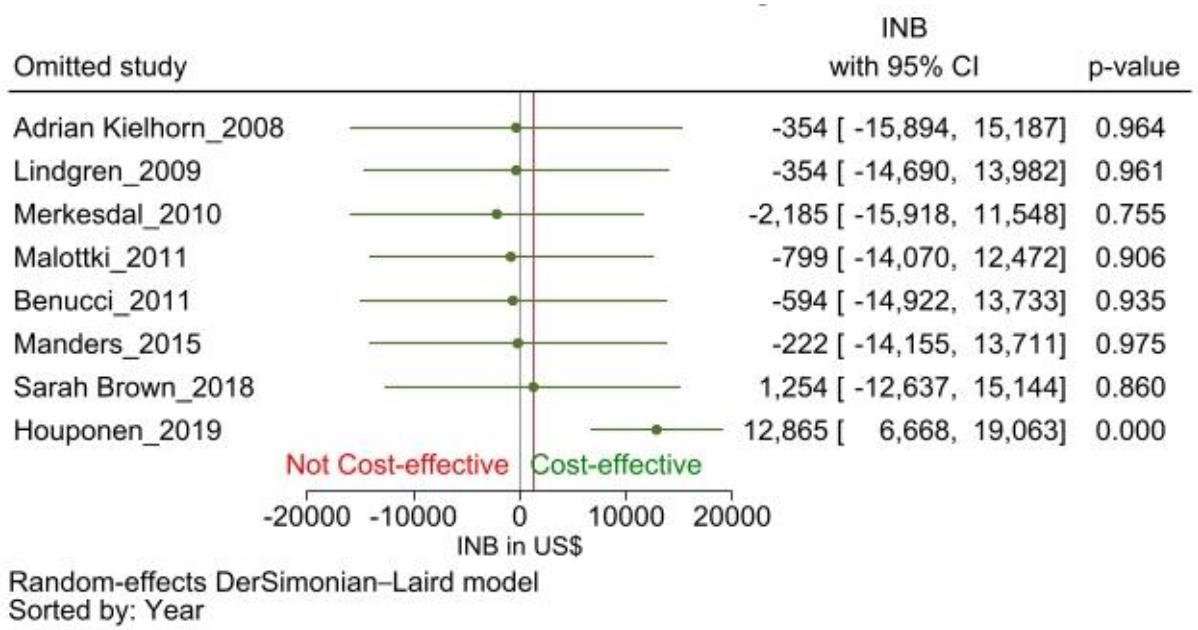
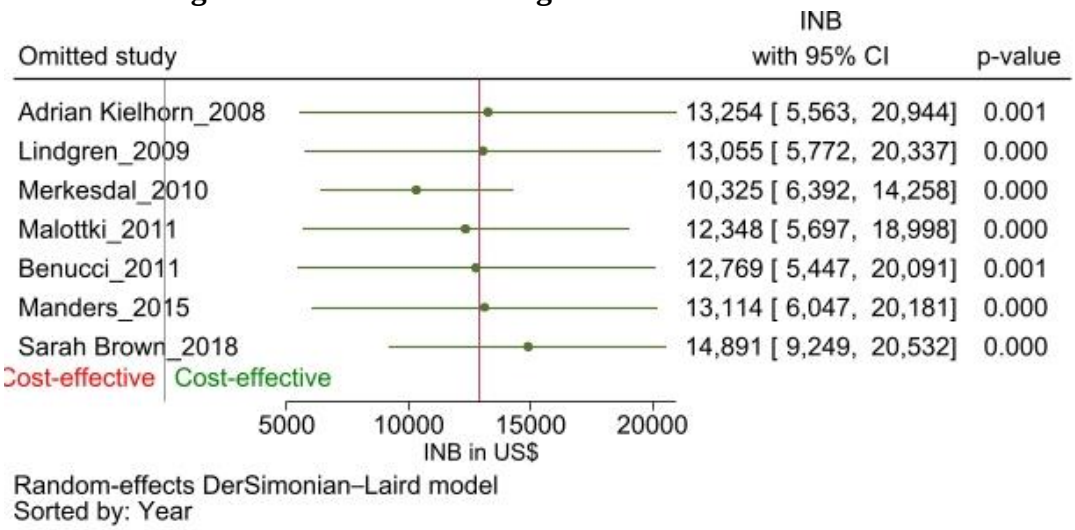


Figure 2.2.18 Leave one out analysis pooled INBs for Rituximab compared to TNFi in Biologics failure after removing outlier



The GRADE quality assessment revealed very low confidence in the pooled cost-effectiveness evidence of Rituximab compared with other DMARDs. We found very low confidence in results for Rituximab with other DMARDs from a health systems perspective. Considering Rituximab compared with other DMARDs, we have low confidence in the results observed for a shorter time horizon (0 to 5 years), (Table 2.2.2).

Table 2.2.2 Summary of Findings of GRADE Assessment

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

P: Adult subjects with rheumatoid arthritis

I: B cell depletion agent–Rituximab

C: Any other DMARDs

O: economic outcomes of incremental cost-effectiveness ratio (ICER), quality-adjusted life years (QALY), or INB

Outcome: Cost-effectiveness (assessed with meta-analysis of cost utility analysis)									
Quality assessment*						**Summary of findings**			**Comments**
No of studies	**Risk of Bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Publication Bias**	**Effect (*10^3 US$)**		**Certainty/Quality**	
						INB	**95%CI**		
Cost-effectiveness of rituximab when compared to other DMARDs (Assessed with meta-analysis).									
18	not serious	serious[a,c]	serious[d]	serious[b]	unlikely but high between-study heterogeneity.	8.76	(0.72 to 16.81)	Å• • • Very Low	Unexplained heterogeneity, downgraded one point each in inconsistency, imprecision and indirectness in intervention
Cost-effectiveness of rituximab when compared to other DMARDs from a health system's perspective (Assessed with meta-analysis)									
13	not serious	serious[a,c]	serious[d]	serious[b]	unlikely	12.91	(3.43 to 22.37	Å• • • Very Low	Unexplained heterogeneity, downgraded one point from inconsistency, imprecision and indirectness.
Cost-effectiveness of rituximab when compared to other DMARDs for a shorter time horizon of between 0 to 5 years (Assessed with meta-analysis)									
4	not serious	serious[a,]	not serious	serious[b]	unlikely	8.49	(1.55 to 15.45)	ÅÅ• • Low	Only four studies included. Unexplained heterogeneity, downgraded one points from inconsistency and one in imprecision

. [a] inconsistency $I^2 \approx 100\%$ [b] studies included have reported a wide confidence intervals [c] high heterogeneity [d] Lack of generalisability *Since all included studies are model based Cost-Utility studies, we have not included the Study design and Number of participants under consideration for assessment.

GRADE Working Group grades of evidence

High certainty: we are very confident that the true effect lies close to that of the estimate of the effect.

Moderate certainty: we are moderately confident in the effect estimate; the true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different.

Low certainty: our confidence in the effect estimate is limited; the true effect may be substantially different from the estimate of the effect.

Very low certainty: we have very little confidence in the effect estimate; the true effect is likely to be substantially different from the estimate of effect

2.2.4 Discussion

We synthesised the evidence on the cost-effectiveness of Rituximab compared with other DMARDs through an SRMA of the published cost-utility studies. We have standardised data extraction and preprocessing from various published studies to conduct a meta-analysis of cost-utility studies and generated pooled INBs with its CI. The INBp from the 18 studies shows that Rituximab is cost-effective compared to other DMARDs. However, on separate analysis, the result loses its robustness when we limit the comparator to other DMARDs used after a biologics' failure, either a csDMARD or a TNFi failure. Also, Rituximab is not cost-effective if used as third-line therapy after biologics' failure. We conducted subgroup analyses to check the robustness of our findings and to understand the considerable heterogeneity in the pooled results. The subgroup analysis revealed that Rituximab is a cost-effective comparator to other DMARDs from the health systems perspective, for studies reported using a 3.5 per cent discount rate and for a shorter time horizon of 0 to 5 years. However, for all the other subgroups, Rituximab was not cost-effective. The leave-one-out analysis suggests that Houponen et al. is a potential outlier, and by removing it, Rituximab becomes significantly cost-effective compared to other DMARDs and cost-effective as a third-line drug compared to TNFi after biologics' failure.

The included model-based studies were limited due to a lack of publicly available sources of data about the effectiveness of specific treatment sequences[109]. Most model-based studies have simplified the actual treatment process in RA and limited the treatment sequence included in the studies[86]. Studies compared treatment sequences replicating the most frequently used regimens in their respective healthcare clinical practice for RA, making a direct comparison difficult[95, 106, 109, 154, 159, 161]. Further, there is no clarity on whether the selected therapies were independent of the reason for the

treatment failure, as reported[109]. In the models with sequence therapy, due to a lack of evidence about the efficacy of drugs following treatment, equivalent drug efficacy was applied independently of the previous therapy [109]. Some studies used inpatient costs based on resource use that is determined according to the patient's HAQ score[86, 109]. Since there was no data that would allow estimating a precise time-to-restart, patients in the rituximab arm in the trials may have received more treatment lines within the simulation time, leading to higher costs[163]. The adverse event rates were assumed to be the same across most studies for all biologics, which might overestimate/overestimate the effectiveness and costs. Also, in some studies, the only adverse event considered was serious infections [154, 161]. The high cost of any added drug in a sequence would have created an expensive/cheaper comparator; hence, pooled results from such studies to be cautiously interpreted.

The importance of B–cells in the pathophysiology of RA has been shown by B Cell Depletion therapy (BCDT) [164, 165]. The BCDT has been shown to be effective in reducing signs and symptoms and slowing RA radiographic progression [164-166]. Second- and third-generation anti-CD20 antibodies have been developed and are being tested for RA, including BCDT agents–Ofatumumab, Obinutuzumab, Ibritumomab, Ocaratuzumab, and B-cell inhibitors such as Belimumab, Atacicept, and Tabalumab. [167] However, their efficacy and safety have not been adequately investigated and approved for use in RA[168]. Several Rituximab biosimilars (BCD-020 [AcellBia™; Biocad], Maball™, and MabTas) have been approved in emerging markets with less stringent regulatory requirements; however, only limited safety data on Rituximab biosimilars is publicly available[169]. It is possible that newer anti-CD20 monoclonals may be more effective than Rituximab at inducing B-cell depletion [170]. Although Belimumab was not effective in phase II clinical trials for RA[171], other promising CD-

20 targeting antibodies (Obinutuzumab, Ibritumomab, Ocaratuzumab) need more clinical trials[167]. It is debated that the strategy of depletion of B cells may not be the better approach than inhibiting B-cell modulatory cytokines[167].

This current evidence synthesis has some limitations, including but not limited to the following: Since INB is not normally distributed, we have no specific tools to assess the publication bias for non-normally distributed effect measures. We used the GRADE approach to assess the outcome quality because there were no specific GRADE guidelines for cost-utility studies. Many RA patients are not effectively treated with the available therapies since economic access to costly medicines can be challenging[172], especially for those staying in lower economies. Patients with RA are at an increased risk for cost-related medication nonadherence, so identifying the most cost-effective drugs for RA is critical. Analysing sequences rather than making traditional head-to-head comparisons was limited due to the unavailability of published studies. When extrapolating the results of the current evidence synthesis to various healthcare contexts, the generalisability of these results to be carefully considered as medication-related costs are often dependent upon the price, dose, route of delivery, and dosing frequency of the drug. Considering drug cost as the main cost driver, a potential price reduction may warrant Rituximab to be cost-effective and provide more value-added care for RA patients. The comparison of Rituximab over TNFi as a 3rd line therapy after a biologics failure needs further evidence to suggest a more robust conclusive cost-effectiveness results. Further analysis should also be done, including real-world evidence in the model inputs using data from clinical trials, especially for data regarding remission or low disease activity and newer biosimilars with a price change. For LICs and LMICs, we recommend generating primary economic evidence to guide policy decisions. However, until then, such pooled evidence on cost-effectiveness may help

stakeholders make decisions.

2.2.5 Conclusion

Rituximab is cost-effective compared to other DMARDs but not cost-effective if used as third-line therapy after biologics' failure. On GRADE quality assessment, we place very low confidence on the pooled cost-effectiveness evidence of Rituximab when compared with other DMARDs. Most of the studies were from HICs, very few from UMICs and LMICs, and none from LICs, highlighting a lack of context-specific evidence and a need to generate the same.

2.3 Systematic review and meta-analysis of cost-utility studies on Janus Kinase inhibitors for Rheumatoid Arthritis

2.3.1 Introduction

Given that JAK-i (Tofacitinib (TOFA), Baricitinib (BARI), Upadacitinib (UPA), Filgotinib (FILG)) are as clinically effective as bDMARDs (4-7), clinicians and policymakers would consider the cost-effectiveness of these drugs when determining the treatment for RA patients. (8) Cost-effectiveness analyses (CEA) collate evidence from multiple sources to comparatively analyse considering both the costs and benefits of the treatment. (8) Therefore, CEAs have been regarded as the "gold standard" for creating fair estimates of the value of health interventions to guide decision-making.(9) While many studies have reported on the cost-effectiveness of JAK-i in RA treatment, there is currently no systematic review of such economic evaluations. Therefore, a comprehensive systematic evaluation and analysis of existing cost-effectiveness evidence are required. Hence, we conducted a systematic review of the available evidence on the cost-effectiveness of JAK-i for RA treatment and calculated the pooled incremental net benefit (INB).

2.3.2 Methods

The SRMA conducted on JAK-i compared to other DMARDs for RA is a part of a broader SRMA and the methods employed for this specific section are consistent with those outlined in Section 2.2.1 and Figure 2.1.1.

2.3.3 Results

Characteristics of included studies: We included seventeen (25-41) relevant studies for systematic review, of which fifteen studies (25, 26, 28-38, 40, 41) were eligible for meta-analysis (Figure 2.1.1). All the studies with JAK-i as an intervention were included for the meta-analysis (n=15), whereas studies that compared JAK-i versus JAK-i (n=2) were included for systematic review only (27, 39). The characteristics of the included studies in the systematic review and meta-analysis are summarised in Table 2.3.1.

Thirteen studies (25, 26, 28, 30-34, 36-38, 40, 41) assessed the cost-effectiveness of JAK-i as second line treatment in RA patients who showed an inadequate response to csDMARDs. Five studies (25, 29, 32, 34, 35) assessed the cost-effectiveness of JAK-i compared to csDMARD/bDMARDs as the third-line treatment for RA patients who showed an inadequate response to TNF-a-i following csDMARD failure. There are no studies which assessed the cost-effectiveness of JAK-i as first line treatment in early RA patients.

Eleven studies (25, 27-30, 32, 33, 37, 38, 40, 41) were from High-income countries (HIC), five studies from upper-middle-income countries (UMICs) (31, 34-36, 39) and only one study from lower middle-income country (LMICs). (26) ICER was calculated from a Health system perspective in eleven studies, (25, 27, 31-36, 38, 39, 41) societal perspective in four studies, (28-30, 37) and payer's perspective in two studies. (26, 40) All studies used a model-based analytical approach, out of which eleven studies (25, 29-35, 38-40) used an event simulation model, and six studies (26-28, 36, 37, 41) used a Markov model. All the studies except Fournier et al., 2019 (27) (ten-year horizon) and Van de Laar et al., 2020 (37) (five-year horizon) used a lifetime horizon for the calculation of costs and QALY (n=15). (25, 26, 28-36, 38-41)

Table 2.3.1 General characteristics of the studies included in systematic review and meta-analysis

Author_ year	Country	Setting	Perspective	Time Horizon	Discount Rate for costs (%)	Reference year	Intervention	Comparator	Remarks
Van De Laar_2020[121]	Netherland	Country	Societal	5 Year	4.0	2019	csDMARD - Ada Seq	csDMARDs- Bari Seq	Dominated
Chen_2019[77]	Taiwan	Country	Payer	Lifetime	3.0	2015	Tofa + MTX	Ada+MTX	Cost effective
Claxton_2018[79]	USA	Risk Group	Health System	Lifetime	3.0	2015	MTX - Tofa - Ada - Aba - Toci - Ritu	MTX - Eta - Ada - Aba - Toci – Ritu	Cost saving
Fatemi_2020[173]	Iran	Risk Group	Payer	Lifetime	7.2	2019	Tofa + MTX	Eta-Ada-Ritu	Cost-effective
Fournier_2019 [43]*	USA	Country	Health System	10 Year	3.0	2018	Sari -Tofa -csDMARD	Ada- Tofa- csDMARD	Dominant
Jansen_2017[158]	USA	Country	Societal	Lifetime	3.0	2016	Eta - Ada - Aba - Toci- Tofa- Ritu - csDMARD	csDMARD	Cost effective
Kuwana_2022[134]	Japan	Country	Health System	Lifetime	3.0	2020	Bari + MTX	csDMARD	Cost effective
Lei Tian_2020[174]	China	Country	Health System	Lifetime	5.0	2018	Tofa-Tnfi-Toci-PC	Toci +PC	Cost saving
Schlueter_2019[175]	Spain	Country	Health System	Lifetime	3.0	2018	Bari	Ada	Cost-effective
Young lee_2015[101]	South Korea	Country	Societal	Lifetime	5.0	2013	Tofa + MTX - Ada + MTX + Eta + MTX - csDMARD	Ada + MTX + Eta + MTX–csDMARD	Cost effective
Muszsbek_2019 [176]	USA	Country	Health System	Lifetime	3.0	2017	Tofa + MTX	Sari + MTX	Dominant
Navarro_2020[109]	Spain	Country	Health System	Lifetime	3.0	2018	Tofa+ MTX - Toci+MTX- Aba+MTX- Ritu+MTX	Toci+ MTX - Abat+MTX - ritu+MTX - certo+MTX	Dominant
SiNi Li_2021(1)[177]	China	Risk Group	Health System	Lifetime	3.0	2019	Bari-Ada-Eta-Toci-PC	Ada + MTX	Cost-effective
SiNi Li_2021(2) [47]*	China	Risk Group	Health System	Lifetime	3.0	2019	TT - Ritu – Tofa	Eta - Aba- Tofa	Cost effective
Young Ha_2021 [178]	South Korea	Risk Group	Societal	Lifetime	5.0	2019	Tofa – BDMARDs	csDMARDs	Cost effective
Tan_2021(1)[154]	China	Country	Health System	Lifetime	3.0	2019	Tofa - Eta - Ritu - Toci	Eta - Ritu - Toci	Dominant
Tan_2021(2)[161]	China	Risk Group	Health System	Lifetime	3.0	2019	Eta - Tofa - Ritu - Toci	MTX	Not cost-effective

*Systematic review, HIC– High-income country, UMIC– Upper middle-income country, LMIC– Lower middle-income country, NR– not reported, RA– Rheumatoid Arthritis, MTX– Methotrexate, Aba– Abatacept, Ritu– Rituximab, Ada– Adalimumab, Toci– Tocilizumab, Goli– Golimumab, Eta– Etanercept, TT– Tripple therapy, Tofa– Tofacitinib, Bari- Baricitinib, Certo- Certolizumab, Sari- Sarilumumab, Lefl– Leflunomide, csdmards– conventional synthetic disease-modifying anti rheumatic drugs, Seq– Sequential, PC- palliative care.

Most studies (n=12) (25, 27, 29, 31-35, 38-41) used a 3 per cent discount rate for costs, three studies used a 5 percent discount rate, (28, 30, 36) Van De Laar et al., 2020(37) used 4 percent and Fatemi et al., 2020(26) used 7.2 percent per annum rate for discounting costs. Country-specific willingness to pay threshold (25, 27-29, 32, 33, 37, 38, 40, 41) was used in ten studies whereas GDP-based WTP(26, 30, 31, 34-36, 39) was used in seven studies.

Studies are classified into five scenarios based on the reported outcome and dispersion measures (17). Most of the studies were in scenario five (n=11) (25, 27, 28, 30-32, 34, 35, 38, 39, 41), followed by four studies in scenario four (26, 33, 36, 40) and one study each under scenario one(29) and three(37). INB variance of Schulter et al., 2019(33) was used for five other studies(25, 27, 28, 31, 32, 38), Tian et al., 2020 (36) for three studies(30, 34, 35) and Fatemi et al., 2021(26) for two studies(27, 41).

Risk of bias assessment: Nearly 94 per cent of the studies justified the perspective used for analysis, indicating a narrow perspective bias. Similarly, most of the studies used the adequate comparator for analysis; hence the treatment comparator bias was low. Reporting and dissemination bias is 52 per cent, whereas limited time horizon bias is low since 94 per cent of the studies justified the time horizons. The methods of data identification were transparent for 59 per cent of studies. Limited scope bias is very high (65 per cent); also, internal consistency was not appropriately evaluated (Figure 2.3.1).

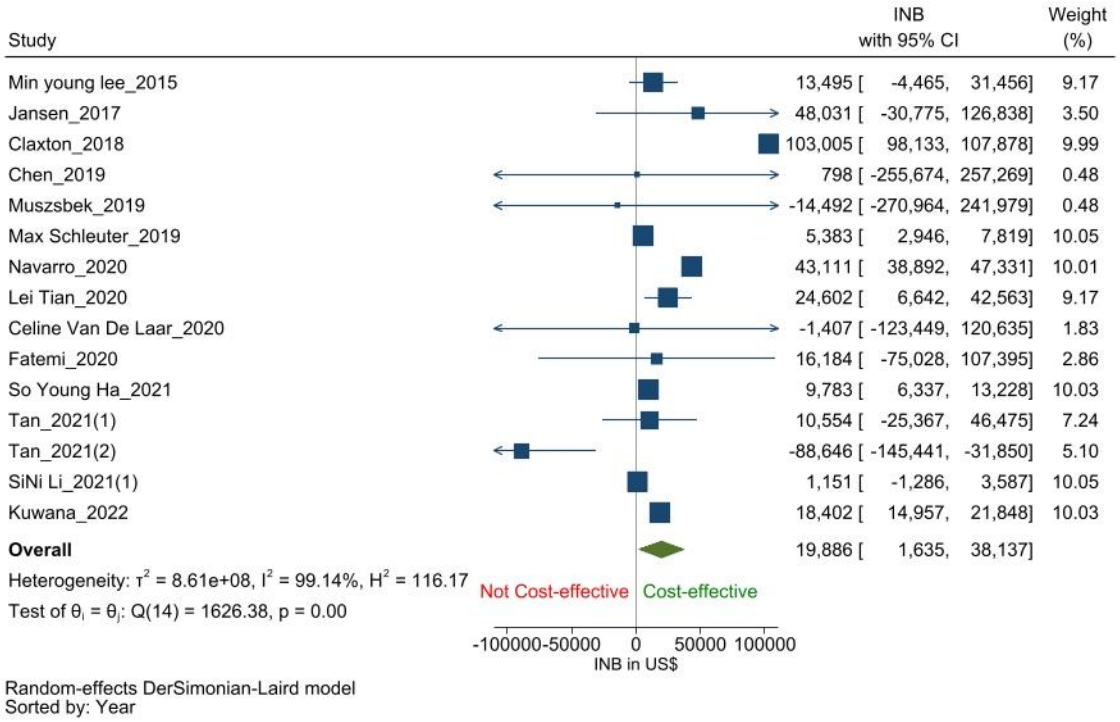
Figure 2.3.1 Assessment of Risk of Bias using ECOBIAS Checklist

Issue Addressed / Author_Year	Fournier_2019	Chen_2019	Navarro_2020	Lei Tian_2020	Van De Laar_2020	Muszbek_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	P	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y
Inefficient comparator bias	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y
Cost measurement omission bias	P	Y	P	Y	P	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	P
Intermittent data collection bias	Y	Y	P	Y	P	Y	Y	Y	P	Y	Y	Y	Y	Y	Y	Y	P
Invalid valuation bias	P	Y	P	Y	P	Y	Y	Y	P	Y	P	Y	Y	Y	P	Y	P
Ordinal ICER bias	Y	Y	P	P	U	Y	Y	Y	P	Y	P	Y	Y	U	P	Y	P
Double-counting bias	P	P	U	Y	U	Y	P	Y	P	Y	P	P	Y	Y	U	U	U
Inappropriate discounting bias	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y
Limited sensitivity analysis bias	U	P	P	P	U	Y	U	P	P	Y	P	Y	Y	P	Y	P	P
Sponsor bias	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y
Reporting and dissemination bias	U	U	U	U	U	Y	U	U	Y	Y	Y	U	Y	Y	Y	Y	Y
Structural assumptions bias	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	P	P	Y	Y	Y
No treatment comparator bias	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y
Wrong model bias	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y
Limited time horizon bias	P	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y
Bias related to data identification	P	Y	P	Y	P	Y	U	P	P	Y	P	Y	Y	Y	Y	Y	Y
Bias related to baseline data	Y	Y	P	P	P	Y	U	P	P	P	P	P	P	P	P	Y	U
Bias related to treatment effects	P	Y	P	P	U	Y	P	P	P	Y	P	P	P	Y	Y	Y	P
Bias related to quality-of-life weights	P	Y	P	Y	P	Y	U	Y	Y	Y	Y	Y	Y	Y	P	Y	P
Non-transparent data incorporation bias	P	Y	P	Y	P	Y	Y	Y	Y	Y	Y	Y	P	Y	Y	Y	P
Limited scope bias	U	P	P	Y	P	Y	P	P	P	Y	Y	Y	U	Y	P	P	U
Bias related to internal consistency	U	U	U	U	U	U	U	U	U	U	U	U	U	U	U	U	U

Cost-effectiveness of JAK-i compared to csDMARDs/bDMARDs:

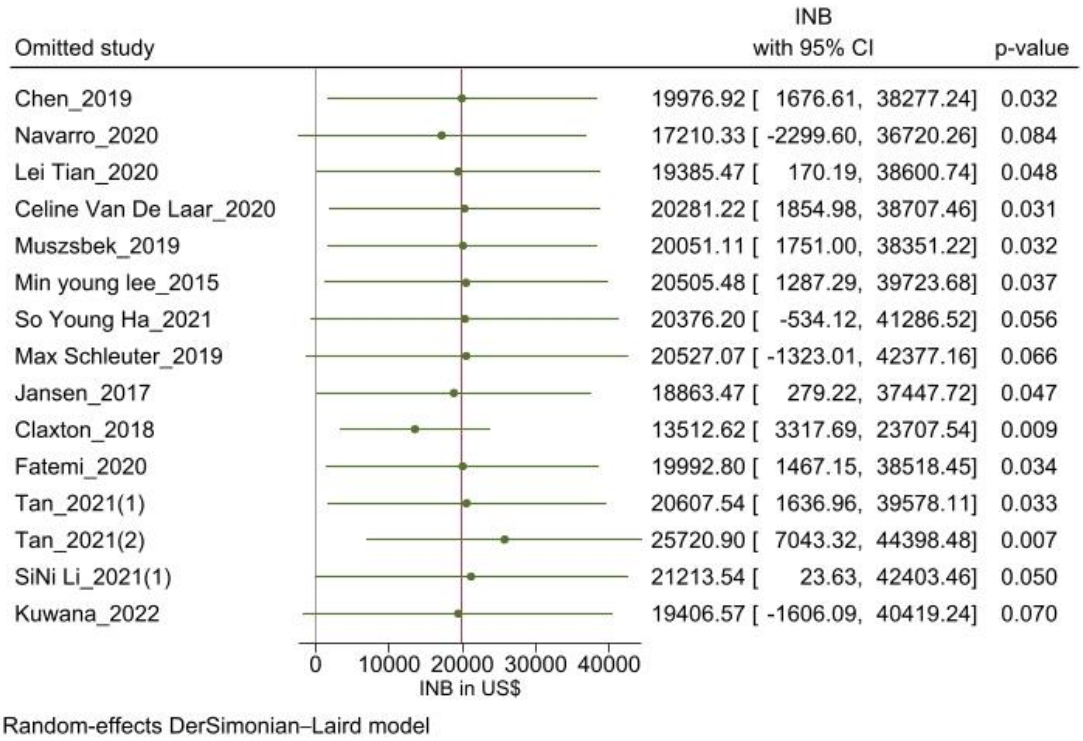
The meta-analysis includes studies that evaluated the cost-effectiveness of JAK-i against csDMARDs/bDMARDs for RA patients with csDMARD failure or csDMARD-TNF-a-i failure. (25, 26, 28-38, 40, 41). The pooled INB (INBp) was $19,886 and 95% CI (1,635 to 38,137) which shows JAK-i is significantly cost-effective compared to csDMARDs and bDMARDS, however with a considerable heterogeneity (I^2 = 99.14) (Figure 2.3.2).

Figure 2.3.2 Pooled INBs for JAKi vs csDMARDs/bDMARDS



As per the leave-one-out sensitivity analysis, two individual studies significantly influence the overall estimate (25, 35). Leaving Claxton et al., cause a decrease in INBp values ($13,512 and 95% CI= 3,317 to 23,707) and Tan et al., cause an increase in INBp ($25,720 and 95% CI= 7,043 to 44,398) (Figure 2.3.3).

Figure 2.3.3 Leave one out analysis for JAKi vs csDMARDs/bDMARDS



The Galbraith plot shows all the studies except two within the 95 per cent confidence interval indicating the possibility of low inconsistency across studies (Figure 2.3.4). The funnel plot showed asymmetry (Figure 2.3.5); however, the Egger's test with a higher p-value (p = 0.561) indicates no significant variability among the studies and no publication bias.

Figure 2.3.4 Galbraith plot for JAKi vs csDMARDs/bDMARDS

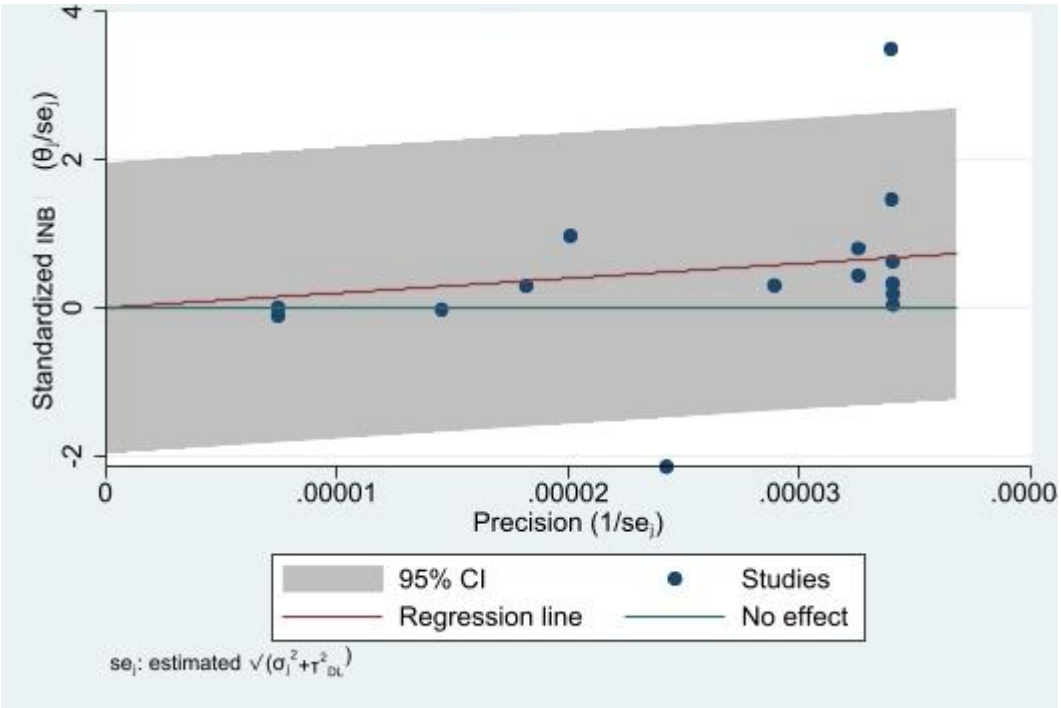
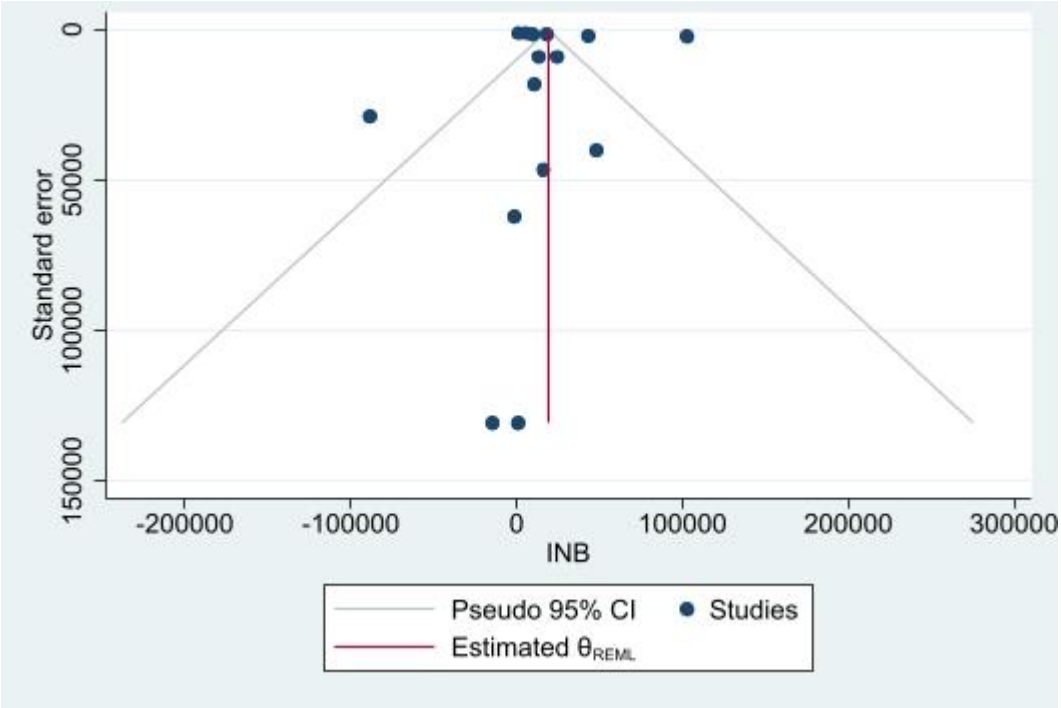


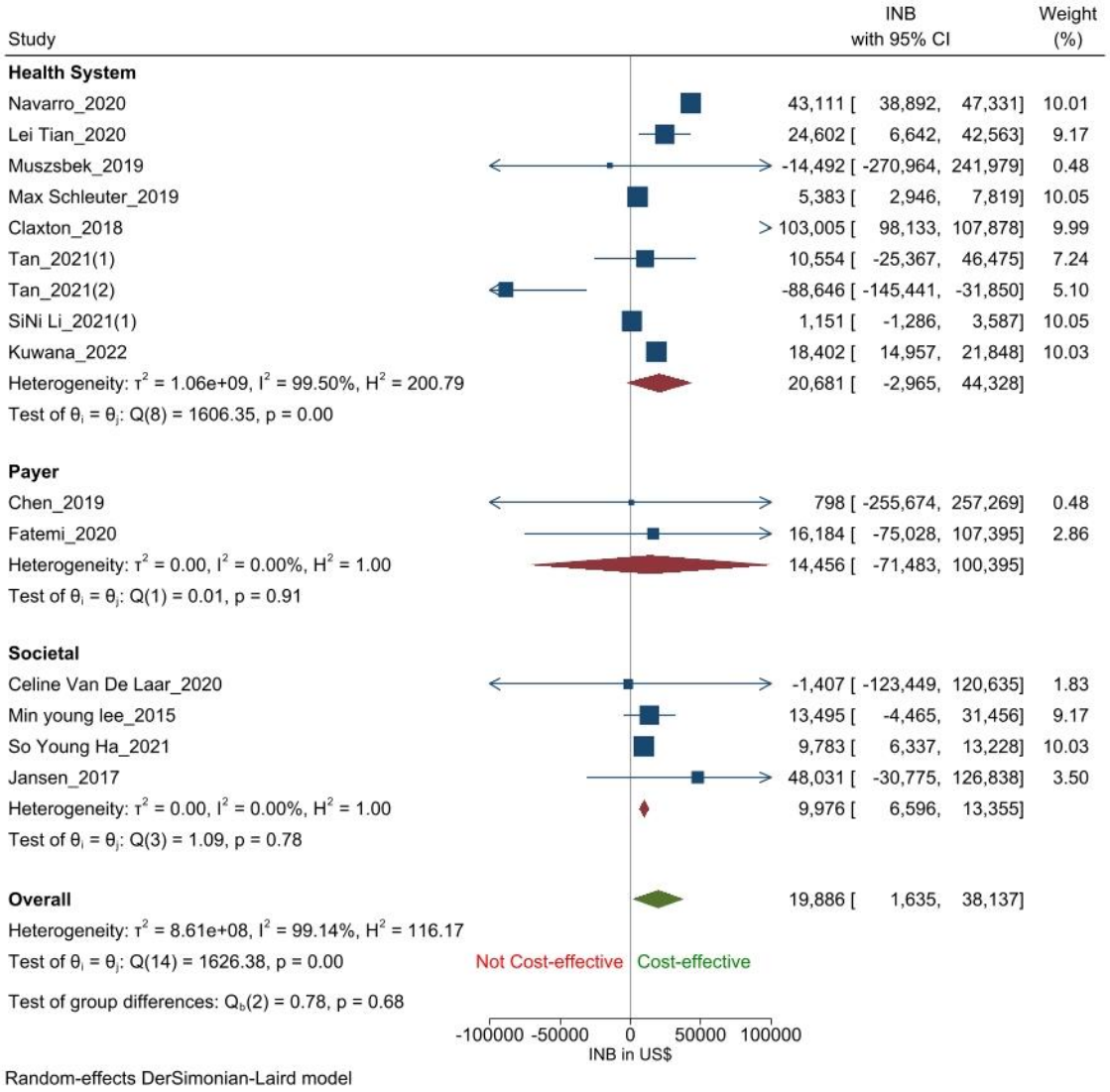
Figure 2.3.5 Funnel plot for JAKi vs csDMARDs/bDMARDS



Subgroup Analysis: Sub-group and sensitivity analyses were performed to explore the source of heterogeneity. Subgroup analysis based on study perspectives showed that JAK-i is cost-effective only from a societal perspective (n=4)(28-30, 37) with a INBp

of $9,976 (6,596 to 13,355) and no heterogeneity (I2=0). However, the intervention is not cost-effective neither from a health-system perspective (n=9) (25, 31-36, 38, 41) (INBp= $20,681, -2,965 to 44,328) nor from a payer's perspective (n=2)(26, 40) (INBp=14,456, -71,483 to 100,395) with a high heterogeneity in health-system perspective subgroup (Figure 2.3.6).

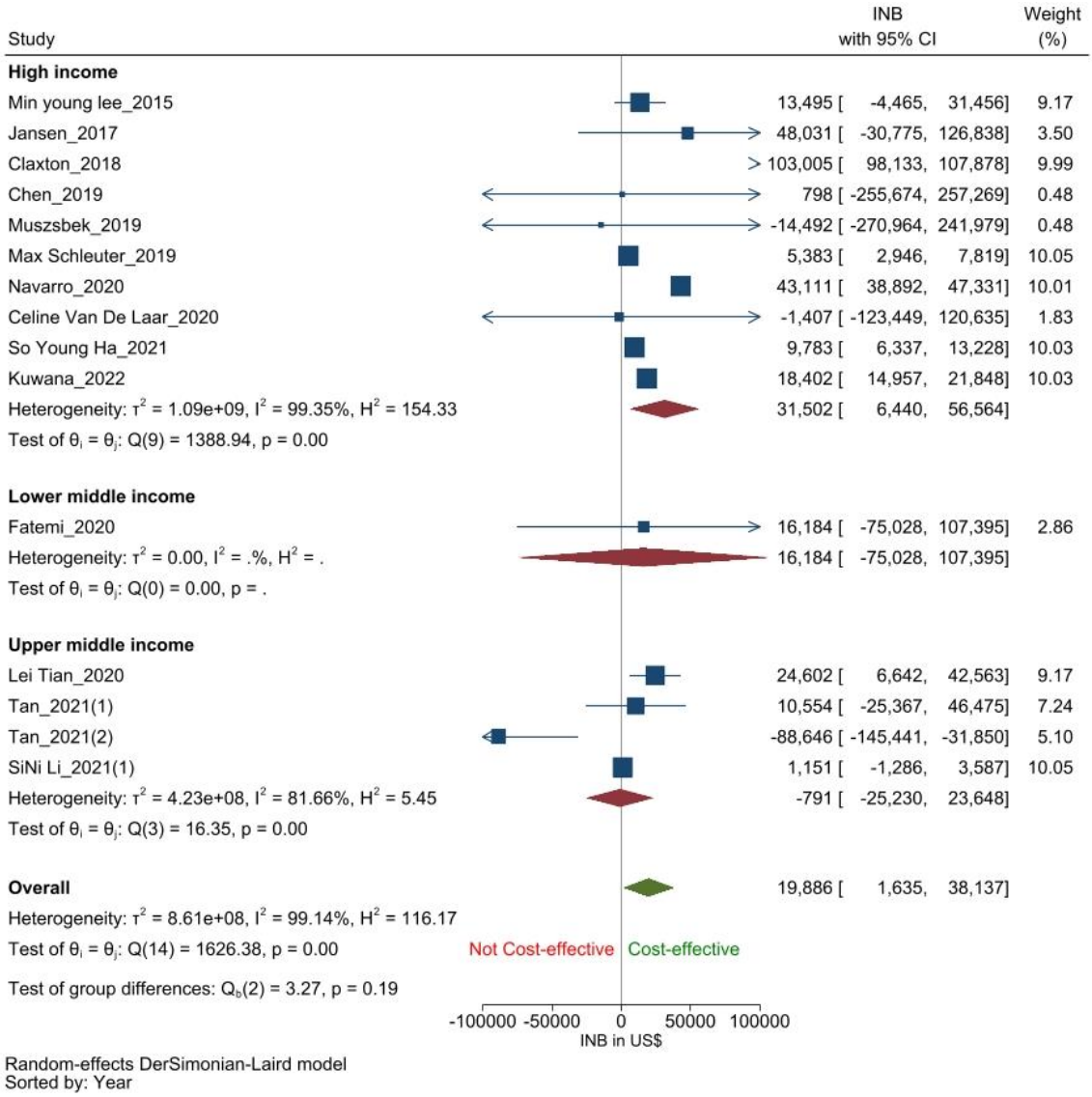
Figure 2.3.6 Subgroup analysis of pooled INBs based on study perspectives



Subgroup analysis based on income-classification found that JAK-i is cost-effective in HICs (n=10)(25, 28-30, 32, 33, 37, 38, 40, 41) with INBp $31,502 (6,440 to 56,564) and high heterogeneity (I2 = 99.35). However, the results were not significant for

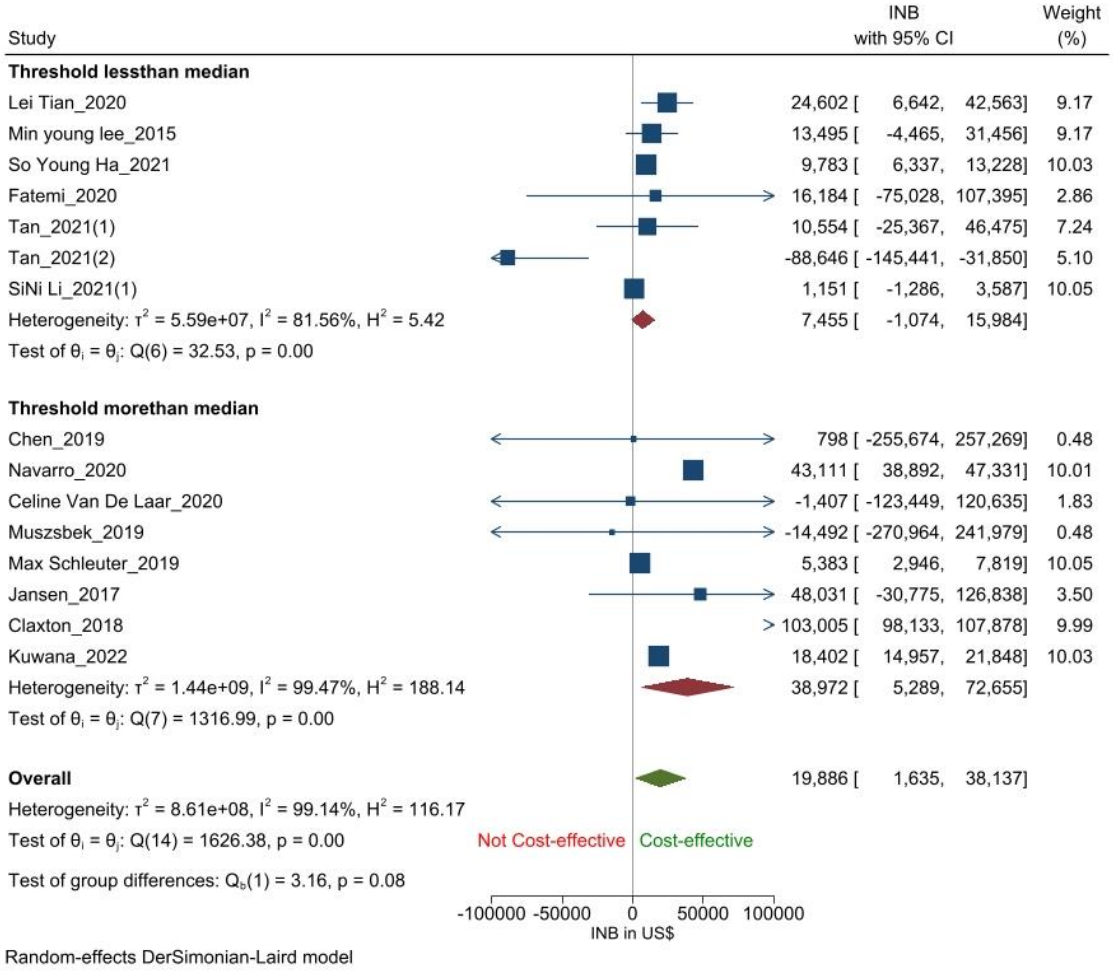
UMICs (n=4) (31, 34-36) with a pooled INB of -$791 (-25,230 to 23,648) with substantial heterogeneity (I2 = 81.66) (Figure 2.3.7).

Figure 2.3.7 Subgroup analysis of Pooled INBs based on Income classification



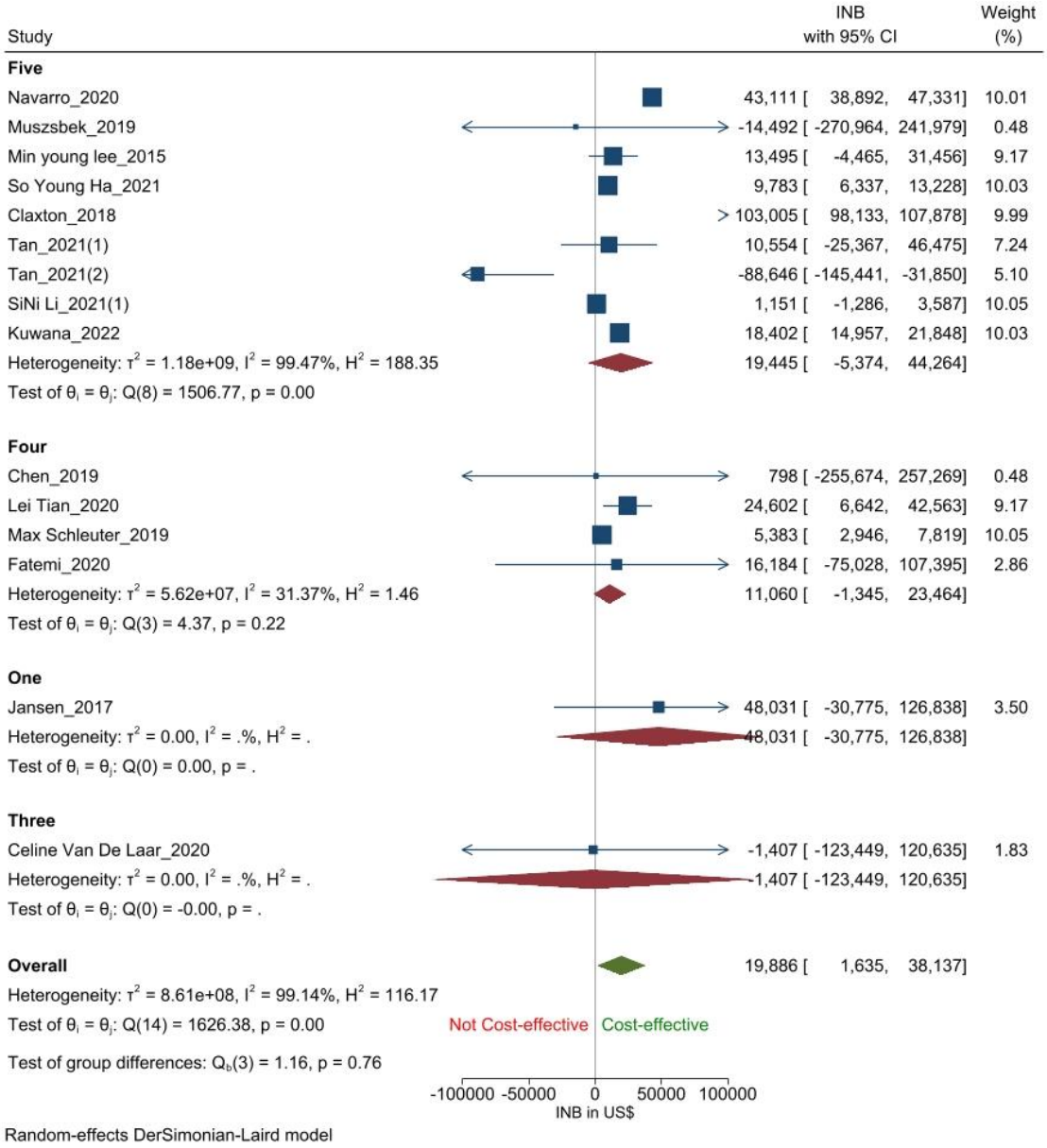
The median threshold used for the analysis is $41,118. JAK-i is significantly cost-effective for the studies when threshold is more than median value (n=8)(25, 29, 32, 33, 37, 38, 40, 41) with INBp $38,972 (95% CI 5,289 to 72,655) and high heterogeneity(I^2 = 99.47). However, JAK-i is not cost-effective for studies when the threshold is less than the median (n=7)(26, 28, 30, 31, 34-36) with an INBp of 7,455 (-1,074 to 15,984) (Figure 2.3.8).

Figure 2.3.8 Subgroup analysis of pooled INBs based on threshold



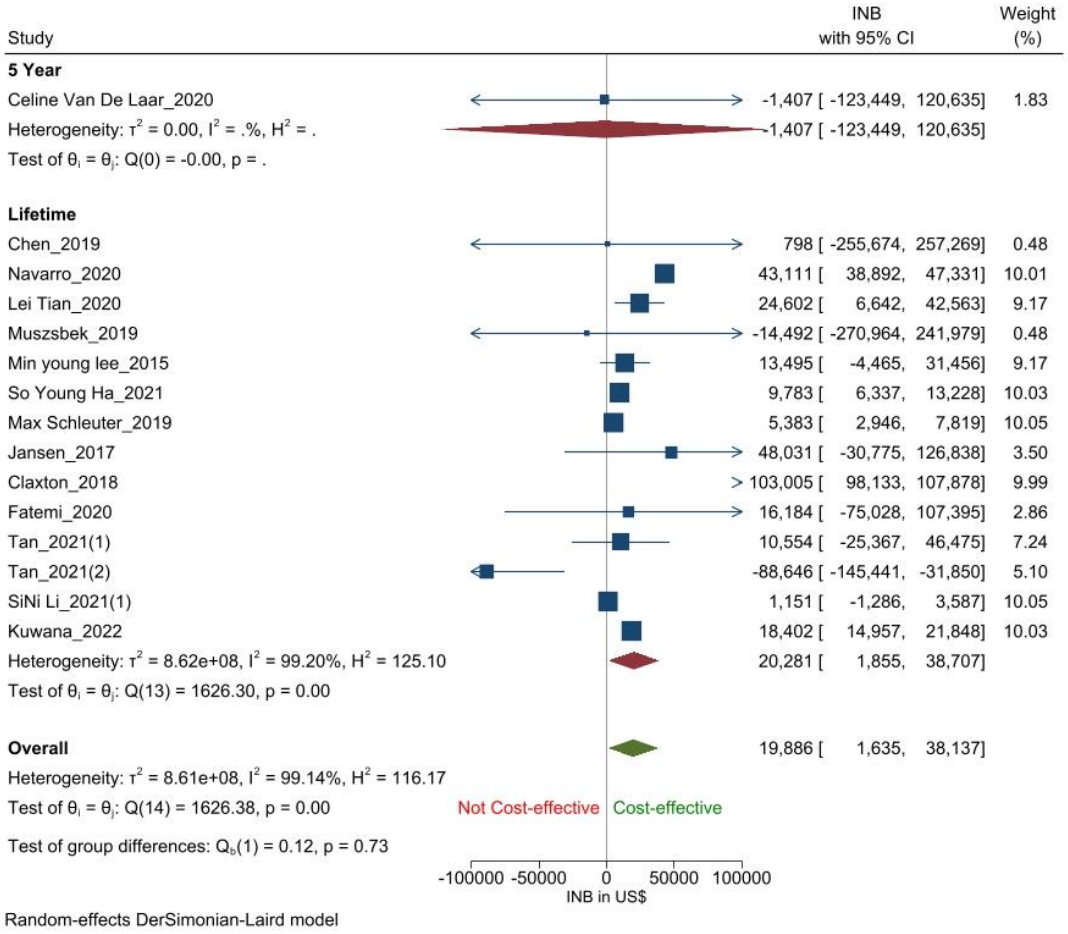
On subgroup analysis based on scenario, JAK-i is not cost-effective in scenario four (n=4)(26, 33, 36, 40) (INBp=$11,060 , -1,345 to 23,464) or scenario five (n=9)(25, 28, 30-32, 34, 35, 38, 41) (INBp=$19,145, -5,374 to 44,264) (Figure 2.3.9).

Figure 2.3.9 Subgroup analysis of pooled INBs based on scenario



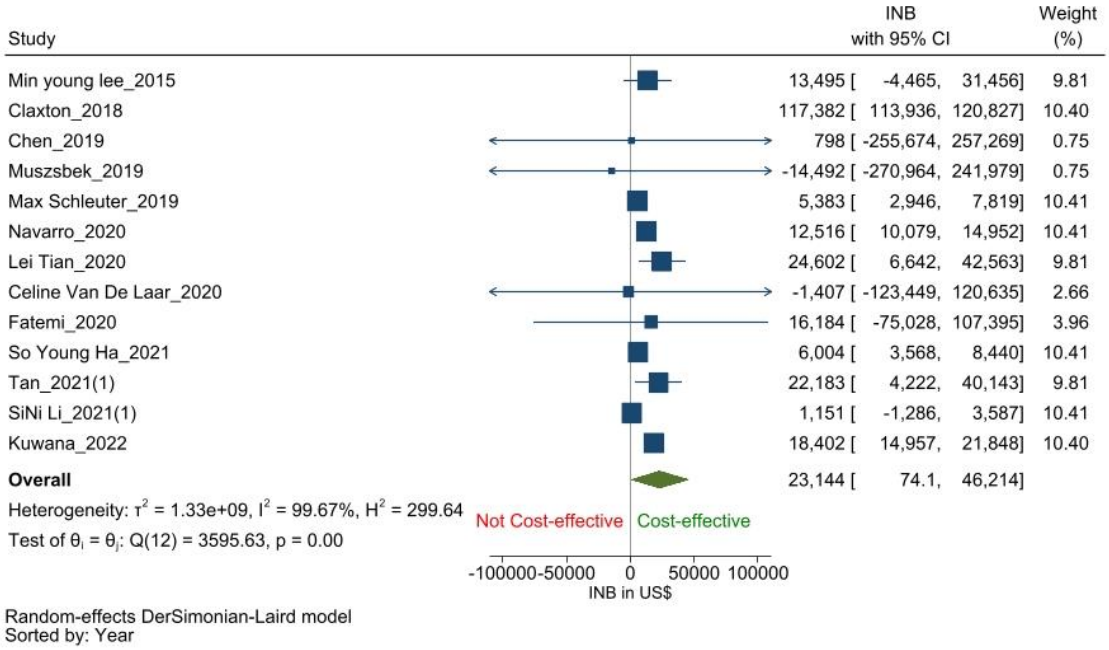
Similarly, on subgroup analysis based on time horizon (n=14), JAK-i is cost-effective with an INBp of $20,281 (1,855 to 38,707) though with high heterogeneity (I2 =99.2%) (Figure 2.3.10).

Figure 2.3.10 Subgroup analysis of pooled INBs based on time horizon



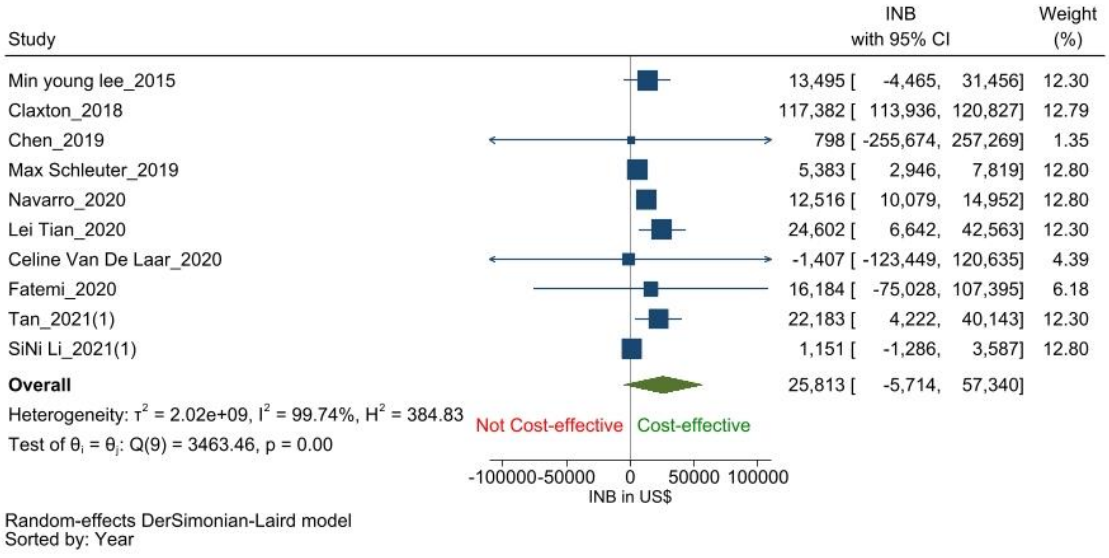
Separate analysis for the cost-effectiveness of JAK-i versus csDMARD/bDMARD as second-line treatment for csDMARD failed RA: Thirteen studies (25, 26, 28, 30-34, 36-38, 40, 41), assessed the cost-effectiveness of JAK-i versus csDMARDs (n=2), TNF-a-i (n=10) or IL-6-i (n=1) as the second-line treatment for csDMARD failed RA patients. The pooled INB from these studies was $23,144 (74.1 to 46,214) with high heterogeneity (I2=99.67%), showing that JAK-i is cost-effective than csDMARDs/bDMARDs as the second-line treatment for csDMARD failed RA patients (Figure 2.3.11).

Figure 2.3.11 Second line JAK-i vs csDMARDs/bDMARDs for csDMARD failed RA patients



Cost-effectiveness of JAK-i versus TNF-a-i as second line treatment for csDMARD failed RA: In a separate analysis, studies which compared JAK-i versus TNF-a-i as second line treatment for csDMARD failed RA were pooled. The results showed that JAK-i is not cost-effective as TNF-a-i (INBp= $25,813, -5,714 to 57,340) with high heterogeneity and I^2=99.74% (Figure 2.3.12).

Figure 2.3.12 Second line JAK-i vs TNF-a-i for csDMARD failed RA patients



However, the leave-one-out analysis found that one outlier (Claxton et al., 2018 (25)) is influencing the overall result (Figure 2.3.13) and omitting the study from the analysis makes the result cost-effective with an INBp $9,402 (3,690 to 15,115) (Figure 2.3.14).

Figure 2.3.13 Leave one out analysis for JAKi vs TNF-a-i for csDMARD failed RA

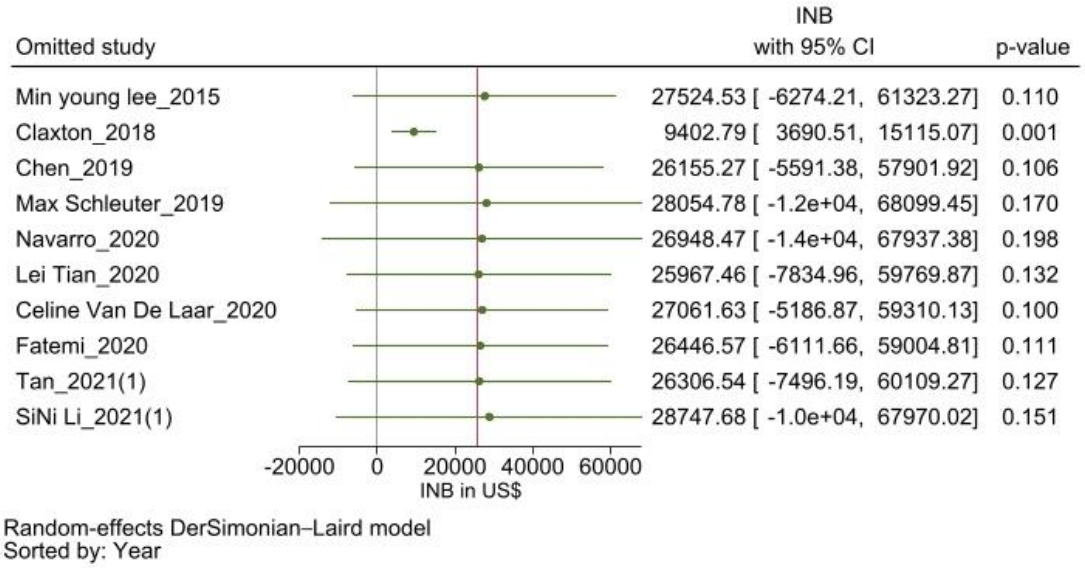
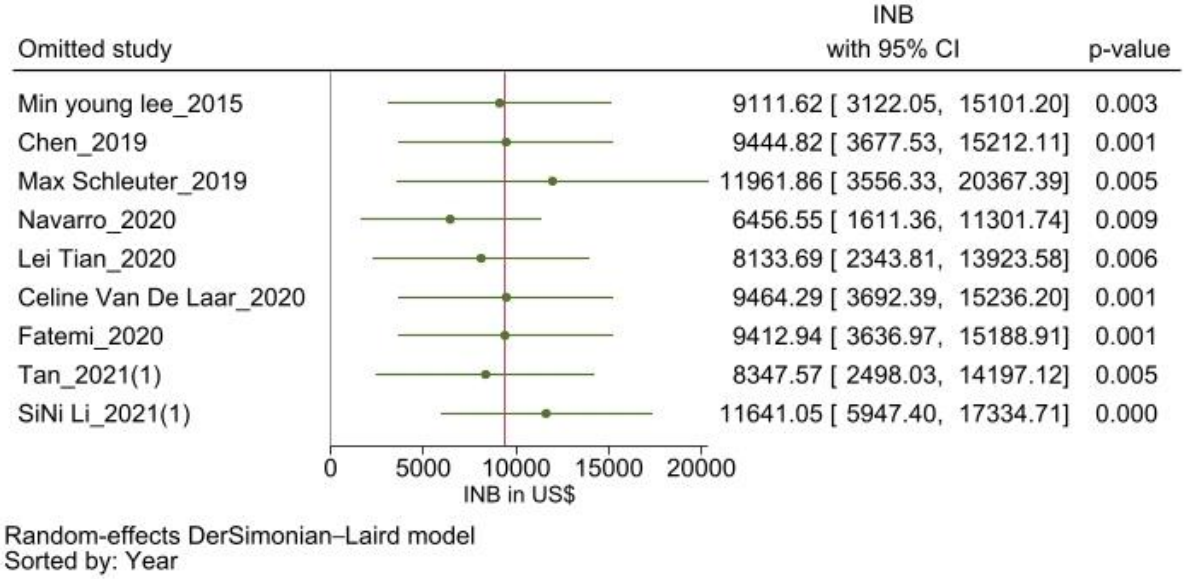
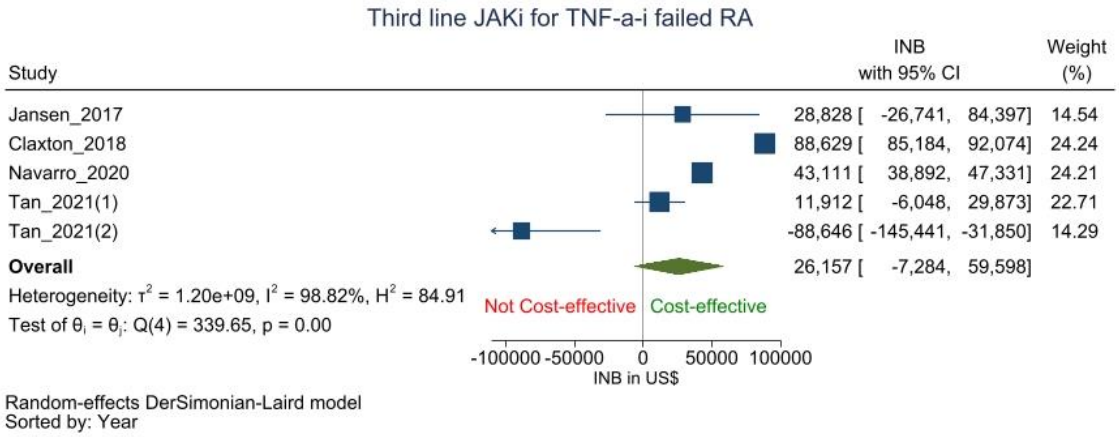


Figure 2.3.14 Leave one out analysis for JAKi vs TNFa-i in csDMARD failure patients after removing the outlier (Claxton, 2018)



Cost-effectiveness of JAK-i versus csDMARDs/bDMARDs as third-line treatment for TNF-a-i failed RA: JAK-i was compared to csDMARD/bDMARDs as the third-line treatment for RA patients who showed an inadequate response to TNF-a-i following csDMARD failure in five studies (25, 29, 32, 34, 35). The pooled INB was $26,157 (-7,284 to 59,598) with high heterogeneity (I2=99.11%) which shows that JAK-i is not cost-effective to csDMARDs/bDMARD as a third-line treatment after cs-DMARD-TNF-a-i failure (Figure 2.3.15).

Figure 2.3.15 Third line JAK-i vs csDMARDs/bDMARDs for csDMARD-TNF-a-i failed RA



Certainty of evidence- GRADE: The GRADE assessment revealed very low confidence in the overall findings and low confidence in separate analysis. The certainty of evidence from a lifetime horizon, societal perspective and HICs is low (Table 2.3.2).

Table 2.3.2 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*						**Summary of findings**			
No of studies	**Risk of Bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Publication Bias**	**Effect (US$)**		**Certainty/Quality**	**Comments**
						INB	**95%CI**		
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)	Å• • • Very Low	Less evidence from low-middle income countries and high unexplained heterogeneity. Varying population with sequential treatment strategy.
Cost-effectiveness of Second line JAK-i vs csDMARDs/bDMARDs for csDMARD failed RA patients (Assessed with meta-analysis).									
13	not serious	serious [a]	serious [b]	serious [c]	unlikely	23,144	(74.1 to 46,214)	ÅÅ• • Low	Less evidence from low-middle income countries and high unexplained heterogeneity. Varying population.
Cost-effectiveness of JAKi compared to others from societal perspective (Assessed with meta-analysis).									
4	not serious	not serious	not serious	serious	unlikely	9,976	(6,596 to 13,355)	ÅÅ• • Low	Less number of studies. Varying population with sequential treatment strategy.
Cost-effectiveness of JAKi compared to others from high income countries (Assessed with meta-analysis).									
10	not serious	serious [a]	serious	serious [c]	unlikely	31,502	(6,440 to 56,564)	ÅÅ• • Low	High unexplained heterogeneity. Varying population with sequential treatment strategy.
Cost-effectiveness of JAKi compared to others from lifetime horizon (Assessed with meta-analysis).									
14	not serious	serious [a]	serious [b]	serious [c]	unlikely	20,281	(1,855 to 38,707)	ÅÅ• • 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

2.3.4 Discussion

A systematic review and meta-analysis were conducted to synthesize the cost-effectiveness evidence of JAK-i for the treatment of moderate to severe RA. The analysis included published manuscripts from peer-reviewed journals. On overall comparison, JAK-i is cost-effective than other csDMARDs/bDMARDs but with high heterogeneity. As a second-line treatment, JAK-i is cost-effective than other csDMARDSs/bDMARDs for csDMARD-failed RA patients, but not cost-effective as a third line treatment for csDMARD-TNF-a-i failed RA patients.

The observations showed a high degree of heterogeneity, which the sub-group analysis could not explain fully. The subgroup analysis based on the income classification of the countries found that the result is cost effective only for HICs and not in LMICs or UMICs. JAK-i is similarly cost-effective from a societal perspective but there are only four studies to support this.

In RA patients who had failed csDMARDs, JAK-i was more cost-effective than other csDMARDS/bDMARDs based on our meta-analysis. However, the results lose their robustness and JAK-i become not significantly cost-effective when we limit the comparator to TNF-a-i alone in a separate analysis. Further, the leave-one-out analysis identified Claxton et al. 2019 (25) as an outlier and pooling by omitting this study (25), JAK-i turn out to be cost-effective than TNF-a-i, indicating the impact of an outlier.

In contrast to the findings of our meta-analysis, the individual studies which constituted our meta-analysis found that JAK-i is significantly cost-effective than TNF-a-i in RA patients who failed csDMARD. The reason being most of these studies reported cost-effectiveness based on ICER (point estimate) without considering any measures of dispersion whereas our meta-analysis reported pooled INB with measures of dispersion

(95% CI) which may explain the discrepancy. The GRADE assessment also rated the certainty of the evidence to be low. Therefore, future studies should consider including measures of dispersion in addition to ICER to increase the robustness of their findings.

Further, the monetary value of currencies was adjusted for inflation and purchasing power parity using the CPI and PPP index to get the pooled estimate for the most recent year. As a result, a few studies that had previously indicated JAK-i to be cost-effective were no longer found to be so after adjusting for the inflation and PPP index.

Drug costs have been the main determinants of cost-effectiveness in most of these studies, while hospitalization costs and the likelihood of serious infections are the other two factors (31). Lower drug cost and oral route of administration make JAK-i more preferable than TNF-a-i. Given the higher costs of biologics, Claxton et al. 2018(25) have hypothesized that using JAK-i as a second or third-line treatment may be less expensive than using it as a fourth-line treatment following two TNF-i failure. Similarly, corticosteroids, which are usually taken in conjunction with DMARDs, are less expensive and beneficial in reducing joint erosion and disease activity in RA. (42, 43) However, a recent study conducted in a real-world setting found that using an oral steroid concurrently did not improve the effectiveness of JAK inhibitors. (44) EULAR also recommends using the lowest possible dose of oral steroids concomitant with bDMARDs/tDMARDs for the shortest time possible; (45) hence, corticosteroids may only have a short-term effect on the cost and effectiveness of JAK-i.

According to clinical effectiveness data, JAK-i is not inferior to TNF-a-i in RA patients who have failed csDMARDs. (4-6, 46-48) Based on National institute for health and care excellence (NICE)'s report, both TOFA and BARI are equally effective as other bDMARDs at treating moderate to severe RA, when used alone or in combination with

MTX. (47-50) However, they are considered to be cost-effective options only for csDMARD IR severe RA patients and not for moderate RA. In bDMARD-IR severe RA patients, TOFA+MTX is cost-effective only when rituximab is contraindicated or not tolerated. (47-50) Further, JAK-i is more frequently linked to serious adverse events, including malignancy and cardiovascular disease (51). According to a recent study by Ytterberg et al., JAK-i is associated with a higher risk of serious infections, blood clots, cancer, and cardiovascular conditions than TNF inhibitors. (52) Based on the study, the european medicines agency (EMA) advised restricting the use of JAK-i in patients above 65 years of age, those at increased risk of serious cardiovascular issues, those who smoke or have smoked for a significant period of time in the past, and those who are at increased risk of cancer. (53) The Food and drug administration (FDA) previously came into a similar conclusion regarding an elevated risk of blood clots and death caused by JAK-i. (54) As a result, the FDA mandated the boxed warning about the risks of fatal blood clots, cancer, severe heart-related events, and death. (55)

Several limitations should be noted when interpreting the conclusions from this study. Most of the included studies were from HICs, while very few were from LMICs or UMICs and none from lower-income countries (LICs). Therefore, the results cannot be generalized to LICs, which warrants the need for cost-utility studies in the LICs setting. The majority of the included studies are model-based and assess the cost-effectiveness of treatment sequences in which JAK-i is one of the treatments in the second, third, or fourth position. Similarly, no CUA studies on other JAK-i such as UPA and FILG were found in systematic search. As a result, rather than the costs and effectiveness of an individual drug, these studies reported the costs and effectiveness of the treatment sequence. Most of the studies were undertaken from the perspective of the payer or health system with different discounting rates for costs and consequences. RA being a

chronic condition, patients suffer high indirect medical and non-medical expenses. Hence, more research that considers these costs from a societal perspective is required.

2.3.5 Conclusion

Meta-analysis suggests that JAK-I is cost-effective when used after csDMARD failure in high income countries but not cost-effective when used after csDMARD-TNF-a-i failure with low certainty of evidence.

Chapter 3 – PRIMARY CROSS-SECTIONAL STUDY

3.1 Health-related quality of life and its association with disease activity/functional status in RA

3.1.1 Introduction

Rheumatoid arthritis (RA) is an inflammatory autoimmune condition with pain and swelling in the wrist, small joints of the hand and feet, shoulders and knees [1, 2]. Recent studies indicate that RA is one of the important causes attributing to the disability-adjusted life years (DALY) both in developed and developing countries [4, 5]. The prevalence of RA in the adult Indian rural population was 0.75%, as reported by a large survey in 1993 [7]. According to the Community Oriented Program for the Control of Rheumatic Diseases (COPCORD) survey conducted between 2004 to 2007, the projected population prevalence of RA in North India was 0.15% and 0.4% in rural and urban areas, respectively [8]. India is one of the countries with the highest Age-standardized incidence rate (22.5-25.0 per 100,000 population) and DALY rate (approximately 70 per 100,000 population) for RA globally in 2017 [6]. RA causes substantial morbidity and mortality and affects about 1% of the global population [3]. The condition worsens over time, causing chronic pain and often incapacitating, which restricts the individuals' everyday routines [1]. As a result, health-related quality of life (HRQoL) in patients with RA is severely impaired in physical health, psychological health, level of independence and social relationship [179]. HRQoL measures are widely used to evaluate patient response to treatment and direct interventions that may improve patients' symptoms and quality of life. Patient-reported outcomes (PROs) such as EuroQoL 's Five-Dimensional Questionnaire (EQ-5D) [180], Short Form (SF)-6D [181] and Health Utilities Index [182] are commonly used to assess and monitor HRQoL.

Among the PROs, EQ-5D is frequently used in RA clinical trials to examine the effectiveness of newer RA treatments [183]. It is also a suggested method by the National Institute for Health and Care Excellence (NICE) for the assessment of health state utilities in health technology assessment (HTA) [184]. EQ-5D measures PROs in five-domains: mobility, self-care, usual activities, pain/discomfort, and anxiety/depression [180, 183, 185]. The single summary index value (also called 'utility score') ranging from zero (death) to one (perfect health), is calculated for each dimension's five (EQ-5D-5L) levels of responses (formerly three levels, EQ-5D-3L). Values less than 0 are possibly signifying health conditions that are deemed worse than death. The EQ-VAS reports the patient's self-rated health on a visual analogue scale of 0 to 100.

In recent years, India has been one of several developing countries shifting towards evidence-based healthcare decision-making [186, 187], which necessitates country-specific health state utilities. There are currently no or few studies on the HRQoL of RA patients in Indian settings [188]. Many EQ5D studies from Asia have been reported in RA [189]. However, utility disparities within the proportion of samples due to severity differences are frequently overlooked in the available literature [189]. As clinical remission has become a plausible outcome of any RA treatment, HRQOL measures specific to disease activity and functional status are necessary. Therefore, this study aims to estimate HRQoL in Indian RA patients of varying severity using the EQ-5D and determine its association with disease activity and functional status.

3.1.2 Methods

The report was prepared following the STROBE (Strengthening the Reporting of Observational Studies in Epidemiology) checklist [190].

Study Design and population: This cross-sectional descriptive hospital-based single-centre study was conducted at a tertiary care private multispecialty hospital in Tamil

Nadu India. Participants in the study included 320 RA patients visiting the outpatient clinic who met the inclusion criteria. Participants were recruited between April and October 2022.

Sampling: A sample size of 320 was arrived based on the prevalence of different severities in RA with 15% relative precision, 95% confidence interval, 10% non-response and design effect of 1. Systematic sampling was used, allowing every third RA patient who meets the inclusion criteria to be included in the study.

Eligibility Criteria: Patients were considered eligible if they were 18 years of age or older, had been diagnosed with RA in accordance with 2010 RA classification criteria [2] and had at least one follow-up visit after diagnosis. RA patients with other rheumatic or autoimmune diseases were excluded. Individuals who didn't speak Tamil or English were also excluded.

Data Collection: Baseline characteristics, including sociodemographic, clinical and laboratory data, were collected from the study participants through personal interviews and by referring to their medical records. A paper-based structured questionnaire was used for data collection which was standardized by pilot data collection. The training was provided to the data collectors on all aspects of the study, such as participant recruitment, data collection and data entry. Data collected were entered into MS Excel through direct data entry. The quality of the data entered was assured by having a second person check the entered data.

Measurement of Disease activity and functional status: Disease activity was assessed using Disease Activity Score-28 (DAS-28) by a trained specialist nurse. DAS-28 is calculated based on assessments of tenderness and/or swelling of 28 joints, the erythrocyte sedimentation rate (ESR), and patients' global assessment of their health on a 10 cm visual analogue scale (VAS) [22] [191]. DAS-28 ≤2.6, >2.6 to ≤3.2, >3.2 to 5.1

and ≥5.1 indicates remission, low disease activity (LDA), moderate disease activity (MDA) and high disease activity (HDA), respectively [22]. The functional status of the study participants was measured using the Indian version of the Health Assessment Questionnaire (HAQ) [192]. HAQ disability index scores of 0-1, 1.1-1.5 and 1.5-3.0 indicate mild, moderate and severe functional disability, respectively [192]

Measurement of HRQol: HRQol was estimated using the EQ-5D-5L questionnaire administered to the participants in a personal interview. The questionnaire covers five domains: mobility, self-care, usual activities, pain/discomfort and anxiety/depression. It explores five levels of problems specified as no problem, slight problems, moderate problems, severe problems and unable to or extreme problems [180, 185]. The levels of perceived problems were coded from 1 to 5, and each state was referred to be a 5-digit code. EQ-5D health states thus elicited were converted to a single index value using the EQ-5D value set for India [193]. The EQ VAS scale was used to assess the self-evaluated health on a scale of 0 to 100.

Data Analysis: Demographic and baseline patient characteristics were reported as mean and standard deviation (SD) for continuous data and number and percentage for categorical data. Mean EQ-5D scores with SD for RA was reported. EQ-5D scores were sub-grouped based on disease activity (measured by DAS-28) and functional status (measured by HAQ). Proportions, mean EQ-5D and mean EQ-VAS for each subgroup were reported with the dispersion measures. Correlation and multiple linear regression analyses were performed to identify independent factors associated with EQ-5D and EQ-VAS. A p-value of less than 0.05 was considered to be statistically significant. All the analyses were performed using and STATA 17.0 [194].

This study was conducted in accordance with the ethical principles of the Declaration of Helsinki. The study protocol was approved by the ethics committee of ICMR-

National Institute of Epidemiology (ICMR-NIE) (NIE/IHEC/202101-01) and CMMH (CMMHEC/21/09). All the study participants had provided written informed consent to participate in the study in the presence of a witness. A copy of the signed informed consent form is maintained in the study records.

3.1.3 Results

Characteristics of study participants: The study included 320 RA patients aged (mean ± standard deviation) 55.57±12.29 yrs, among which 88.1% were females. 76.5% of the females were homemakers. The mean disease duration was 8.65 ± 7.47 years. The predominant comorbidity observed among the patients was hypertension (31.9%), followed by Type 2 Diabetes (26.6) and Thyroid Disease (26.6%). Other comorbidities included heart attack (0.9%), coronary artery disease (1.6 %), hyperlipidemia (5%), asthma (3.4%) and cancer (1.6%). 18.5% of patients had undergone cataract surgery. Among the females, 17.73 % had undergone a hysterectomy, out of which 82% had it done years before the onset of RA. Most patients (94.38%) reported joint pain as their first symptom at diagnosis. The most common symptom self-reported by the participants at baseline visit was also joint pain (89.38%) followed by joint swelling (67.50%), morning stiffness (65.63%), tarsal tunnel, carpal tunnel syndrome (31.25%), subcutaneous nodule (20.31%), radiographic erosion (12.19%), fever (12.19%), and Raynaud's phenomenon (7.19%). 83.75% of patients had elevated ESR (Males:>15mm/hr, Females: >20mm/hr). A majority (85%) of the study participants had moderate/high disease activity (DAS-28>3.2), and 32.8% had a severe functional disability (HAQ >1.5). The study participants' baseline characteristics are tabulated in Table 3.1.1

Table 3.1.1 Characteristics of Study Participants

		N=320, Mean (SD) or n (%)
Age (in years)		55.57 (12.29)
Females		282 (88.1%)
Literate		286 (89.4%)
Working		66 (21.2%)
Urban		299 (93.4%)
Not smoking		310 (96.9%)
Alcohol use		9 (2.8%)
Weight (in Kgs)		65.83 (14.14)
Height (in cms)		155.21 (7.74)
Body mass index		27.43 (5.62)
Rheumatoid factor	Positive	236 (73.7%)
	Negative	69 (22.6%)
	Not Available	15 (4.7%)
Anti-cyclic citrullinated peptide	Positive	188 (58.8%)
	Negative	80 (25.0%)
	Not Available	52 (16.2%)
DAS-28		4.71 (1.38)
HAQ		1.08 (0.65)
Disease duration (years)		8.65 ± 7.47
Self-reported comorbidities		
Hypertension		102 (31.9%)
Diabetes mellitus		85 (26.6%)
Heart attack		3 (0.9%)
CAD		5 (1.6 %)
Hyperlipidemia		16 (5.0%)
Asthma		11 (3.4%)
Thyroid		85 (26.6%)
Cancer		5 (1.6%)
Laboratory results		
Haemoglobin (g/dL)		11.59 (5.45)
RBC count ($x10^9$/L)		6.73 (25.66)
WBC count ($x10^9$/L)		8120.05 (5402.33)
Platelet count ($x10^9$/L)		1395.17 (20053.63)
ESR (mm/hour)		43.08 (23.01)
Random Blood Glucose (mg/dL)		132.84 (52.34)
Blood Urea (mg/dL)		24.66 (8.16)
Aspartate Transaminase (U/L)		24.25 (10.21)
Alanine transaminase (ALT)(IU/L)		22.78 (14.70)
Alkaline Phosphatase (IU/L)		88.08 (28.15)

DAS-Disease activity score; HAQ- Health Assessment Questionnaire; RBC- Red Blood Cells; WBC- White Blood Cells

syndrome (37.81%), dry mouth (35.94%), weight loss (32.50%), dry eyes (31.56%),

Table 3.1.2 HRV parameters of RA patients

HRV parameters	Median ± IQR
Sample size	314
Average RR (ms)	762.1±133.3
Median RR (ms)	761.5±134.8
SDRR ms	32.6±31.5
CVRR	0.04±0.38
Average rate BPM	78.8±13.9
SD rate BPM	3±2.2
SDSD (ms)	27.2±42.8
RMSSD (ms)	27.2±42.8
pRRx%	1.1±8.1
SD 1 $(ms)^2$	19.2±30.3
SD 2 $(ms)^2$	39.6±32.1
SDARR (ms)	0.00±4.9
Total power $(ms)^2$	875.1±1898.8
VLF power $(ms)^2$	289.7±481.9
LF power $(ms)^2$	186.8±426.3
HF power $(ms)^2$	261.7±928.9
LF/HF	0.6±1.02

SDRR- Standard deviation of RR intervals; CVRR- Coefficient of variation; BPM- beats per minute; SD- standard deviation; SDSD- Standard deviation of successive RR interval differences; RMSSD-Root mean square of successive RR interval differences; pRRx%- percentage of RR interval; SD 1 ms^2- Standard deviation of the differences between adjacent RR intervals; SD 2 ms^2- Standard deviation of the differences between adjacent RR intervals calculated over a larger number of intervals; VLF-Very low frequency; LF-Low frequency; HF-high frequency ; ms-milli seconds.

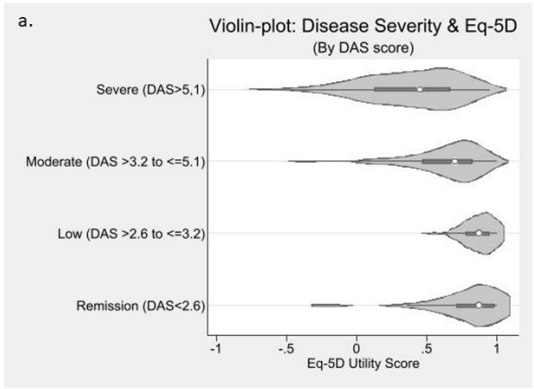
The EQ-5D utility score was 0.54±0.36, and the EQ-VAS was 63.05±18.54. Based on the EQ-5D domain, 49.6% had at least moderate problems in mobility, 74.4% had at least moderate pain/discomfort, and 53.1% had at least moderate problems in anxiety/depression. Most of the patients had no problem/slight problem in self-care (77.8%) and carrying out their usual activities (63.1%) (Table 3.1.2).

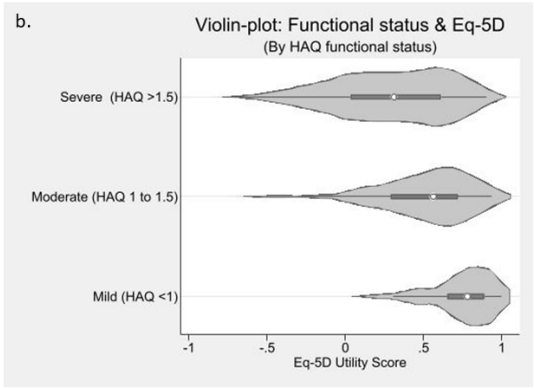
Table 3.1.3 Descriptive statistics of EQ5D Domains

	Mobility N (%)	Self-care N (%)	Usual activities N (%)	Pain/ Discomfort N (%)	Anxiety/ Depression N (%)
No problem	84 (26.3%)	182 (56.9%)	120 (37.5%)	21 (6.6%)	89 (27.8%)
Slight problem	77 (24.1%)	67 (20.9%)	82 (25.6%)	61 (19.1%)	61 (19.1%)
Moderate problem	115 (35.9%)	56 (17.5%)	93 (29.1%)	139 (43.4%)	84 (26.3%)
Severe problem	43 (13.4%)	12 (3.8%)	22 (6.9%)	76 (23.8%)	59 (18.4%)
Extreme problem	1 (0.3%)	3 (0.9%)	3 (0.9%)	23 (7.2%)	27 (8.4%)

EQ-5D utility scores and EQ-5D VAS significantly differed between RA patients based on disease activity and functional status (Figure 3.1.1 and Table 3.1.3). The utility score was lowest in patients with high disease activity (DAS>5.1) (0.365 (0.302 to 0.429)) and severe functional disability (HAQ>1.5) (0.276 (0.204 to 0.348)).

Figure 3.1.1 Relationship between disease activity and functional status and EQ-5D score





Disease activity	N=320	EQ5D (Mean & 95% CI)
Remission (DAS<2.6)	21 (6.6%)	0.773 (0.642 to 0.904)
Low (DAS>2.6 to ≤3.2)	27 (8.4%)	0.862 (0.812 to 0.911)
Moderate (DAS>3.2 to ≤5.1)	141 (44.1%)	0.611 (0.561 to 0.661)
Severe (DAS>5.1)	131 (40.9%)	0.365 (0.302 to 0.429)

Functional Status	N=320	EQ5D (mean & 95% CI)
Mild (HAQ <1)	159 (49.7%)	0.738 (0.706 to 0.770)
Moderate (HAQ 1 to 1.5)	56 (17.5%)	0.485 (0.398 to 0.572)
Severe (HAQ >1.5)	105 (32.8%)	0.276 (0.204 to 0.348)

Table 3.1.4 Relationship between disease activity and functional status and EQ-VAS

	N=320 n(%)	Mean EQ VAS (%) (mean & 95% CI)
Disease activity		
Remission (DAS<2.6)	21 (6.6%)	82.14 (73.86 to 90.43)
Low (DAS>2.6 to ≤3.2)	27 (8.4%)	78.52 (72.61 to 84.42)
Moderate (DAS>3.2 to ≤5.1)	141 (44.1%)	64.81 (61.84 to 67.77)
Severe (DAS>5.1)	131 (40.9%)	55.03 (52.39 to 57.67)
Functional Status		
Mild (HAQ <1)	159 (49.7%)	71.42 (68.51 to 74.33)
Moderate (HAQ 1 to 1.5)	56 (17.5%)	59.21 (55.56 to 62.87)
Severe (HAQ >1.5)	105 (32.8%)	52.43 (49.68 to 55.18)

DAS-Disease activity score; EQ-5D- EuroQol five dimensions; EQ VAS- EuroQol Visual Analogue Scale; HAQ- Health Assessment Questionnaire

Correlation and multiple linear regression analyses: Correlation among EQ-5D utility values, age, BMI, ESR, disease duration, HAQ score, EQ5D VAS and DAS-28 score was analyzed. Based on the correlation results, HAQ and Age were considered independent variables to predict the EQ-5D utility values in a multiple linear regression model. The fitted regression model was: [EQ-5D = 0.665 - 0.376 (HAQ) + 0.005 (Age)]. The overall regression was statistically significant [R^2 = 0.485, df=(2, 317), F-value= 151.02, p<0.001]. It was observed that HAQ (β=-0.690, p<0.001) and age (β=0.177, p<0.001) significantly predicted EQ-5D utility values (Table 3.1.4).

Table 3.1.5 Results of Correlation analysis

Correlation coefficient	EQ-5D	Age	BMI	ESR	Disease duration	HAQ Score	VAS Disease activity	DAS-28 Score
EQ-5D		0.122*	-0.081	-0.180**	0.003	-0.676**	-0.354**	-0.492**
Age	0.122*		-0.018	0.107	0.237**	0.079	0.041	0.069
BMI	-0.081	-0.018		0.011	-0.008	0.027	-0.048	0.049
ESR	-0.180**	0.107	0.011		0.060	0.263**	0.126*	0.475**
Disease duration	0.003	0.237**	-0.008	0.060		0.197**	0.030	0.014
HAQ Score	-0.676**	0.079	0.027	0.263**	0.197**		0.381**	0.505**
VAS Disease activity	-0.354**	0.041	-0.048	0.126*	0.030	0.381**		-0.483**
DAS-28 Score	-0.492**	0.069	0.049	0.475**	0.014	0.505**	-0.483**	
*. Correlation is significant at the 0.05 level (2-tailed).								
**. Correlation is significant at the 0.01 level (2-tailed).								

BMI-Body mass index; DAS-Disease activity score; EQ-5D- EuroQol five dimensions; EQ VAS-EuroQol Visual Analogue Scale; ESR-Erythrocyte sedimentation rate; HAQ- Health Assessment Questionnaire

However, in situations with only the availability of DAS-28 score, to predict EQ-5D utility values. A multiple regression model was built with DAS-28, and age significantly predicted the EQ-5D. The fitted regression model was: [EQ-5D = 0.898 - 0.130 (DAS-28) + 0.005 (age)]. The overall regression was statistically significant [R^2 = 0.262, df=(2, 317), F-change= 57.56, p <0.001]. It was found that DAS-28(β=-0.503, p<0.001) and Age(β=0.157, p=0.001) significantly predicted EQ-5D utility values.

However, considering situations with only the availability of the DAS-28 score, a multiple regression model was built with DAS-28 and Age. The fitted regression model was: [EQ-5D = 0.898 - 0.130 (DAS-28) + 0.005 (Age)]. The overall regression was statistically significant [R^2 = 0.262, df=(2, 317), F-change= 57.56, p <0.001]. It was found that DAS-28 (β=-0.503, p<0.001) and Age (β=0.157, p=0.001) significantly

predicted EQ-5D utility values.

3.1.4 Discussion

In this cross-sectional study, we have estimated the mean EQ-5D utility score of RA patients and the majority reported at least slight problems in the EQ-5D-5L pain/discomfort domain. Utility scores were lowest in patients with high disease activity and severe functional disability. HAQ and age independently predicted EQ-5D in correlation analysis.

This is the first study that presents the health utility score for RA in India. An EQ-5D index value of 0.44±0.30 was observed for a subgroup of Indian RA patients with moderate-to-severe disease activity in the GO-MORE study, which examined the efficacy and safety of golimumab [188]. A meta-analysis of EQ-5D studies in RA from Asia found that lower EQ-5D scores were associated with more severe disease activity, advancing age, and female gender, with a pooled mean EQ-5D utility of 0.66. (0.63 to 0.69) [189]. Similar to this, a meta-analysis of EQ-5D studies from European nations found that patients receiving biologic therapy had a utility score of 0.66 (0.63 to 0.69), and patients receiving non-biologic treatment had a utility score of 0.38 (0.23 to 0.53) [195]. Most of our study population had moderate to severe disease, resulting in lower utility, with pain and anxiety being the most affected domains. In our study, disease activity and functional status substantially impacted RA patients' health utilities. According to the literature, patients with RA had lower HRQoL utility scores than the general population, and strongly linked to disease activity as measured using DAS-28 [196]. Similarly, HRQoL utility values (EQ-5D) and functional status (HAQ scores) were moderately to strongly associated [197].

In general, characteristics including age, sex, comorbidities, urban/rural location, and others factors may also impact HRQoL utilities [198]. As people get older and their health

deteriorates, utility values also tend to decrease [198]. In our study, correlation and regression analysis found age to be an independent predictor of EQ-5D. Likewise, it was noticed that men had a higher HRQoL than women in most studies that reported on sex-specificHRQoL utility values [199]. However, in our study, there was no significant difference in utility scores between male and female patients with RA. However, it is to be noted that most of our study participants are females.

Our study has a few limitations. The sample's representativeness of the target population could not be guaranteed because our study was a hospital-based single-centre study, which warrants similar multi-centre studies in the future. At least 60% of the participants in our study had co-morbid conditions. However, owing to the small size, distinct EQ-5D scores for RA with each comorbidity could not be determined. Since measuring HRQoL is becoming an integral component of assessing health technologies, our study results will be a source of data for cost-utility studies in RA in India when new interventions for RA become available.

3.1.5 Conclusion

In conclusion, RA significantly impacts HRQoL, and interventions focussing on pain and anxiety management are essential. The study’s EQ-5D values, as well as its measures of association with HAQ and DAS-28, could help estimate HRQoL while conducting economic evaluation studies in RA.

3.2 Assessing the out-of-pocket expenditure in RA

3.2.1 Introduction

Rheumatoid arthritis (RA) is a chronic autoimmune disease causing inflammation, pain, and stiffness that afflicts women up to five times more than men [1]. It causes significant morbidity and mortality, affecting 1% of the world population [3]. In India, the prevalence of RA is estimated to be 0.7% [200] which is higher than the global prevalence of 0.46% [201]. Most of RA patients suffer long-lasting illnesses, which significantly reduce their levels of physical activity and negatively impact their quality of life [202]. The treatment of RA has evolved over the last few decades, particularly since the advent of biological/targeted DMARDs [203]. Conventional synthetic disease-modifying anti-rheumatic drugs (csDMARDs) are prescribed as the first-line treatment for RA according to the standard treatment guidelines [204, 205]. With csDMARDs failure, newer treatments such as biological /targeted DMARDs are recommended [206].

RA treatment is expensive, particularly with biologics/targeted therapies, which has a significant economic impact [206]. The healthcare system in India is characterized by a mix of public and private providers. The majority of Indians seek treatment from the private sector, where over two-thirds of overall health spending is through out-of-pocket [207]. The high cost of care and a lack of health insurance coverage exacerbate the financial strain on households in the lower-socioeconomic strata [208].

RA exacerbates tremendous economic and social consequences in terms of lower quality of life, higher medical costs, productivity loss, and early retirement [92, 209]. Prior studies have revealed that increasing out-of-pocket spending can lead to financial catastrophe for households, especially from lower-middle-income countries (LMICs) [210-212]. However, no such studies are conducted in RA from an Indian setting. Given this context, data on out-of-pocket expenditure (OOPE) and catastrophic health

expenditure (CHE) among RA patients as well as the proportion of families experiencing CHE, are needed to estimate the economic burden. The purpose of the study is to estimate the burden of CHE and its major determinants of RA patients and their households and to give an insight into the economic impact of RA in Tamil Nadu, India.

3.2.2 Methods

We conducted a cross-sectional descriptive hospital-based single-centre study at a tertiary care private multispecialty hospital in Tamil Nadu, India. The study comprised 320 RA patients who visited the outpatient clinic from April to October 2022 and satisfied the inclusion criteria. Sample size estimation was performed apriori with 15% relative precision, 95% confidence interval (CI), 10% non-response, and a design effect of 1. Using systematic sampling, every third RA patient who met the inclusion criteria was included in the study. RA Patients over 18 years who have had at least one follow-up visit following diagnosis are considered eligible for participation in the study. Patients with RA who also had other rheumatic or autoimmune disorders were not included.

A pretested paper-based structured interview schedule available in English and Tamil was used to collect information from the study participants. Along with personal and household income details, socio-demographic data, such as age, gender, location, education level, occupation, household size, number of earning members in the household, as well as health care utilization data on the number of visits to the hospital, hospitalizations, medicine costs, physician fee, lab test charges were collected. We also collected non-medical costs such as food, accommodation, and transportation for the patient and the caregiver. Further data on insurance availability, premiums paid, and reimbursement were also collected. The rigorous training of interviewers on all aspects of the study helped to maintain quality data collection. The collected data were entered

into Microsoft Excel, version 2019 [213], and the quality of the data entry was ensured by having a second-person review. Out of the total 320 participants interviewed, five were not included in the calculation of CHE due to their refusal to disclose income details.

Data Analysis: Demographic and baseline patient characteristics were reported using frequencies, percentages, mean, median, standard deviation (SD), and interquartile range (IQR). Income, direct medical, direct non-medical, indirect cost, and OOPE were expressed as mean (95% CI) or median (IQR). All costs are reported in Indian rupee (₹) and US dollar ($), with a conversion factor of 1 US$ = ₹82.4 [214].

CHE is defined as health expenditure that exceeds a certain threshold of a patient's/family's ability to pay, and medical expenses over and above the threshold are considered a significant financial burden for households. Based on previous research [210, 215-217], we defined CHE as spending more than 10% of the total household annual income on medical expenses due to RA and estimated the proportion of CHE. Also, as sensitivity analysis, we reported CHE considering 5% and 20% of the total household annual income scenarios.

Pearson's Chi-square test for association was used to identify statistical significance, and multivariable logistic regression analyses were performed to identify major determinants associated with CHE. We also used concentration indices and the Lorenz curve to report the inequality in household annual income and CHE among the study participants. The concentration index measures inequality in the distribution of a variable of interest. The concentration index value ranges from -1 to 1, with -1 indicating that the outcome is concentrated in the lower socioeconomic group. A value of 1 suggests that the result is concentrated among the higher socioeconomic group. The Lorenz curve, which depicts the cumulative percentage of the outcome versus the variable of interest, is a graphical representation of the concentration index. The degree

of inequality in the distribution of the outcome is represented by the gap between the 45-degree line of equality and the Lorenz curve. Violin plots are used to visualize the distribution and the density of multiple variables. A p-value <0.05 was considered statistically significant. All the analyses were performed using Stata V.17 [218].

3.2.3 Results

General characteristics of study participants:

The majority of the study participants were females (88.1%) with mean age (SD) of 55.57±12.29 years. Almost 93 per cent of participants were from urban, and 89.4 per cent were literate. The patient's household size ranged from 1 to 12, with a median (IQR) of 4 (2), and nearly 77 per cent of the households had one to three earning members in their family. Less than 3 per cent of the participants have smoking and alcohol consumption habits. As per BMI, 34.7 per cent were overweight, 28.1 per cent were healthy, 27.2 per cent were obese, and the rest (3.4%) were underweight. The mean disease duration among the participants was 8.65 ± 7.47 years with a median (IQR) of 7 (33), and 85 per cent of the study participants had moderate to severe disease activity [disease activity score (DAS)28>3.2]. At the same time, nearly 33 per cent reported a severe functional disability [Health Assessment Questionnaire (HAQ)>1.5]. Only 8.1 per cent of participants said having health insurance, and 51.4 per cent of patients were assessed to have CHE. Table 3.2.1 depicts the general characteristics of the 320 RA patients examined in this study.

Table-3.2.1 General characteristics of study participants and frequency of facing CHE.

Variables	Categories	Numbers (n=320)	Frequency of facing CHEs (n=315)		Sig
			CHE- No (N= 153)	CHE-Yes (N= 162)	
Gender	Male	38 (11.9)	21 (13.7)	17 (10.5)	0.379
	Female	282 (88.1)	132 (86.3)	145 (89.5)	
Age	18 to 30 years	8 (2.5)	7 (4.5)	1 (0.6)	0.148
	30 to 50 years	103 (32.2)	48 (31.4)	53 (32.7)	
	50 to 70 years	174 (54.4)	83 (54.3)	88 (54.3)	
	More than 70 years	35 (10.9)	15 (9.8)	20 (12.4)	
Place of residence	Urban	299 (93.4)	148 (97.3)	147 (90.7)	0.029
	Rural	21 (6.6)	5 (2.3)	15 (9.3)	
Household size	1 to 2	103 (32.2)	37 (24.2)	66 (40.7)	<0.001
	3 to 5	168 (52.5)	94 (61.4)	72 (44.4)	
	More than 5	37 (11.5)	21 (13.7)	15 (9.3)	
	Not Reported	12 (3.8)	1 (0.7)	9 (5.6)	
Education status	Literate	32 (10.0)	146 (95.4)	136 (84.0)	0.003
	Illiterate	286 (89.4)	6 (3.9)	25 (15.4)	
	Not reported	2 (0.6)	1 (0.7)	1 (0.6)	
Employment status	Working	66 (20.6)	42 (27.5)	24 (14.8)	0.009
	Not working	245 (76.6)	105 (68.6)	135 (83.3)	
	Not reported	9 (2.8)	6 (3.9)	3 (1.9)	
Household Earning members	None	13 (4.1)	1 (0.7)	12 (7.4)	<0.001
	1 to 3	270 (84.3)	133 (87.7)	136 (84.0)	
	4 and above	21 (6.6)	17 (10.2)	3 (1.8)	
	Not Reported	16 (5.0)	2 (1.4)	11 (6.8)	

Variables	Categories	Numbers (n=320)	Frequency of facing CHEs (n=315)		Sig
			CHE- No (N= 153)	CHE-Yes (N= 162)	
Household Income quartile #	First	124 (39.4)	11 (7.2)	113 (69.7)	<0.001
	Second	51 (16.1)	23 (15.0)	28 (17.3)	
	Third	68 (21.6)	51 (33.3)	17 (10.5)	
	Fourth	72 (22.9)	68 (44.5)	4 (2.5)	
Smoking	Yes	9 (2.8)	3 (2.0)	6 (3.7)	0.353
Drinking	Yes	8 (2.5)	2 (1.3)	6 (3.7)	0.177
BMI	Underweight (<18.5)	11 (3.4)	6 (3.9)	5 (3.1)	0.084
	Healthy (18.5 to <25)	90 (28.1)	46 (30.1)	41 (25.3)	
	Overweight (<25 to 30)	111 (34.7)	60 (39.2)	50 (30.9)	
	Obesity (>30)	87 (27.2)	31 (20.3)	56 (34.5)	
	Not reported	21 (6.6)	10 (6.5)	10 (6.2)	
Insurance availability	Yes	26 (8.1)	15 (9.8)	11 (6.8)	0.331
Carpal tunnel	Yes	100 (31.3)	43 (28.1)	55 (34.0)	0.263
	No	220 (68.7)	110 (71.9)	107 (66.0)	
Tarsal tunnel	Yes	121 (37.8)	57 (37.2)	63 (38.9)	0.765
	No	199 (62.2)	96 (62.8)	99 (61.1)	
Disease Duration	Less than 1 year	44 (13.8)	26 (17.0)	18 (11.1)	0.188
	1 to 5 years	81 (25.3)	40 (26.1)	40 (24.7)	
	5 to 10 years	86 (26.9)	33 (21.6)	51 (31.5)	
	10 to 20 years	88 (27.5)	46 (30.1)	41 (25.3)	
	More than 20 years	21 (6.6)	8 (5.2)	12 (7.4)	
Rheumatoid Factor	Positive	237 (74.0)	111 (72.6)	122 (75.3)	0.278
	Negative	69 (21.6)	38 (24.8)	31 (19.1)	

Variables	Categories	Numbers (n=320)	Frequency of facing CHEs (n=315)		Sig
			CHE- No (N= 153)	CHE-Yes (N= 162)	
	Not reported	14 (4.4)	4 (2.6)	9 (5.6)	
Anti-cyclic citrullinated peptide	Positive	188 (58.8)	90 (58.8)	95 (58.6)	0.988
	Negative	80 (25.0)	39 (25.5)	41 (25.3)	
	Not reported	52 (16.2)	24 (15.7)	26 (16.1)	
Functional status	Mild (HAQ <1)	159 (49.7)	84 (54.9)	73 (45.1)	
	Moderate (HAQ 1 to 1.5)	56 (17.5)	26 (17.0)	30 (18.5)	0.191
	Severe (HAQ >1.5)	105 (32.8)	43 (28.1)	59 (36.4)	
Disease activity	Remission (DAS <2.6)	21 (6.6)	13 (8.5)	8 (4.9)	0.020
	Low (DAS 2.6 to <3.2)	27 (8.4)	17 (11.1)	9 (5.6)	
	Moderate (DAS 3.2 to <5.1)	141 (44.1)	73 (47.7)	67 (41.4)	
	Severe (DAS>5.1)	131 (40.9)	50 (32.7)	78 (48.1)	

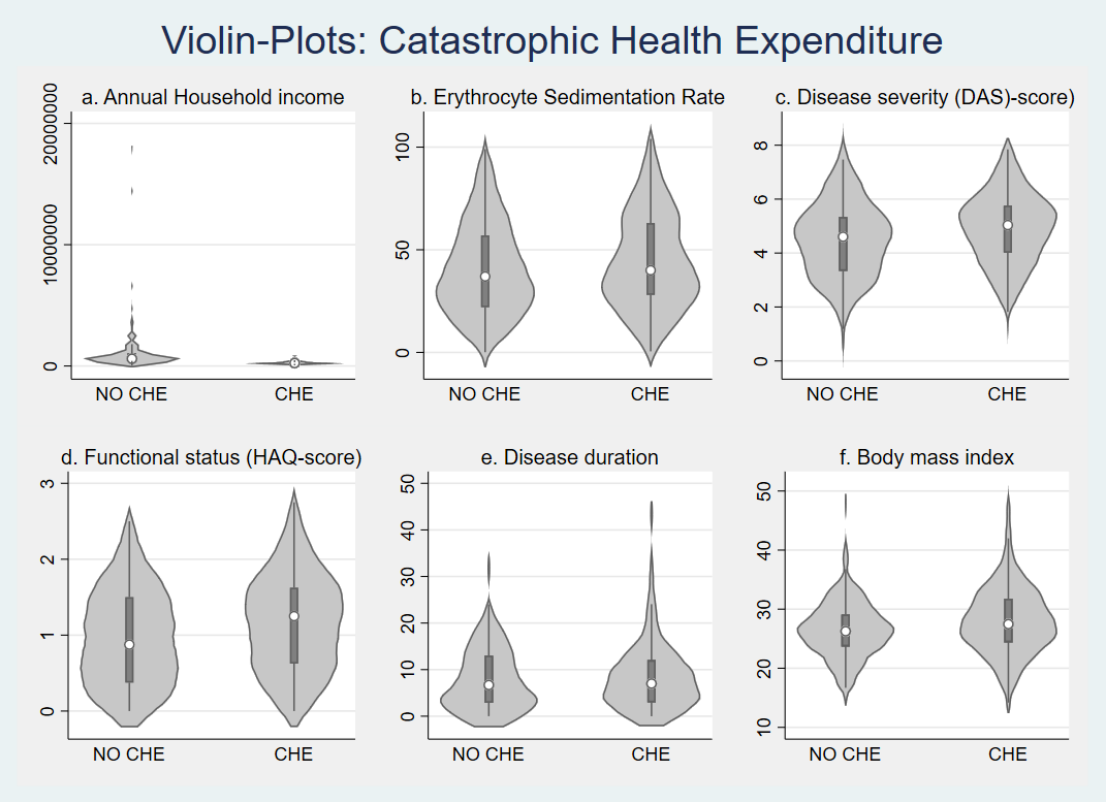
Figures in parathesis are percentage to row total #n=315

Income and health expenditure pattern among RA patients: The mean (95% CI) household annual income of the participants was ₹710,492 (540,155 to 880,828) with a median (IQR) of ₹360,000 (420,000) [$4,369 ($5,097)]. The mean (95% CI) annual health expenditure for treating RA was estimated at ₹44,700 (41,710 to 47,690) with a median (IQR) of ₹39,210 (25,500) [$476 ($310)]. The corresponding mean (95% CI) and median (IQR) OOPE among RA patients per household were ₹40,698 (38,249 to 43,148) [$494 ($464 to $424)] and ₹36,450 (23,070) [$442 ($280)] respectively.

Catastrophic health expenditure and its major determinants among RA patients: Households experiencing CHE owing to RA were 51.4% (n=162). The burden was shown to be higher in some subpopulations, including urban persons (90.7%), females (89.5%), families with 1 to 3 earning members (84.0%), patients with lower education levels (84.0%), and elderly (>50 years) (66.7%). Similarly, CHE is more prevalent among obese persons (34.5%), patients with more than five years of illness (64.3%), Rheumatoid factor (RF) positive (75.3%), Anti–citrullinated protein antibody (Anti-CCP) positive (58.6%), and people with severe RA (48.1%). The presence of CHE is more evident among patients in the first (69.7%) and second (17.3%) income quartiles and patients with mild HAQ (45.1%) (Table 3.2.1).

The violin plots (Figure 3.2.1) show a significant difference in the distribution of annual household income, erythrocyte sedimentation rate (ESR), disease severity, functional status, disease duration, and body mass index (BMI) for CHE and no CHE categories.

Figure 3.2.1 Violin plots for catastrophic health expenditure



The median (IQR) of ESR is 40 (35), DAS28 is 5.04 (1.74), HAQ score is 1.25 (1), and BMI 27.47 (7.3) are high among people experiencing CHE. Similarly, a higher disease duration is found among patients who experience CHE with a median (IQR) of 7 (9). Similarly, the median (IQR) household annual income of those who experience CHE is ₹240,000 (120,000), much lower than that of non-CHE people [₹600,000 (600,000)]. The number of earning members and income quartiles were the primary predictors of CHE in RA patients; families with no earning member and one to three earning members had an odds ratio (OR) (95% CI) of 68 (6.29 to 735.3) and 5.79 (1.66 to 20.23), respectively (*p<0.001*). Patients in the first income quadrant had a greater likelihood of suffering CHE with an OR (95% CI) of 174 (53.48, 570.18) (p<0.001). Other major drivers were unemployed patients [OR=2.25 (1.28 to 3.95)], participants from urban [OR=0.33 (0.12 to 0.93)], families with less than five members [OR=0.43 (0.26 to 0.71)], all with p<0.001 (Table 3.2.2).

Table-3.2.2 Association between facing CHEs and Household Characteristics from logistic regression.

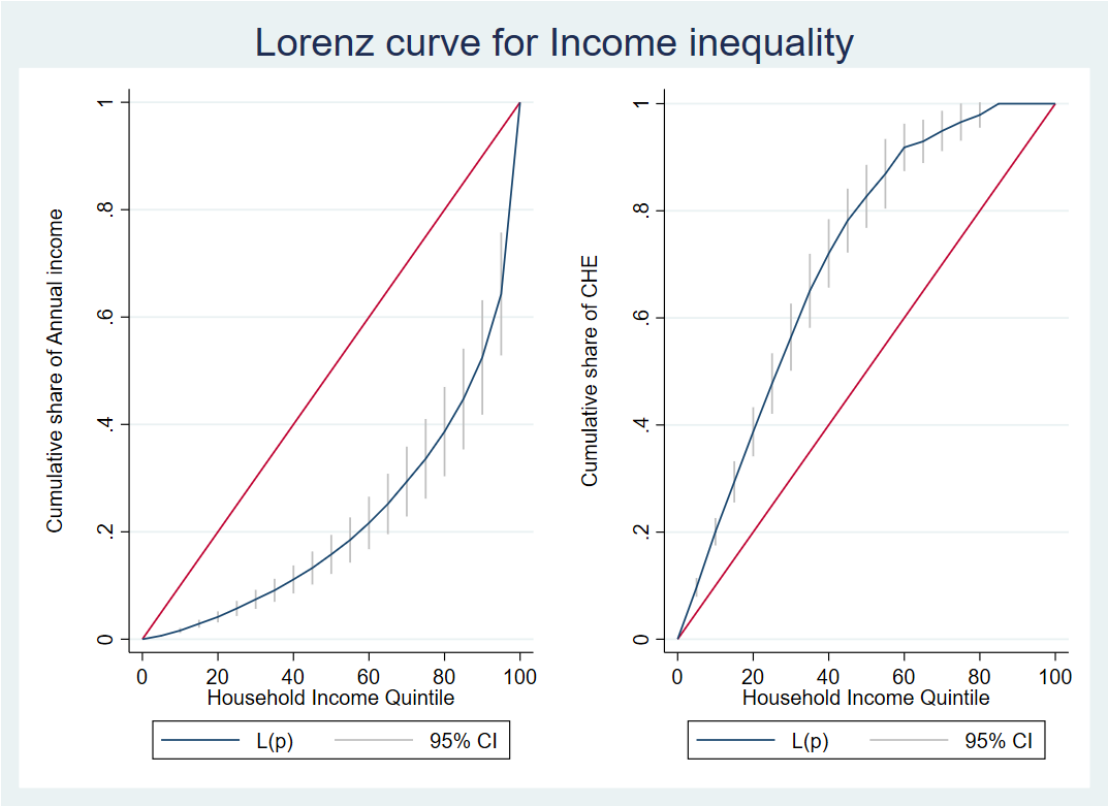
Variables	Categories	Crude odds ratio (95%CI)	Adjusted odds ratio (95%CI)
Place of residence	Rural	Referent	
	Urban	0.33 (0.12,0.93) *	0.14 (0.01, 1.12)
Household size	1 to 2	Referent	
	3 to 5	0.43 (0.26,0.71) *	0.49 (0.22, 1.11)
	More than 5	0.40 (0.18, 0.87)	0.48 (0.14, 1.63)
	Not reported	5.04 (0.61, 41.40)	1.84 (0.02, 169.10)
Education status	Literate	Referent	
	Illiterate	4.47 (1.78,11.24) *	1.47 (0.36, 5.95)
	Not reported	1.07 (0.66,17.33)	0.17 (0.00, 7.14)
Employment status	Working	Referent	
	Not working	2.25 (1.28, 3.95) *	1.25 (0.48, 3.28)
	Not reported	0.88 (0.20, 3.82)	0.01 (0.00, 0.24)
Household Earning members	4 and above	Referent	
	None	68.0 (6.29, 735.3) *	37.24 (1.09, 1277.26)
	1 to 3	5.79 (1.66, 20.23) *	4.65 (0.59, 36.34)
	Not Reported	31.17 (4.46, 217.60) *	5.80 (0.17, 194.30)
Household Income quintile	Fourth	Referent	
	First	174 (53.48, 570.18) *	**218.74 (55.29, 865.45)**
	Second	20.69 (6.55, 65.32) *	**21.49 (5.95, 77.58)**
	Third	5.67 (1.79, 17.86) *	**5.20 (1.47, 18.35)**
BMI	Healthy (18.5 to <25)	Referent	
	Underweight (<18.5)	0.93 (0.27, 3.29)	2.98 (0.42, 20.99)
	Overweight (<25 to 30)	0.93 (0.53, 1.65)	1.22 (0.49, 3.08)
	Obesity (>30)	2.03 (1.10, 3.72) *	3.15 (1.13, 8.78)
	Not reported	1.12 (0.42, 2.97)	2.44 (0.43, 13.80)
Disease activity	Remission (DAS <2.6)	Referent	
	Low (DAS 2.6 to <3.2)	0.86 (0.26,2.84)	1.09 (0.12, 9.83)
	Moderate (DAS 3.2 to <5.1)	1.49 (0.58, 3.82)	0.76 (0.13, 4.42)
	Severe (DAS>5.1)	2.54 (0.98, 6.55)	1.97 (0.34, 11.43)

* p<0.05, Bold in adjusted are significant at p<0.05

When the potential risk factors for CHE in RA patients were examined, significant differences were found in family size, education level, job status, number of earning members, household income quartiles, BMI, and disease activity (Table 3.2.1). We used multivariate logistic regression to determine the effects of the above said factors on the likelihood that participants will have CHE. The logistic regression model was statistically significant ($p<0.001$), $\chi 2 = 221.77$, and explained 51% (Nagelkerke R^2) of the variance in CHE. Sensitivity analyses found that 78.4% (n=247) and 22.5% (n=71) of the households faced CHE, using 5% and 20% of household annual income thresholds for calculating CHE.

Concentration index for income inequality: The concentration index for annual household income with a score of 0.56 ($p<0.001$) indicates that income is concentrated among the upper quintile (4^{th} and 5^{th}) participants. The Lorenz curve (Figure 3.2.2a) shows that participants in the 5^{th} quintile contributed roughly 40% of total income. On the contrary, the concentration index and Lorenz curve for CHE with a score of -0.41 ($p<0.05$) show that CHE is concentrated among participants in the lower income groups (Figure 3.2.2b). Almost 80% of the CHE is contributed by low-income and lower-middle-income patients.

Figure 3.2.2 Lorenz curve for income inequality among the study participants



3.2.4 Discussion

The study aimed to estimate the burden of CHE and OOPE and their major determining factors on households with RA patients in Tamil Nadu, India. The study found that the majority of the RA patients were female, literate, and from urban areas. The mean disease duration was 8.65 years, with 85% of the participants having moderate-to-severe disease activity. The mean household annual income was ₹710,492, concentrated mostly among the higher-income patients, with a mean annual health expenditure for treating RA estimated at ₹44,700.

The average OOPE per household was ₹40,698. Nearly half of the households experienced CHE, with a higher burden seen in rural areas and among those with lower income and education levels. The findings of this study provide vital information on the economic impact of RA on households of RA patients. The CHE burden is high among illiterates, females, and aged urban participants. There is also a substantial

variation in the distribution of income, illness severity, functional status, disease duration, and BMI between the CHE and no CHE groups. CHE is more prevalent in individuals with more severe illnesses, longer disease duration and low median income. Both disease severity and disease duration result in a longer and more intensive treatment cycle, which results in higher treatment costs and CHE. The burden of CHE was more likely to be influenced by family size, number of earning members, education, occupational status, and income.

The proportion of CHE was higher among lower-income households. Our findings showed that as the income of the household increased, the proportion of CHE decreased. Low-income families often choose not to seek healthcare to avoid financial hardships [219] and OOPE caused by high healthcare costs and inadequate insurance coverage [207, 211, 220]. The lower insurance coverage rate among the participants and higher healthcare costs for RA likely contributed to an increased proportion of CHE due to the increased cost of treating rheumatoid arthritis incurred as OOPE. Households with no earning member and unemployed patients had a higher OR for having CHE than their counterparts. It is plausible that when the total household's income is low, it becomes more vulnerable to financial difficulties [219, 220].

The estimated mean disease duration in our study is high, and studies have found that greater treatment costs are related to longer disease duration [221]. A study conducted in India in 2006 [222] reported a cost burden of ₹16,758, which is equal to ₹49,142 after adjusting for inflation in 2022. Other studies conducted globally have reported average annual treatment costs for RA patients, with a 2001 study in the United States estimating $9,519 [223] and a Scottish study estimating £4,444 [224]. Similarly, the average annual total cost for patients with high disease activity was $13,303.6 more than for patients in remission [221]. Previous research has shown that the incidence of CHE is about six times higher in the low-income group [215]. Financial protection schemes

remain ineffective with the continued rise in health expenditure, which continues to contribute to CHE [219]; lower insurance coverage is a concern, as it will exacerbate CHE among RA patients [215].

The study revealed that CHE is a major concern for RA patients and their families. The government of India has already implemented several schemes, such as Ayushman Bharat [225] and Rashtriya Swasthya Bima Yojana [226], to reduce OOPE and CHE by providing financial support to manage healthcare costs and ensuring health insurance availability. Additionally, government subsidies and regulating the price of essential medicines through Jan Aushadhi reduce the financial burden on patients who pay out of pocket.

This study provides the CHE burden in RA patients and highlights the need for improved access to quality healthcare services and financial protection for RA patients in India. There are several limitations to consider when interpreting the findings. The study design was cross-sectional, hospital-based, and single-centre, limiting the generalizability of the results to other regions and populations in India. Information on the source and amount of borrowing and selling of assets, which may have influenced household spending patterns, was not analysed due to data restrictions. Recall bias may have also impacted the estimation of direct and indirect costs and OOPE. Although participants were reluctant to share income information, multiple alternative questions were asked to address this issue. Despite these limitations, the study provides valuable insights into the economic impact of RA on patients and their households in terms of CHE and OOPE in India. Further research is needed to assess the economic impact of RA in other regions of India.

3.2.5 Conclusion

The overwhelming majority of RA-related health costs are borne by patients, which they pay out of pocket, resulting in a CHE burden for more than half of them. Higher treatment costs along with improper health insurance coverage resulted in a higher OOPE and CHE among RA patients. The results underscore the need for comprehensive approaches to strengthening public health policies along with financial risk protection and quality care in India.

Chapter 4 – MODEL-BASED ECONOMIC EVALUATION

Cost-utility analysis of TNF-alpha inhibitors, B-cell inhibitors and JAK inhibitors versus csDMARDs for RA treatment

4.1 Introduction

Rheumatoid arthritis is a progressive disease and often debilitating with persistent joint pains, which restricts the daily activities of the individuals [1]. In the preceding decades it is reported that RA patients gradually lose their functional ability and almost 30-50% of patients progress to severe disease requiring assistance for self-care activities within 15 years of disease onset [9]. However, with early diagnosis and newer treatment of RA in recent years, the progression of joint damage may be delayed, thereby preventing permanent impairment [10]. Recent development of novel instruments to assess the disease activity has facilitated newer treatment strategies to avert irreversible joint damage and disease progression [11 12]. The invention of newer targeted therapies have increased the arsenal of RA pharmacotherapy [13]. Early therapy with disease modifying anti rheumatic drugs (DMARDs) is the usual pharmacotherapy of care that retards disease progression efficiently with the potential to achieve remission or a state of low disease activity [14].

The first-line DMARD for RA is Methotrexate (MTX), a conventional synthetic DMARD (csDMARD), prescribed either as monotherapy or in combination with glucocorticoids where 40% to 50% of patients attain remission or low disease activity [17]. Other csDMARDs include Sulfasalazine (3-4 g/day), Leflunomide (20 mg/day) and Hydroxychloroquine (HCQS) (400 mg/day) [18]. On failing treatment with csDMARDs, biologic synthetic DMARDs (bDMARDs) (Tumor Necrosis Factor-alpha (TNF-a), Interleukin-6 (IL-6) and B-cell inhibitors) and targeted synthetic DMARDs (tsDMARDs) (Janus kinase (JAK) inhibitors) are applied sequentially either as monotherapy or with MTX, where 75% of those patients achieve the treatment goals in time [16]. Biologic or targeted therapies in combination with MTX or other csDMARDs are more efficacious than monotherapies [19]. It has been reported that most of the bDMARDs and tsDMARDs have similar efficacy when combined with MTX [20]. Though clinically effective, the higher cost of these drugs makes them less affordable. In this regard, considering cost-effectiveness of these drugs when determining the

treatment for RA patients is imperative.

The existing evidence on cost-effectiveness of bDMARDs (TNF-a and B-cell inhibitors) and tsDMARDs (JAK inhibitors) compared to csDMARDs, are predominantly from the developed countries. As the cost-effectiveness of interventions could be context specific and hence such results from developed countries may not be suitable for developing countries like India. Further, expensiveness of treatment costs for RA patients warrants the need to generate economic evidence for cost-effective treatment selection in resource-limited settings like India. Hence, this study aims to conduct a cost-utility analysis of newer RA pharmacotherapies to aid for evidence-based policy decision making.

4.2 Methods

We conducted a cost-utility analysis (CUA) using a time inhomogeneous Markov model to calculate and compare the costs and QALY of TNF-alpha inhibitors, B-cell inhibitors and JAK inhibitors compared to conventional synthetic DMARDs for RA treatment in MTX non-responders.

The project proposal was presented to Institutional Human Ethics Committee of ICMR-National Institute of Epidemiology and exemption was sought before study initiation.

4.2.1 PICO

Population: Patients with moderate to severe Rheumatoid arthritis non-respondent to csDMARDs (MTX)

Intervention (all the drugs are given in combination with Methotrexate (MTX15mg/week):

Sequential treatment strategies with TNF-alpha inhibitors or B-cell inhibitors or JAK inhibitors. The treatment strategy and dosages of the interventions is based on the EULAR recommendations for RA treatment [227]. The intervention drug is the first drug

in the sequence and the treatment strategies are named after the first drug. On failure to the intervention drug, individuals switch to the next drug in the sequence as given in the treatment strategy (Fig 4.2.1).

TNF-a inhibitors

Adalimumab 40mg (ADA40), Infliximab 3mg (IFX3), Etanercept 50mg (ETN50), Golimumab 50mg (GOL50) and Certolizumab pegol 200mg (CZP200).

B-cell inhibitor

Rituximab 2x1000mg (RTX2x1000)

JAK inhibitors

Tofacitinib 5mg (TOF5), Tofacitinib 10mg (TOF10) and Baricitinib 4mg (BARI4)

Comparator:

csDMARDs

Hydroxychloroquine 400mg (HCQS400), Leflunomide 20mg (LEF20), Sulfasalazine 500mg (SFZ500)

Outcome: Incremental Cost-effectiveness Ratio (ICER) or Incremental Net Benefit (INB)

Time Horizon: Lifetime horizon

Perspective: Disaggregated societal perspective

Discounting: All future costs and consequences were discounted at 3% as per WHO guidelines along with sensitivity analysis with 0 to 6% per annum.

Willingness to pay (WTP) threshold: We applied Gross Domestic Product (GDP) per capita based on WHO guideline for willingness to pay threshold and considered ICER

of less than one GDP per capita as highly cost-effective, one-to-three GDP/capita as cost-effective, and more than three GDP/capita as not cost-effective [228]. Thus, India's 2022 GDP per capita of INR ₹ 1,91,288 has been considered the cost-effectiveness threshold value per QALY gained [229].

Table 4.2.1 Model input parameters

Input Parameters	Mean (CI/SE/SD)	Distribution	Source
Response Rate (ACR20)			
ADA40*	0.72 (0.66 to 0.78)	Beta	Meta-analysis
IFX3*	0.65 (0.61 to 0.68)	Beta	Meta-analysis
ETN50*	0.84 (0.78 to 0.9)	Beta	Meta-analysis
GOL50*	0.58 (0.4 to 0.75)	Beta	Meta-analysis
CZP200*	0.64 (0.56 to 0.72)	Beta	Meta-analysis
RTX2x1000*	0.61 (0.39 to 0.82)	Beta	Meta-analysis
TOF5*	0.62 (0.49 to 0.75)	Beta	Meta-analysis
TOF10*	0.59 (0.51 to 0.67)	Beta	Meta-analysis
BARI4*	0.71 (0.64 to 0.78)	Beta	Meta-analysis
HCQS400*	0.55 (0.09)	Beta	Meta-analysis
LEF20/SFZ500	0.42 (0.36 to 0.48)	Beta	Meta-analysis
Triple Therapy (MTX+HCQS+SFZ)	0.37 (0 to 0.74)	Beta	Meta-analysis
Avg effectiveness of all TNF-a inhibitors (pooled)	0.57 (0.21 to 0.94)	Beta	Meta-analysis
Avg effectiveness of all b/tDMARDs (pooled)	0.6 (0.51 to 0.69)	Beta	Meta-analysis
Withdrawal due to AEs (within 6 months)			
ADA40*	0.037 (0.024 to 0.05)	Beta	Meta-analysis
IFX3*	0.031 (0.019 to 0.043)	Beta	Meta-analysis
ETN50*	0.041 (0.02 to 0.062)	Beta	Meta-analysis
GOL50*	0.005 (0 to 0.011)	Beta	Meta-analysis
CZP200*	0.07 (0.026 to 0.114)	Beta	Meta-analysis
RTX2x1000*	0.004 (0 to 0.011)	Beta	Meta-analysis
TOF5*	0.001 (0 to 0.005)	Beta	Meta-analysis
TOF10*	0.006 (0 to 0.015)	Beta	Meta-analysis
BARI4*	0.039 (0.011 to 0.067)	Beta	Meta-analysis
HCQS400*	0.037 (0.062)	Beta	Meta-analysis
LEF20/SFZ500	0.201 (0.153 to 0.249)	Beta	Meta-analysis
Avg effectiveness of all TNF-a inhibitors (pooled)	0.007 (0.003 to 0.011)	Beta	Meta-analysis
Withdrawal probability due to AEs & LOE in long term			
ADA40*	0.017 (0.001)	Beta	[230]
IFX3*	0.034 (0.002)	Beta	[231]
ETN50*	0.027 (0.003)	Beta	[232]

GOL50*	0.035 (0.013)	Beta	[233]
CZP200*	0.026 (0.002)	Beta	[234]
RTX2x1000*	0.033 (0.003)	Beta	[235]
TOF5*	0.011 (0.001)	Beta	[236]
TOF10*	0.01 (0)	Beta	[236]
BARI4*	0.002 (0.002)	Beta	[237]
HCQS400*	0.126 (0.013)	Beta	[238]
LEF20/SFZ500	0.11 (0.01)	Beta	[239]
Avg effectiveness of all TNF-a inhibitors (pooled)	0.017 (0.001)	Beta	[230]
Proportion of Total Adverse Events			
ADA40*	0.044	Beta	Meta-analysis
IFX3*	0.041	Beta	Meta-analysis
ETN50*	0.163	Beta	Meta-analysis
GOL50*	0.012	Beta	Meta-analysis
CZP200*	0.112	Beta	Meta-analysis
RTX2x1000*	0.032	Beta	Meta-analysis
TOF5*	0.016	Beta	Meta-analysis
TOF10*	0.013	Beta	Meta-analysis
BARI4*	0.027	Beta	Meta-analysis
HCQS400* (MTX data has been used)	0.031	Beta	Meta-analysis
LEF20/SFZ500 (MTX data has been used)	0.031	Beta	Meta-analysis
Triple Therapy (MTX+HCQS+SFZ)	0.135	Beta	Meta-analysis
Proportion of patients achieving remission			
ADA40*	0.373 (0.207 to 0.319)	Beta	Meta-analysis
IFX3*	0.301 (0.162 to 0.228)	Beta	Meta-analysis
ETN50*	0.398 (0.243 to 0.416)	Beta	Meta-analysis
GOL50*	0.305 (0.038 to 0.306)	Beta	Meta-analysis
CZP200*	0.306 (0.159 to 0.219)	Beta	Meta-analysis
RTX2x1000*	0.259 (0.028 to 0.266)	Beta	Meta-analysis
TOF5*	0.323 (0.139 to 0.222)	Beta	Meta-analysis
TOF10*	0.332 (0.122 to 0.268)	Beta	Meta-analysis
BARI4*	0.387 (0.24 to 0.311)	Beta	Meta-analysis
HCQS400*	0.236 (0.059)	Beta	Meta-analysis
LEF20/SFZ500	0.199 (0.05 to 0.13)	Beta	Meta-analysis
Triple Therapy (MTX+HCQS+SFZ)	0.032 (0.002 to 0.062)	Beta	Meta-analysis
Proportion of patients achieving LDA		Beta	
ADA40*	0.305 (0.191 to 0.239)	Beta	Meta-analysis
IFX3*	0.3 (0.173 to 0.215)	Beta	Meta-analysis
ETN50*	0.302 (0.212 to 0.288)	Beta	Meta-analysis
GOL50*	0.258 (0.106 to 0.184)	Beta	Meta-analysis
CZP200*	0.29 (0.143 to 0.215)	Beta	Meta-analysis
RTX2x1000*	0.291 (0.116 to 0.216)	Beta	Meta-analysis
TOF5*	0.355 (0.156 to 0.242)	Beta	Meta-analysis
TOF10*	0.267 (0.118 to 0.196)	Beta	Meta-analysis
BARI4*	0.288 (0.177 to 0.234)	Beta	Meta-analysis

HCQS400*	0.473 (0.076)	Beta	Meta-analysis
LEF20/SFZ500	0.144 (0.102 to 0.187)	Beta	Meta-analysis
Triple Therapy (MTX+HCQS+SFZ)	0.124 (0 to 0.283)	Beta	Meta-analysis
Proportion of patients achieving MDA			
ADA40*	0.322 (0.195 to 0.259)	Beta	Meta-analysis
IFX3*	0.399 (0.238 to 0.278)	Beta	Meta-analysis
ETN50*	0.3 (0.203 to 0.293)	Beta	Meta-analysis
GOL50*	0.437 (0.198 to 0.294)	Beta	Meta-analysis
CZP200*	0.404 (0.203 to 0.296)	Beta	Meta-analysis
RTX2x1000*	0.45 (0.197 to 0.315)	Beta	Meta-analysis
TOF5*	0.322 (0.108 to 0.253)	Beta	Meta-analysis
TOF10*	0.401 (0.189 to 0.281)	Beta	Meta-analysis
BARI4*	0.325 (0.201 to 0.261)	Beta	Meta-analysis
HCQS400*	0.291 (0.064)	Beta	Meta-analysis
LEF20/SFZ500	0.217 (0.167 to 0.266)	Beta	Meta-analysis
Triple Therapy (MTX+HCQS+SFZ)	0.207 (0.025 to 0.389)	Beta	Meta-analysis
Utilities			
Remission (DAS<3.1) (u_rem)	0.78 (0.65 to 0.9)	Beta	[240]
Moderate disease activity (u_mod)	0.61 (0.56 to 0.66)	Beta	[240]
Low disease activity (u_low)	0.73 (0.65 to 0.8)	Beta	Primary study (unpublished)
High disease activity (u_sev)	0.37 (0.3 to 0.43)	Beta	Primary study (unpublished)
Health state at entry to the model (u_entry)	0.49 (0.3 to 0.66)	Beta	Avg. of u_mod and u_sev
u_Pneumonia	0.47 (0.01)	Beta	[241]
u_Hepatitiis_B	0.68 (0.02)	Beta	[242]
u_Herpes_zoster	0.79 (0.04)	Beta	[243]
u_Malignancy (lung cancer)	0.68 (0.04)	Beta	[244]
u_Tuberculosis	0.69 (0.01)	Beta	[245]
u_URTI	0.93 (0.09)	Beta	[246]
u_UTI	0.76 (0.02)	Beta	[247]
u_cardiacfailure	0.68 (0.05)	Beta	[248]
u_Lymphomas	0.83 (0.02)	Beta	[249]
u_IR	0.76 (0.09)	Beta	[250]
u_NMSC	0.71 (0)	Beta	[251]
u_serious infections	0.47 (0.01)	Beta	[241]
Costs			
ADA40	17680 (5901.53)	Gamma	[252,253]
IFX3	31627.33 (2818.62)	Gamma	[254]
ETN50	14001.93 (3431.57)	Gamma	[255,256]
GOL50	46838.67 (5260.91)	Gamma	[257,252]
CZP200	7208 (1802)	Gamma	[252]
RTX2x1000	17400 (3507.14)	Gamma	[252, 255, 256]
TOF5	34.39 (5.02)	Gamma	[252]
TOF10	68.79 (0)	Gamma	[252]
BARI4	2121.14 (1126.85)	Gamma	[252, 257]
HCQS400	5.85 (5.45)	Gamma	[252, 253, 258]

LEF20	15.43 (6.01)	Gamma	[252]
SFZ500	3.85 (2.24)	Gamma	[252, 253]
MTX7.5	21.2 (6.1)	Gamma	[252, 253, 258]
Infusion	81.61 (8.16)	Gamma	[258]
Nursing staff	18.12 (1.81)	Gamma	[258]
Transport	1026.98 (3402.08)	Gamma	Primary study (unpublished)
c_Pneumonia	32073 (49306.17)	Gamma	[259]
c_Hepatitiis_B	37389.98 (1912.5)	Gamma	[260]
c_Herpes_zoster	7650 (3880.34)	Gamma	[252, 255]
c_Malignancy	12420 (3481.67)	Gamma	[259]
c_Tuberculosis	17711.96 (4066.61)	Gamma	[261, 262]
c_URTI	7580.93 (3842.5)	Gamma	[263]
c_UTI	1800 (80722.53)	Gamma	PMJAY
c_cardiacfailure	190742.55 (3750)	Gamma	[264]
c_Lymphomas	15000 (44.69)	Gamma	[259]
c_IR	178.76 (0)	Gamma	[265]
c_serious infections	32073 (3402.08)	Gamma	[259]

4.2.2 Data Collection

Transition probabilities and Proportions

The data on transition probabilities for the input parameters of the model were collected through systematic search and meta-analysis or from published literature based on a hierarchy of evidence, including.

- systematic review and meta-analysis (SRMA) of randomized controlled trials (RCTs)
- RCTs
- SRMA of observational studies
- Clinical trials, and
- Observational studies

The data on proportion of ACR20/50/70 response, adverse events (AEs), withdrawal due to adverse events and mortality for the interventions were obtained through systematic search and meta-analysis of RCTs. Probability of age specific all-cause mortality was obtained from census data [266].

Cost

Direct medical costs (DMC) including cost of intervention, cost of administering interventions, cost of treating adverse events were considered. Cost of travel was the only direct non-medical cost considered. Cost of the intervention drugs were obtained from sources including Jan Aushadhi, Pradhan Mantri Jan Arogya Yojana (PMJAY), National Health System Cost Database for India [258] and Market place (Indiamart and Medindia). Cost of adverse events were obtained from Chief Minister's Comprehensive Health Insurance Scheme (CMCHIS), PMJAY, market places (Medplus, Apollo, Indiamart and Indiasurgery) and primary studies from India [267-269]. A mean cost was estimated when data is available from multiple sources. All the costs were adjusted using the consumer price index (2022) and reported in Indian National Rupees (INR). The cost data are provided in Table 4.2.1

Utility

Health state utilities used in the model were obtained from primary cross-sectional study conducted in a single center in Tamil Nādu (unpublished), published systematic review and meta-analysis [240] and from Tuff's registry [270]. The details of utility data are provided in Table 4.1

4.2.3 Model Framework

Individuals with rheumatoid arthritis (RA) who enter the model are in an active disease state and have not responded to csDMARD (methotrexate (MTX). Upon entering the model, these individuals initiate one of the intervention strategies as given in Fig 4.21. If they achieve a 20% improvement according to the American College of Rheumatology criteria (ACR20) within six months (1st cycle), they are considered responders and continue with the same drug. In case of non-response, they proceed to

the next state, where they switch to another drug from the same class. Those who achieve a response within the following six months (2nd cycle) while receiving the second drug in the sequence remain in the second state and continue the treatment. Non-responsive patients move to the third state and switch to a different DMARD from another class. Individuals who reach the third state are assumed to be taking either one of the biological or targeted synthetic DMARDs until death. Throughout the treatment, patients may undergo death from any state due to adverse events related to the intervention drug or due to all-cause mortality. In each state, responders can fall into three categories: those in remission, those in a state of low disease activity, or those in a state of moderate disease activity. Each of these groups have distinct health utilities associated with their respective health states. In the initial two cycles of the model, the ACR20 response rate at 6 months (as obtained through meta-analysis) was used to distinguish non-responders from responders. As the model progressed to subsequent cycles, withdrawal probability was used to classify non-responders who transitioned to the next state. This withdrawal probability was based on two factors: loss of efficacy (indicating that the drug is no longer effective in controlling the disease) and adverse events (negative side effects that may lead to discontinuation of the drug). By incorporating this withdrawal probability, the model accounted for changes in treatment response over time and allowed for a more dynamic representation of the cohort's progression through different health states.

4.2.4 Model Assumptions

- The cohort entering the model is assumed to have moderate or severe disease activity, as they have not responded to MTX.
- The estimation of drug costs in the model is based on the assumption that treatment schedules follow standard protocols.

- For individuals entering the model, an average utility value is applied, considering both moderate and severe disease activity.
- Individuals are assumed to remain in the moderate-severe disease state for up to six months, regardless of their response to the drug. After six months, they are transitioned into remission, low disease activity (LDA), or moderate disease activity (MDA) states based on their response to the intervention drug during the first cycle.
- During the first six months or first cycle, it is assumed that the cost of adverse events or the utility loss due to adverse events is not considered.
- Individuals who achieve remission, LDA, or MDA with the intervention drug are assumed to remain in the same health state for the rest of their lifetime, except for those who discontinue the intervention drug due to either loss of efficacy or adverse events.
- For individuals who do not respond to the intervention drug, they progress to the next state and switch to another drug from the same class.
- Individuals who take the third drug in the treatment sequence are assumed to continue taking either one or the other b/tDMARD (biological or targeted synthetic disease-modifying antirheumatic drug) until death.
- The model classifies responders and non-responders to the intervention drug based on the ACR20 response rate. Specifically, individuals achieving ACR20, ACR50, and ACR70 are assumed to be in the MDA, LDA, and remission states, respectively [271].
- It was assumed that those who responded positively to the intervention in first cycle experienced sustained remission for up to one year (up to second cycle) [234, 272].

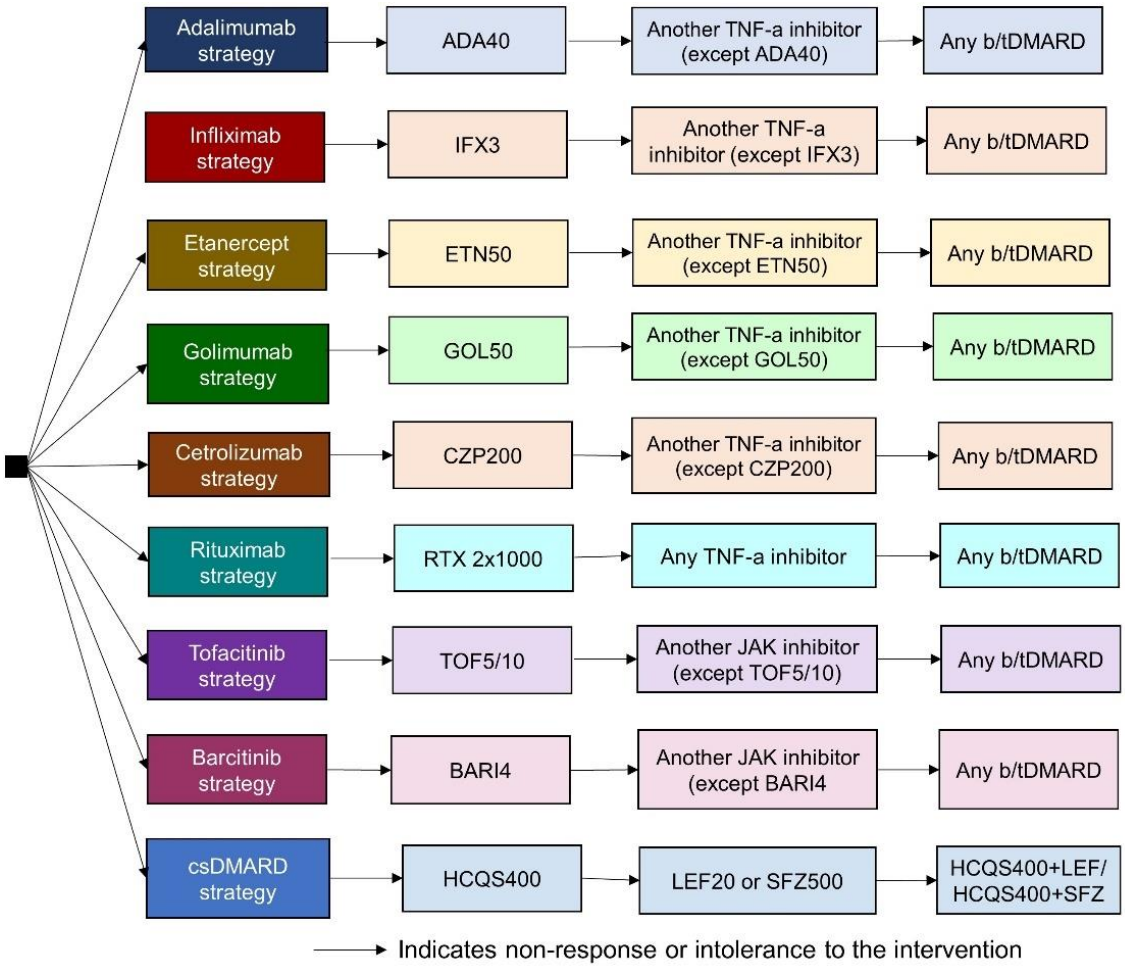


Figure 4.2.1 Treatment Strategies

The treatment strategy and dosages of the interventions is based on the EULAR recommendations for RA treatment. Individuals with RA start one of these treatment strategies on entering the model. Upon non-response/intolerance to the first drug in the sequence in the first cycle, individuals switch to another drug within the same class in the second cycle. If non-responsive or intolerant to the second drug in the sequence, then individuals switch to taking any b/tDMARD including ADA40, IFX3, ETN50, GOL50, CZP200, RTX 2x1000, TOF5, TOF10 OR BARI4 from the third cycle until response/death.

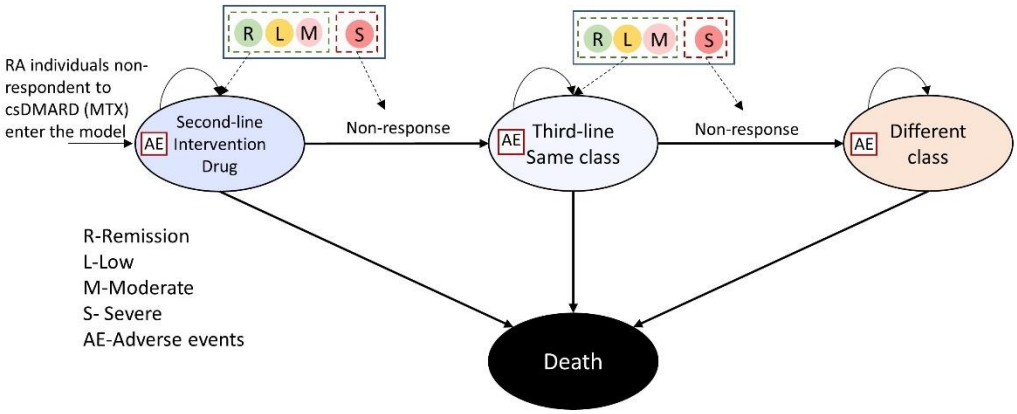


Figure 4.2.2 Schematic representation of Markov model
Model is adapted from Tian L et el 2020 ([174])

4.2.5 Cost-effectiveness Analysis

Half-cycle correction was performed for the costs and QALYs. The lifetime total cost and total Quality-Adjusted Life Years (QALYs) gained were calculated for each intervention. The total cost comprised the intervention cost and the cost of treating adverse events. QALYs were estimated by combining the disease-state-specific utility and adverse-event-specific utility using a multiplicative method (ref), considering a baseline value of 1 for perfect health.

The formula used to calculate QALYs is as follows:

$$QALY = Life\ years * u\_HS * u\_AE$$

where

Life years represent the number of years a person remains in a particular health state.

u_HS represents the utility (quality of life) associated with the specific disease state (remission, low disease activity, moderate disease activity, high disease activity).

u_AE represents the utility (quality of life) associated with experiencing adverse events.

The QALY for each state includes the sum of QALYs for all health states (remission/LDA/MDA/HDA). The total QALY for an intervention was estimated by summing up the QALYs of all states in the model. The incremental cost per QALY (ICER) is calculated as follows:

$$ICER = \frac{Cost\ of\ intervention - Cost\ of\ comparator}{QALY of\ intervention - QALY\ of\ comparator}$$

This ICER represents the difference in total cost and total QALY gained between the two interventions, giving an indication of the cost-effectiveness of one intervention compared to the other. Cost-effectiveness Ratio (CER) was calculated for each intervention to aid comparison of cost-effectiveness between the interventions. CER is calculated as follows:

$$CER = \frac{Cost\ of\ intervention}{QALY of\ intervention}$$

Apart from ICER and CER, Net Monetary Benefit (NMB) and Incremental Netbenefit (INB) were also calculated using the formula given below:

$$NMB = Qaly\ of\ intervention * lambda - Cost\ of\ intervention$$

where lambda is the willingness to pay threshold (1 GDP)

$$INB = NMB\ of\ intervention - NMB\ of\ comparator$$

4.2.6 Sensitivity analysis

The robustness of the model was assessed using sensitivity analysis, including one-way sensitivity analysis and probabilistic sensitivity analysis (PSA)

One Way Sensitivity Analysis (OWSA)

In one-way sensitivity analysis, 95% CI values for utility values and 25% upper/lower values for the other model input parameters were used and reported as tornado diagrams.

Probabilistic Sensitivity Analysis (PSA)

PSA was performed with 5000 Monte Carlo simulations based on its data distribution. Transitional probabilities and utilities were simulated using beta

distribution, whereas costs were simulated using Gamma distribution. Results are reported as Cost-effectiveness (CE) plane.

4.2.7 Scenario Analysis

In the scenario analysis, we explored the impact of cost reduction on the cost-effectiveness of the interventions by lowering the cost of all the intervention drugs by different percentages: 25%, 50%, and 75%. By implementing these cost reductions, we recalculated the total cost and total QALYs gained for each intervention over the lifetime and compared them to the original baseline scenario to observe the changes in cost-effectiveness.

4.3 Results

4.3.1 Cost-effectiveness analysis

Based on a probabilistic approach, from disaggregated societal perspective, we assessed the cost-effectiveness of TNF-i (ADA40, IFX3, ETN50, GOL50, CZP200), B-cell inhibitor (RTX2x1000) and JAK-i (TOF5, TOF10 and BARI4) compared to conventional synthetic DMARDs (Table 4.3.1)

TNF-α inhibitors

In the base-case analysis, the ICER of ADA40, IFX3, ETN50, GOL50, and CZP200 in combination with MTX compared to csDMARDs (including MTX) is ₹24,62,235, ₹22,80,550, ₹29,81,552, ₹31,09,207 and ₹19,60,391 respectively which is substantially higher than three times the GDP. Therefore, none of the interventions including TNF-a inhibitors, B-cell inhibitors and JAK inhibitors are cost-effective than continuing treatment with csDMARDs in RA patients refractory to csDMARDs including methotrexate.

Table 4.3.1 Cost-effectiveness Analysis results: Base-case

Intervention	Cost	QALY	LY	NMB	Inc. Cost	Inc. QALY	Inc. LY	INB	ICER per QALY	ICER per LY
Comparator (csDMARDs)	₹ 3,06,650	6.88	13.37	₹ 10,08,536						
ADA40	₹ 58,40,958	9.12	13.84	₹ -40,95,817	₹ 55,34,308	2.25	0.48	₹ -51,04,354	₹ 24,62,235	₹ 1,15,66,919
IFX3	₹ 50,37,575	8.95	13.79	₹ -33,25,567	₹ 47,30,925	2.07	0.43	₹ -43,34,104	₹ 22,80,550	₹ 1,11,21,627
ETN50	₹ 76,76,824	9.35	13.90	₹ -58,88,788	₹ 73,70,175	2.47	0.54	₹ -68,97,324	₹ 29,81,552	₹ 1,37,08,596
GOL50	₹ 61,45,206	8.75	13.42	₹ -44,70,813	₹ 58,38,556	1.88	0.06	₹ -54,79,349	₹ 31,09,207	₹ 9,94,46,219
CZP200	₹ 44,75,835	9.00	13.83	₹ -27,53,834	₹ 41,69,185	2.13	0.46	₹ -37,62,370	₹ 19,60,391	₹ 90,21,172
RTX2x1000	₹ 39,07,530	9.93	13.72	₹ -20,08,829	₹ 36,00,880	3.05	0.35	₹ -30,17,365	₹ 11,80,444	₹ 1,02,30,635
TOF5	₹ 28,98,695	9.35	13.93	₹ -11,09,580	₹ 25,92,046	2.48	0.57	₹ -21,18,116	₹ 10,46,206	₹ 45,64,263
TOF10	₹ 31,63,394	9.28	14.03	₹ -13,88,108	₹ 28,56,745	2.41	0.66	₹ -23,96,645	₹ 11,87,703	₹ 43,30,996
BARI4	₹ 43,11,650	8.68	14.22	₹ -26,51,599	₹ 40,05,000	1.80	0.85	₹ -36,60,135	₹ 22,21,481	₹ 46,79,636

B-cell inhibitors

The ICER of RTX2x1000 in combination with MTX compared to csDMARDs (including MTX) was ₹ 11,80,444 in the base case analysis which is greater than three times the GDP, hence not cost-effective.

JAK inhibitors

ICER was ₹10,46,206 for TOF5 and ₹11,87,703 for TOF10, both of which are greater than three times the GDP, hence not cost-effective as compared to csDMARDs (including MTX). Similarly, the ICER of BARI4 compared to csDMARDs was ₹22,21,481, which is greater than three times the GDP, hence not cost-effective.

4.3.2 Sensitivity Analysis

OWSA

The most influential parameters on ICER shared among all interventions were found to be the Utility of Remission (u_rem), utility of severe RA (u_sev), Discount Rate of Utility (Disc rate_utility), Discount Rate of Cost (Disc rate_cost) and ACR20 response rate of Triple therapy (TP_TT_ACR20). However, it is crucial to emphasize that these changes did not reach a level of cost-effectiveness according to the established criteria. Further, the ICER was notably impacted by certain variables for specific interventions.

In the case of ADA40 vs csDMARDs, the Cost of ADA40 (c_ADA), ACR20 response rate of ADA40 (TP1_ADA40_ACR20) and Proportion of patients achieving remission with ADA40 (P2_ADA40_Rem) exhibited changes in the ICER greater than 10% (Fig 4.3.1).

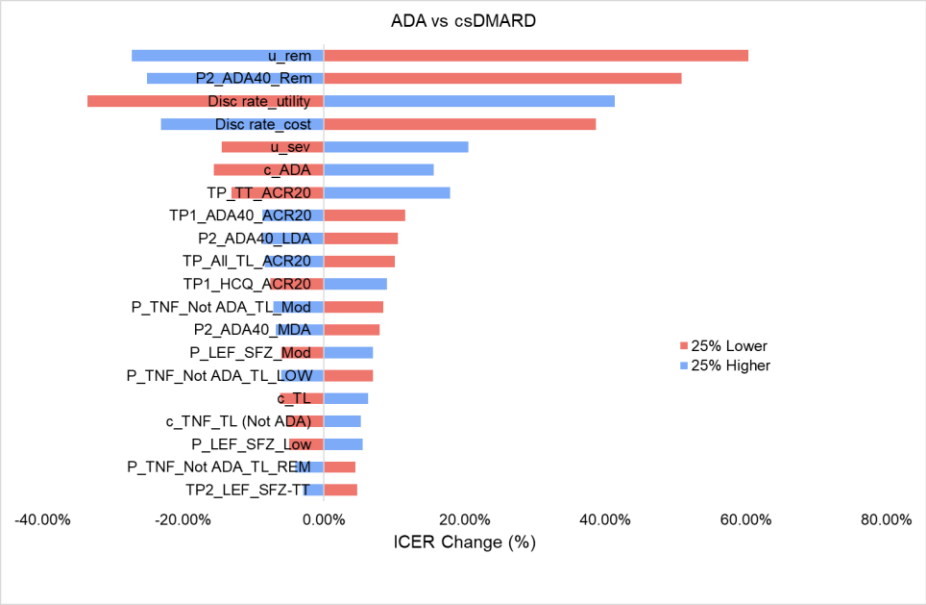


Figure 4.3.1 One-way sensitivity analysis for ADA40 vs csDMARDs

One-way sensitivity analysis was conducted using 25% higher and lower values of all the transitional probabilities, cost, and utility values. The red bars show the effect on the ICER of applying the lower limit (-25%) of the specific parameter, while the blue bars show the effect on the ICER of applying the upper limit (+25%) of the specific parameter.

In the comparison between IFX3 and csDMARDs, several parameters were identified to be significantly influencing the ICER with changes exceeding 10%. These parameters include the average cost of all tumor necrosis factor-alpha (TNF-a) inhibitors excluding IFX (c_TNF_TL (Not IFX)), the proportion of individuals achieving Remission (P_TNF_TL_Rem), the proportion of individuals in low disease activity (P_TNF_TL_Low), and the proportion of individuals in moderate disease activity (P_TNF_TL_Mod) with any TNF-a inhibitor. Moreover, the pooled ACR20 response rate of all biologic/targeted synthetic disease-modifying antirheumatic drugs (b/tDMARDs) (TP_All_TL_ACR20) also exerted a noteworthy impact on the ICER, surpassing the 10% threshold for change (Fig 4.3.2).

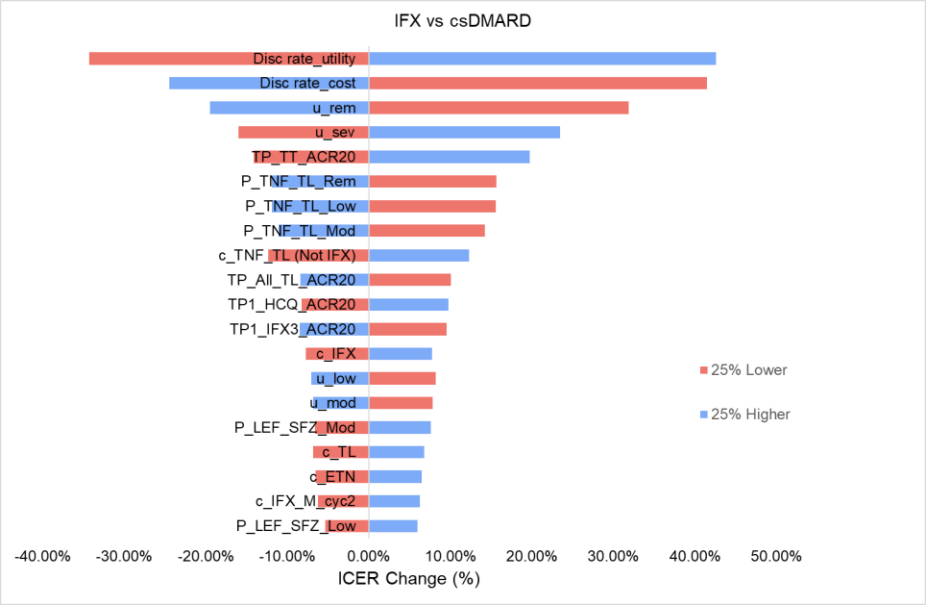


Figure 4.3.2 One-way sensitivity analysis for IFX3 vs csDMARDs

One-way sensitivity analysis was conducted using 25% higher and lower values of all the transitional probabilities, cost, and utility values. The red bars show the effect on the ICER of applying the lower limit (-25%) of the specific parameter, while the blue bars show the effect on the ICER of applying the upper limit (+25%) of the specific parameter.

On comparing ETN50 and csDMARDS, it was observed that the cost of Etanercept (c_ETN) had a significant impact on the ICER resulting in a change of 19%, in addition to the common influential parameters such as Utility of Remission (u_rem), utility of severe RA (u_sev), Discount Rate of Utility (Disc rate_utility), Discount Rate of Cost (Disc rate_cost) and ACR20 response rate of Triple therapy (TP_TT_ACR20) shared across the interventions (Fig 4.3.3).

In the case of GOL50 vs csDMARDs, several parameters including the proportion of individuals achieving Remission (P_TNF_Not GOL_TL_REM), the proportion of individuals in low disease activity (P_TNF_Not GOL_TL_LOW), and the proportion of individuals in moderate disease activity (P_TNF_Not GOL_TL_Mod) with any TNF-a inhibitor excluding GOL50, pooled ACR20 response rate of all biologic/targeted synthetic disease-modifying antirheumatic drugs (b/tDMARDs) (TP_All_TL_ACR20), ACR20 response rate of HCQS400 (TP1_HCQ_ACR20), cost

of Golimumab (c_GOL) exerted a noteworthy impact on the ICER, surpassing the 10% threshold for change (Fig 4.3.4).

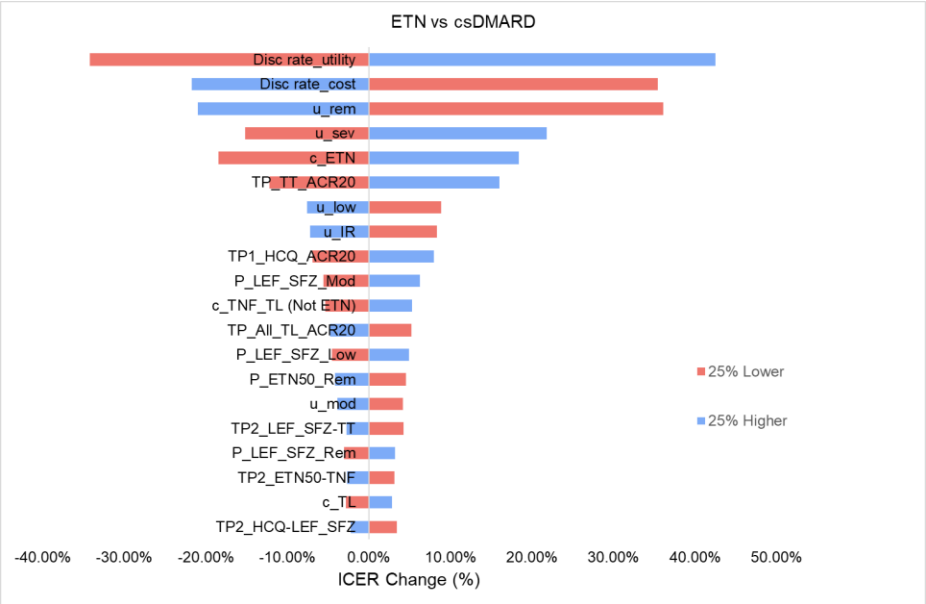


Figure 4.3.3 One-way sensitivity analysis for ETN50 vs csDMARDs

One-way sensitivity analysis was conducted using 25% higher and lower values of all the transitional probabilities, cost, and utility values. The red bars show the effect on the ICER of applying the lower limit (-25%) of the specific parameter, while the blue bars show the effect on the ICER of applying the upper limit (+25%) of the specific parameter.

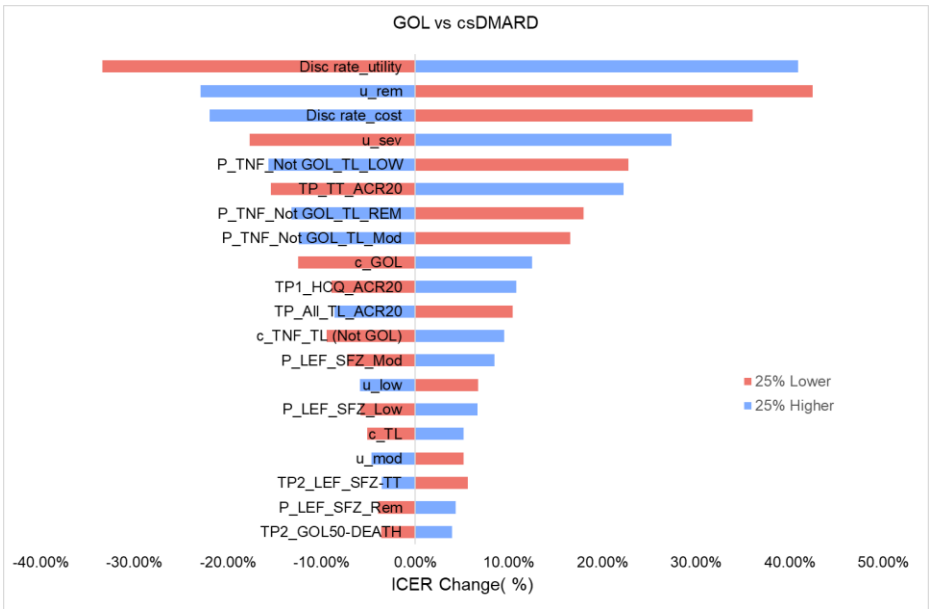


Figure 4.3.4 One-way sensitivity analysis for GOL50 vs csDMARDs

One-way sensitivity analysis was conducted using 25% higher and lower values of all the transitional probabilities, cost, and utility values. The red bars show the effect on the ICER of applying the lower limit (-25%) of the specific parameter, while the blue bars show the effect on the ICER of applying the upper limit (+25%) of the specific parameter.

When comparing CZP200 with csDMARDs, parameters such ACR20 response rate of CZP200 (TP1_CZP_ACR20), average cost of all TNF-a inhibitors excluding CZP200 (c_TNF_TL (Not CZP)), Proportion of individuals achieving remission/LDA/MDA with any TNF-a inhibitor other than CZP (P_TNF_Not CZP_TL_REM, P_TNF_Not CZP_TL_LOW, P_TNF_Not CZP_TL_Mod) and pooled ACR20 response rate of all biologic/targeted synthetic disease-modifying antirheumatic drugs (b/tDMARDs) (TP_All_TL_ACR20) were seen to cause changes greater than 10% in the ICER (Fig 4.3.5).

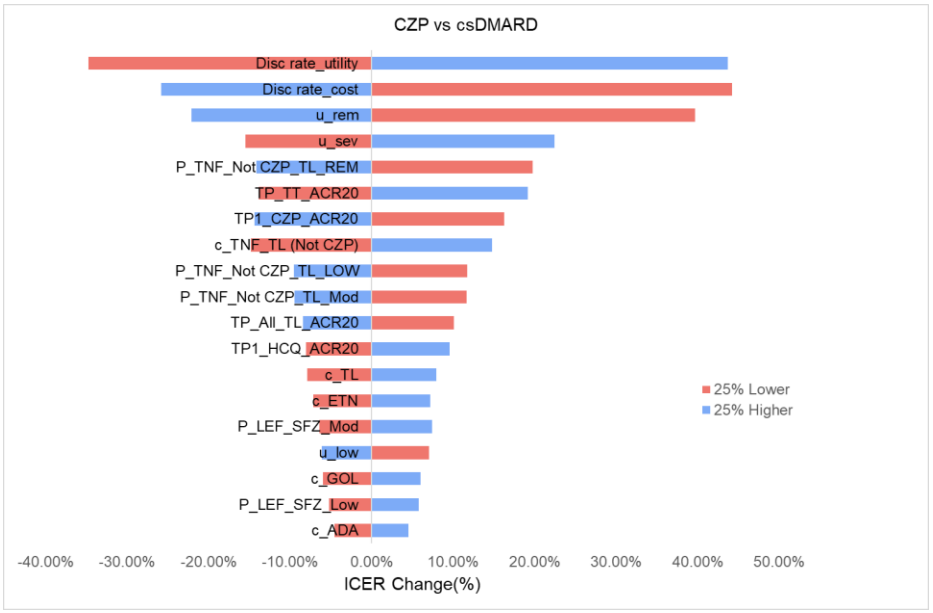


Figure 4.3.5 One-way sensitivity analysis for CZP200 vs csDMARDs

One-way sensitivity analysis was conducted using 25% higher and lower values of all the transitional probabilities, cost, and utility values. The red bars show the effect on the ICER of applying the lower limit (-25%) of the specific parameter, while the blue bars show the effect on the ICER of applying the upper limit (+25%) of the specific parameter.

In RTX vs csDMARDs comparison, ACR20 response rate with RTX 2x1000 (TP1_RTX_ACR20) and average cost of all the TNF-a inhibitor (c_TNF_TL) exhibited a change of 13% and 15% respectively in the ICER, in addition to the addition to the common influential parameters shared across the interventions (as previously stated) (Fig 4.3.6).

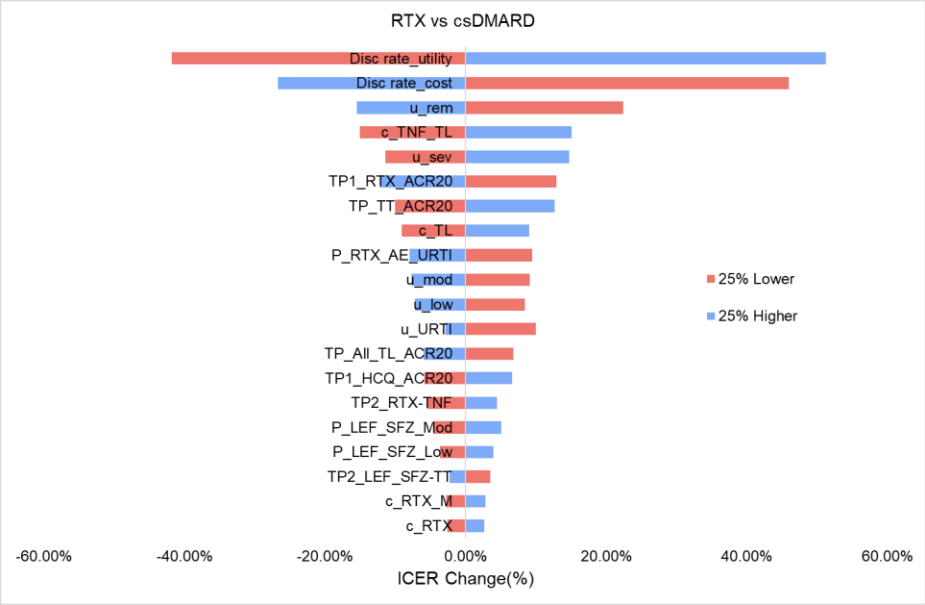


Figure 4.3.6 One-way sensitivity analysis for RTX 2x1000 vs csDMARDs

One-way sensitivity analysis was conducted using 25% higher and lower values of all the transitional probabilities, cost, and utility values. The red bars show the effect on the ICER of applying the lower limit (-25%) of the specific parameter, while the blue bars show the effect on the ICER of applying the upper limit (+25%) of the specific parameter.

In the comparison between the JAK inhibitor TOF5/TOF10 and csDMARDs, alongside the common influential parameters shared across all interventions (as previously stated), the following factors exhibited a change greater than 10% in the ICER: ACR20 response rate of TOF5/10 (TP1_TOF5/10_ACR20), Average cost of all TNF-a inhibitors (c_TNF_TL), Pooled average cost of all biologic/targeted synthetic disease-modifying antirheumatic drugs (b/tDMARDs) (c_TL) (Fig 4.3.7, 4.3.8).

In the case of BARI4 vs csDMARDs, the cost of BARI4 (c_BARI), proportion of individuals achieving remission with JAK inhibitor other than BARI4 (P_JAK_Not BARI_TL_REM), the ACR20 response rate of BARI4 (TP1_BARI4_ACR20), utility value of moderate RA (u_mod) and the ACR20 response rate of HCQ400 (TP1_HCQ_ACR20) were seen to influence the ICER by causing a substantial change which is greater than 10% change (Fig 4.3.9).

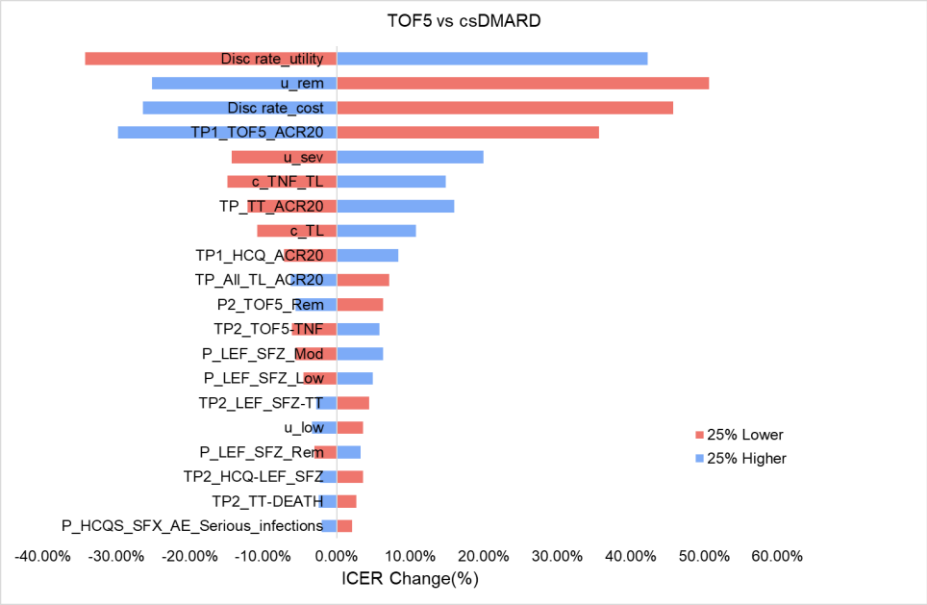


Figure 4.3.7 One-way sensitivity analysis for TOF5 vs csDMARDs

One-way sensitivity analysis was conducted using 25% higher and lower values of all the transitional probabilities, cost, and utility values. The red bars show the effect on the ICER of applying the lower limit (-25%) of the specific parameter, while the blue bars show the effect on the ICER of applying the upper limit (+25%) of the specific parameter.

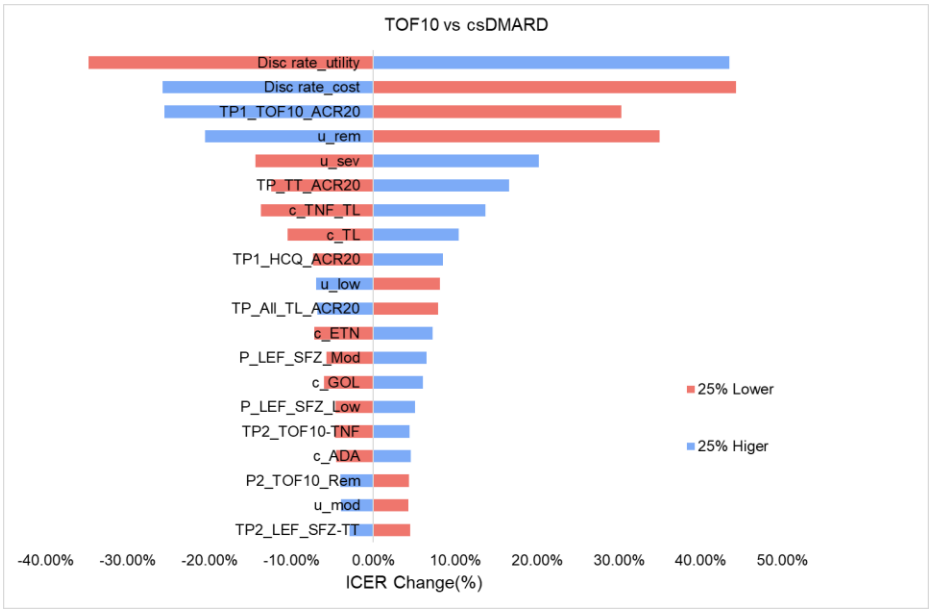


Figure 4.3.8 One-way sensitivity analysis for TOF10 vs csDMARDs

One-way sensitivity analysis was conducted using 25% higher and lower values of all the transitional probabilities, cost, and utility values. The red bars show the effect on the ICER of applying the lower limit (-25%) of the specific parameter, while the blue bars show the effect on the ICER of applying the upper limit (+25%) of the specific parameter.

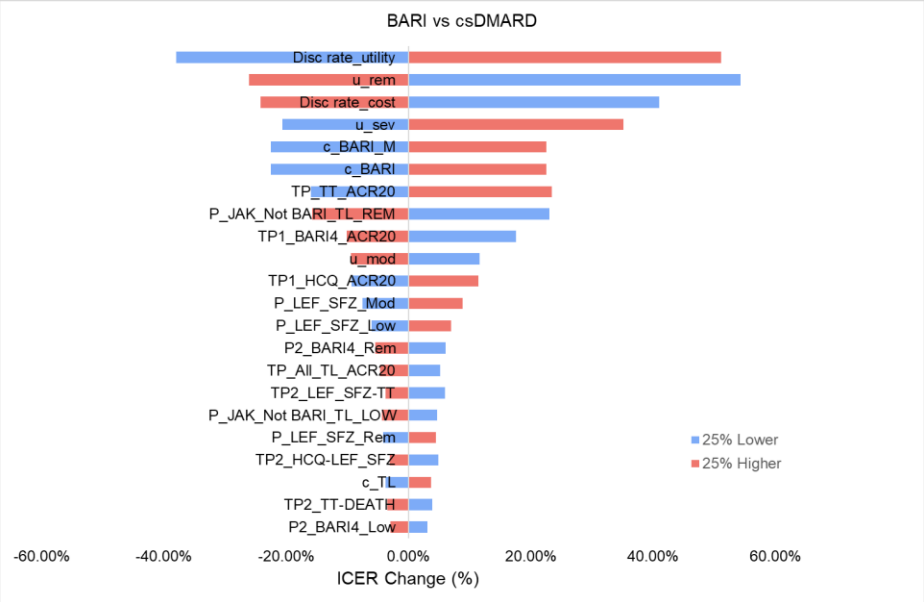


Figure 4.3.9 One-way sensitivity analysis for BARI4 vs csDMARDs

One-way sensitivity analysis was conducted using 25% higher and lower values of all the transitional probabilities, cost, and utility values. The red bars show the effect on the ICER of applying the lower limit (-25%) of the specific parameter, while the blue bars show the effect on the ICER of applying the upper limit (+25%) of the specific parameter.

PSA

PSA performed with 5000 Monte Carlo simulations for each of the intervention drug including ADA40+MTX, IFX+MTX, ETN+MTX, GOL+MTX, CZP+MTX, RTX+MTX, TOF5+MTX, TOF10+MTX and BARI4+MTX vs. csDMARDs showed that all the ICER points were distributed in the upper-right quadrant of the CE-plane, suggesting that none of the interventions (b/tDMARDs) in our study were cost-effective than csDMARDs considering a WTP of 1 GDP. The mean stochastic ICERs were in line with the base case result for all the interventions indicating no uncertainty (Table 4.3.2).

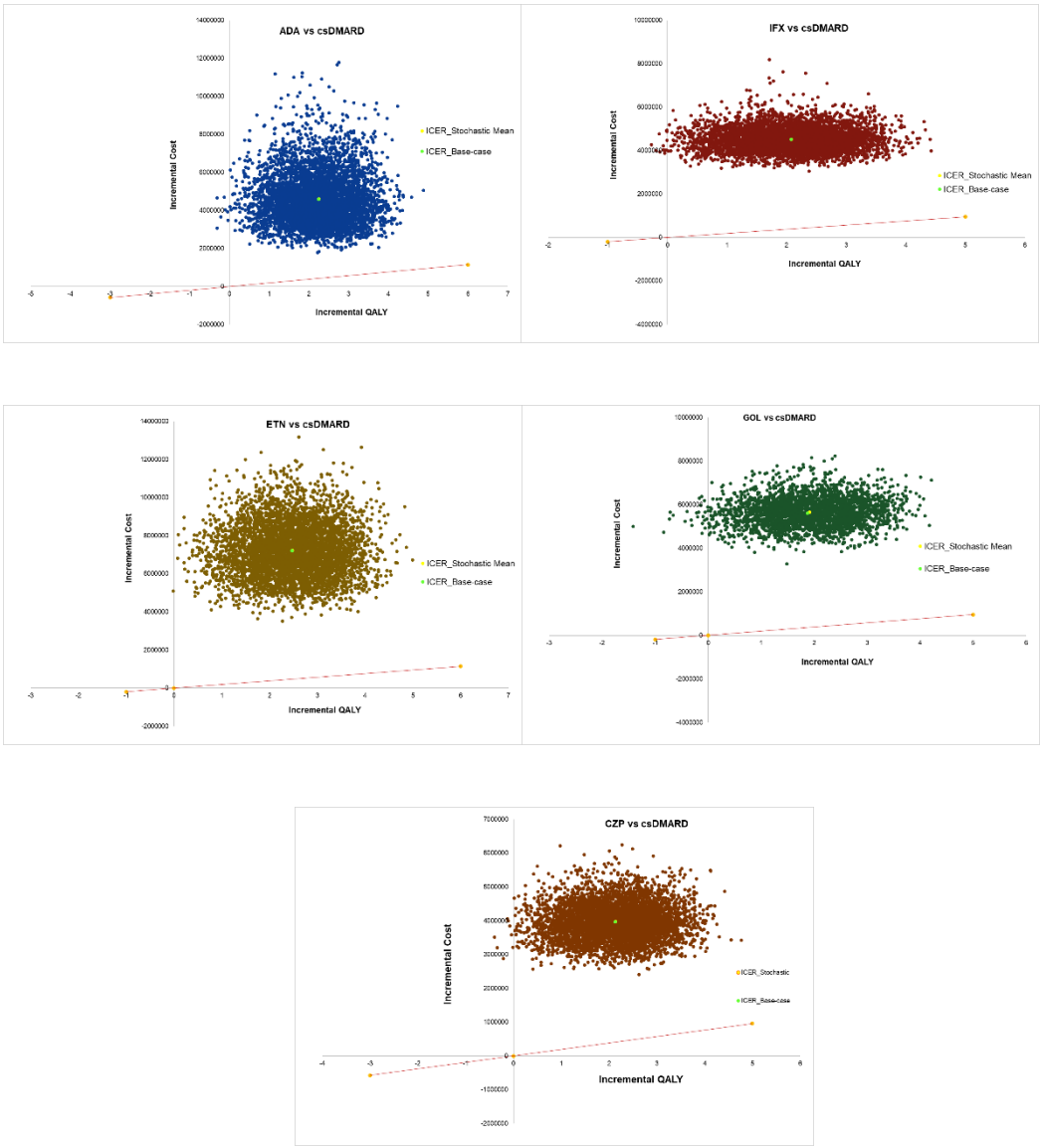


Figure 4.3.9 CE-plane for TNF-a inhibitors vs csDMARDs

Table 4.3.2 Deterministic versus Stochastic ICER values

Intervention	ICER/QALY		95% CI
	Base-case	Stochastic mean	
ADA40	₹ 24,62,235	₹ 20,45,169	₹ 9,15,686 to ₹ 71,33,083
IFX3	₹ 22,80,550	₹ 21,70,792	₹ 12,06,578 to ₹ 71,33,083
ETN50	₹ 29,81,552	₹ 29,11,094	₹ 15,35,481 to ₹ 83,11,923
GOL50	₹ 31,09,207	₹ 29,57,558	₹15,28,178 to ₹ 1,44,99,070
CZP200	₹ 19,60,391	₹ 18,56,854	₹ 10,18,885 to ₹ 68,58,144
RTX2x1000	₹ 11,80,444	₹ 10,68,451	₹ 6,08,184 to ₹ 24,25,764
TOF5	₹ 10,46,206	₹ 9,89,190	₹ 5,38,664 to ₹ 29,25,621
TOF10	₹ 11,87,703	₹ 11,25,501	₹ 6,38,863 to ₹ 32,56,714
BARI4	₹ 22,21,481	₹ 18,61,555	₹5,35,639 to ₹ 47,41,444

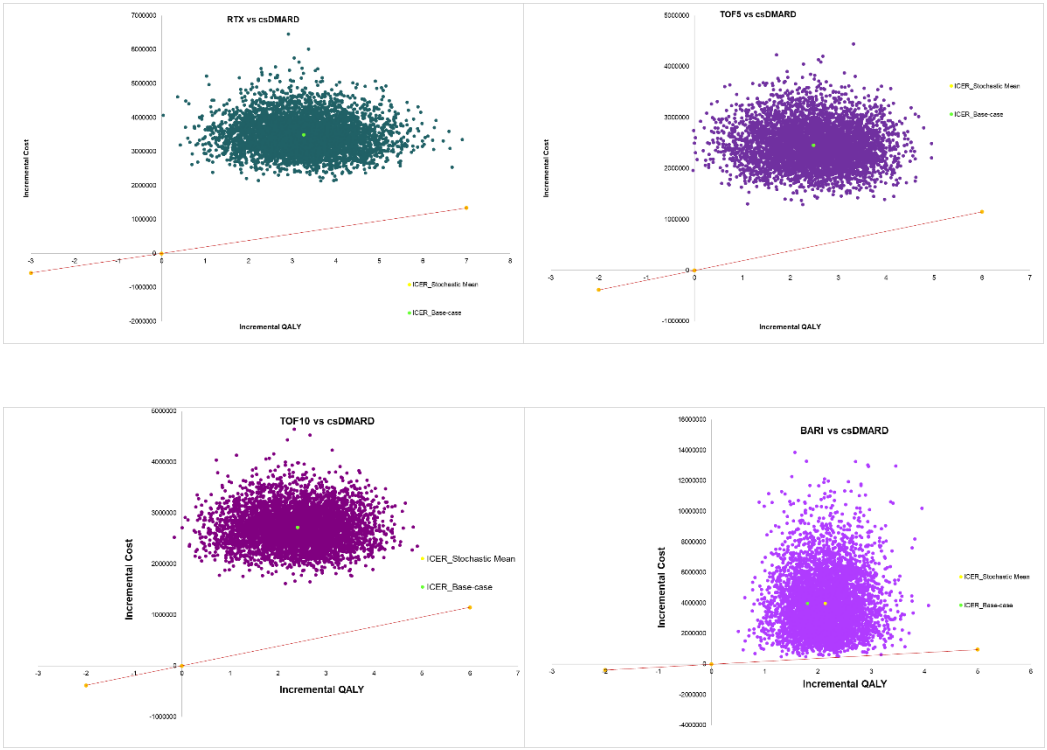


Figure 4.3.9 CE-plane for B-cell and JAK inhibitors vs csDMARDs

4.3.3 Scenario Analysis

With 25% cost reduction, none of the interventions were cost-effective. With 50% cost reduction, RTX2x1000, TOF5 and TOF10 were cost-effective considering a WTP of 3GDP. With 75% reduction in cost, most of the interventions except ETN50 and GOL50 were cost-effective considering a WTP of 3GDP. However, while considering only TOF5 was cost-effective than csDMARDs with 75% reduction in cost.

Table 4.3.2 Scenario Analysis (25% reduction in cost of all interventions)

Intervention	Cost	QALY	LY	NMB	Inc. Cost	Incremental QALY	Incremental LY	INB	ICER per QALY	ICER per LY
Comparator (csDMARD)	₹ 3,06,650	6.88	13.37	₹10,08,536						
ADA40	₹ 44,00,818	9.12	13.84	₹26,55,677	₹ 40,94,168	2.25	0.48	₹-36,64,213	₹ 18,21,511	₹85,56,970
IFX3	₹ 38,07,153	8.95	13.79	₹20,95,145	₹ 35,00,503	2.07	0.43	₹-31,03,682	₹16,87,423	₹ 82,29,107
ETN50	₹ 57,77,026	9.35	13.90	₹39,88,989	₹ 54,70,376	2.47	0.54	₹-49,97,526	₹ 22,13,002	₹1,01,74,953
GOL50	₹ 46,35,622	8.75	13.42	₹29,61,230	₹ 43,28,973	1.88	0.06	₹-39,69,766	₹ 23,05,308	₹7,37,33,981
CZP200	₹ 33,83,078	9.00	13.83	₹16,61,076	₹ 30,76,428	2.13	0.46	₹-26,69,613	₹ 14,46,566	₹66,56,693
RTX2x1000	₹ 29,56,921	9.93	13.72	₹10,58,220	₹ 26,50,271	3.05	0.35	₹-20,66,756	₹ 8,68,815	₹75,29,815
TOF5	₹ 21,92,834	9.35	13.93	₹4,03,718	₹ 18,86,184	2.48	0.57	₹-14,12,254	₹ 7,61,305	₹33,21,330
TOF10	₹ 23,90,970	9.28	14.03	₹6,15,684	₹ 20,84,320	2.41	0.66	₹-16,24,220	₹ 8,66,565	₹31,59,954
BARI4	₹ 32,52,621	8.68	14.22	₹15,92,571	₹ 29,45,972	1.80	0.86	₹-26,01,107	₹ 16,34,062	₹34,42,216

QALY-Quality Adjusted Life Years; LY-Life Years; NMB-Net Monetary Benefit; INB- Incremental Net Benefit; ICER- Incremental cost-effectiveness Ratio

Table 4.3.3 Scenario Analysis (50% reduction in cost of all interventions)

Intervention	Cost	QALY	LY	NMB	Incremental Cost	Incremental QALY	Incremental LY	Incremental NMB	ICER per QALY	ICER per LY
Comparator (csDMARDs)	₹3,06,650	6.88	13.37	₹10,08,536						
ADA40	₹29,60,677	9.12	13.84	₹12,15,537	₹26,54,028	2.25	0.48	₹-22,24,073	₹11,80,787	₹55,47,021
IFX3	₹25,76,731	8.95	13.79	₹8,64,723	₹ 22,70,081	2.07	0.43	₹-18,73,260	₹10,94,296	₹53,36,587
ETN50	₹38,77,228	9.35	13.90	₹20,89,191	₹ 35,70,578	2.47	0.54	₹-30,97,727	₹14,44,452	₹ 66,41,310
GOL50	₹31,26,039	8.75	13.42	₹14,51,646	₹ 28,19,390	1.88	0.06	₹-24,60,183	₹15,01,410	₹4,80,21,743
CZP200	₹22,90,320	9.00	13.83	₹5,68,319	₹ 19,83,671	2.13	0.46	₹-15,76,855	₹ 9,32,741	₹42,92,213
RTX2x1000	₹20,06,312	9.93	13.72	₹1,07,611	₹16,99,662	3.05	0.35	₹-11,16,148	₹5,57,185	₹48,28,994
TOF5	₹14,86,972	9.35	13.93	₹3,02,144	₹ 11,80,322	2.48	0.57	₹-7,06,392	₹4,76,404	₹20,78,397
TOF10	₹16,18,545	9.28	14.03	₹1,56,741	₹ 13,11,895	2.41	0.66	₹-8,51,795	₹ 5,45,426	₹19,88,912
BARI4	₹21,93,593	8.68	14.22	₹5,33,542	₹ 18,86,943	1.80	0.86	₹-15,42,078	₹10,46,644	₹ 22,04,795

QALY-Quality Adjusted Life Years; LY-Life Years; NMB-Net Monetary Benefit; INB- Incremental Net Benefit; ICER- Incremental cost-effectiveness Ratio

Table 4.3.4 Scenario Analysis (75% reduction in cost of all interventions)

Intervention	Cost	QALY	LY	NMB	Incremental Cost	Incremental QALY	Incremental LY	Incremental NMB	ICER per QALY	ICER per LY
Comparator (csDMARDs)	₹3,06,650	6.88	13.37	₹10,08,536						
ADA40	₹15,20,537	9.12	13.84	₹2,24,604	₹12,13,887	2.25	0.48	₹-7,83,933	₹5,40,063	₹25,37,071
IFX3	₹13,46,309	8.95	13.79	₹3,65,699	₹10,39,659	2.07	0.43	₹-6,42,837	₹5,01,169	₹24,44,067
ETN50	₹19,77,429	9.35	13.90	₹1,89,393	₹16,70,780	2.47	0.54	₹-11,97,929	₹6,75,902	₹31,07,666
GOL50	₹16,16,456	8.75	13.42	₹57,937	₹13,09,806	1.88	0.06	₹-9,50,600	₹6,97,511	₹2,23,09,505
CZP200	₹11,97,563	9.00	13.83	₹5,24,439	₹8,90,913	2.13	0.46	₹-4,84,098	₹4,18,916	₹19,27,734
RTX2x1000	₹10,55,703	9.93	13.72	₹8,42,998	₹7,49,054	3.05	0.35	₹-1,65,539	₹2,45,556	₹21,28,173
TOF5	₹7,81,110	9.35	13.93	₹10,08,006	₹4,74,460	2.48	0.57	₹-531	₹1,91,503	₹ 8,35,464
TOF10	₹8,46,120	9.28	14.03	₹9,29,166	₹5,39,471	2.41	0.66	₹-79,371	₹2,24,287	₹ 8,17,870
BARI4	₹11,34,564	8.68	14.22	₹5,25,487	₹8,27,915	1.80	0.86	₹-4,83,050	₹4,59,225	₹ 9,67,375

QALY-Quality Adjusted Life Years; LY-Life Years; NMB-Net Monetary Benefit; INB- Incremental Net Benefit; ICER- Incremental cost-effectiveness Ratio

Table 4.3.5 Cost to effectiveness Ratio of all interventions

Intervention	Cost	QALY	CER
csDMARDs	₹ 3,06,650	6.8754	₹ 44,600.95
TOF5	₹ 28,98,695	9.3530	₹ 3,09,922.29
TOF10	₹ 31,63,394	9.2807	₹ 3,40,858.17
RTX2x1000	₹ 39,07,530	9.9259	₹ 3,93,671.91
BARI4	₹ 43,11,650	8.6783	₹ 4,96,833.43
CZP200	₹ 44,75,835	9.0021	₹ 4,97,197.92
IFX3	₹ 50,37,575	8.9499	₹ 5,62,865.39
ADA40	₹ 58,40,958	9.1231	₹ 6,40,239.31
GOL50	₹ 61,45,206	8.7532	₹ 7,02,049.52
ETN50	₹ 76,76,824	9.3473	₹ 8,21,284.92

4.4 Discussion

In this model-based cost-utility analysis, we aimed to assess the cost-effectiveness of TNF-alpha inhibitors, B-cell inhibitors, and JAK inhibitors as treatment options for RA compared to csDMARDs. RA is a chronic autoimmune disease that significantly impacts patients' quality of life and healthcare resources. As newer and more targeted therapies have been introduced, evaluating their economic implications alongside clinical efficacy becomes crucial. By employing a Markov model, we were able to simulate the long-term outcomes and associated costs for each intervention, considering their impact on quality-adjusted life years (QALY) and life years (LY). Our analysis provides valuable insights into the relative cost-effectiveness of these treatment options, aiding healthcare decision-makers in optimizing resource allocation and improving patient outcomes.

The variation in cost-effectiveness among the evaluated interventions underscores the complexity of decision-making in RA treatment. In the base case analysis, all TNF-alpha, B-cell, and JAK inhibitors yielded negative net benefits compared to csDMARDs. Additionally, at the current price these drugs were found to be not cost-

effective when compared to csDMARDs for India. The costs of these interventions outweighed their incremental gains in quality-adjusted life years (QALY) and life years (LY) compared to csDMARDs. Given the incremental benefits they provide, it indicates that their use may not be economically justified. However, the results changed when the cost of biologic/targeted DMARDs (b/tDMARDs) was reduced in scenario analyses.

Scenario analyses were conducted to assess the impact of cost reductions for all b/tDMARDs by 25%, 50%, and 75%. When the scenario analysis considered a 25% and 50% reduction in the cost of all b/tDMARDs and one GDP threshold, the findings were consistent with the base case analysis, with all interventions still exhibiting negative net benefits and higher ICER per QALY. When the cost of b/tDMARDs was reduced by 75%, Tofacitinib 5mg (JAK inhibitor) had an ICER per QALY near the one GDP threshold of India, suggesting cost-effectiveness advantages over csDMARDs; however it exhibited negative net benefits.

When we consider a three GDP threshold, and a 50% reduction in the cost of b/tDMARDs, B-cell inhibitors - Rituximab 2×1000mg and JAK inhibitors - Tofacitinib 5mg, Tofacitinib 10mg becomes cost-effective. When the cost of b/tDMARDs is reduced by 75%, then JAK inhibitors - Tofacitinib 5mg, Tofacitinib 10mg, Baricitnab 4mg - and TNF-alpha inhibitors - Certolizumab Pegol 200mg - and B-cell inhibitors - Rituximab 2×1000mg becomes cost-effective. However, all of these drugs exhibit negative net monetary benefit in each scenarios. Hence these interventions are still associated with more costs than the overall benefits they provide.

These results emphasize the significant impact of drug pricing on the overall cost-effectiveness of RA treatments. Reducing the cost of b/tDMARDs could potentially

lead to more favourable cost-effectiveness profiles for these interventions, making them attractive choices for healthcare decision-makers. It is essential to consider the limitations associated with the model and assumptions used, which could influence the results.

Sensitivity analysis revealed some level uncertainty in the cost-effectiveness estimates. The probabilistic sensitivity analysis provided a more comprehensive perspective by incorporating uncertainty into the results. The stochastic mean ICERs were very close to base-case ICERs; however the 95% confidence intervals around the incremental cost-effectiveness ratios (ICERs) for each intervention were higher indicating some level of uncertainty around the cost-effectiveness estimates. This highlights the importance of carefully considering the parameters and assumptions used in the model and interpreting the findings cautiously. Considering a broader aspect in economic evaluation, the Cost Effect Ratios (CER) for the different drugs used in RA show that csDMARDs appears to be the most cost-effective option followed by Tofacitinib 5mg, Tofacitinib 10mg, Rituximab 2×1000mg, Baricitnab 4mg, and Certolizumab Pegol 200mg.

Our analysis revealed that b/tDMARDs demonstrated significantly higher costs than csDMARDs, without showing a significant difference in QALY gain. This was reflected in the high incremental cost-effectiveness ratio (ICER) for b/tDMARDs, indicating that they may not be a cost-effective option when compared to csDMARDs at the Indian willing-to-pay threshold, and the same has been observed from previous studies [92]. ccording to reported studies, when considering early RA treatment, commencing with MTX (Methotrexate) alone may be a more favorable therapeutic approach compared to TNF-alpha inhibitors, despite showing similar improvements in

disease activity and Quality-Adjusted Life Years (QALYs) from a cost-effectiveness standpoint. This preference is attributed to the higher cost associated with anti-TNF medications [112]

Even though using b/tDMARDs improves the quality of life of individuals with RA, the higher cost of b/tDMARDs drugs makes them not cost-effective. Among the bDMARDs, rituximab was reported as a cost-effective option. [74] Fournier et al. found that sarilumab exhibited dominance over adalimumab in terms of improved health outcomes and decreased costs over a longer time horizon, indicating better treatment persistence. Conversely, patients who initiated treatment with adalimumab tended to discontinue earlier, resulting in increased costs associated with subsequent treatment. [43]

Despite the lower QALYs, Tofacitinib is reported to be more cost-effective than Etanercept and dominant compared to Adalimumab; however, the results were very sensitive to price changes of these medications. [39] Despite minimal variations in the QALYs gained across different bDMARDs, csDMARDs sequences and biosimilars, using etanercept or adalimumab biosimilars as second-line biological treatments proves to be the most cost-effective option with similar clinical outcomes. Due to significant cost disparities. [85] Low-cost biosimilars can result in substantial cost savings while maintaining equal clinical effectiveness. Such cost-effectiveness considerations are essential for healthcare decision-making when maximising affordability without compromising patient outcomes. [42]

The availability and accessibility of b/t DMARDs may vary across different regions or countries, potentially impacting the feasibility and cost-effectiveness of specific treatment strategies. Additionally, the study's results were sensitive to changes in b/tDMARD costs, suggesting that the cost-effectiveness estimates are subject to

fluctuations in drug pricing. Hence, it is essential to account for variations in drug prices and explore the potential cost-effectiveness of biosimilars alongside other treatment options to conduct further assessments and inform optimal decision-making in RA management.

The study has some limitations that should be considered when interpreting its findings. The study is limited due to the lack of evidence from the Indian context. However, most of the input parameters used in our economic model have been obtained through systematic review and meta-analysis, which may increase the reliability of the data. The model assumes a cohort of RA patients with moderate to severe disease activity who have failed methotrexate. We did not consider individuals with multiple csDMARD failures. This limitation is attributed to the available data. The model focused on treatment strategies rather than explicit health states and assumed fixed health states once achieved during the first six months of treatment and were unable to capture direct transitions between different health states (eg., moderate to remission or remission to low disease activity). This limitation stemmed from the unavailability of relevant data, which restricted the exploration of such transitions through a sub-Markov model. Another limitation pertains to the data used for treatment response assessment. The model evaluates treatment response based on the achievement of ACR20 improvement within six-month cycles rather than DAS data, primarily due to data availability constraints.

In the model, we have only considered withdrawal of interventions due to lack of efficacy and adverse events. However, in reality, patients may discontinue DMARDs due to factors like comorbidities, patient preferences or physician preferences. Additionally, the model does not account for tapering or withdrawal of intervention

drugs in cases of sustained remission or low disease activity. The study's findings are limited to the specific population and setting considered in the analysis. Extrapolating the results to other populations or healthcare systems may lead to different conclusions. Another limitation of the analysis is that indirect costs such as productivity loss, time off work due to the disease, or caregiver costs were not considered. The exclusion of these costs might lead to an underestimation of the economic burden of RA.

Indeed, despite its limitations, the study gains strength due to several key components. Firstly, most of the input parameters used in the economic model were obtained through a systematic search and meta-analysis. This method of data collection increases the reliability and credibility of the information used in the study.

Secondly, the inclusion of time-varying transition probabilities based on real-world evidence further enhances the predictive accuracy of the model. By incorporating data from real-world scenarios, the model becomes more representative of the dynamic nature of disease progression and treatment outcomes.

Moreover, the study's reliance on EULAR treatment guidelines as the foundation for the model adds clinical validity to its findings. By aligning with established guidelines, the study's recommendations are more likely to be consistent with current best practices in the management of RA.

Lastly, the incorporation of sequential therapy in the management of RA within the model accounts for the treatment approach commonly used in clinical practice. This consideration makes the study's findings more applicable and relevant to real-life clinical decision-making processes.

By incorporating these components, the study strengthens its potential to provide valuable insights and guidance in RA treatment despite its inherent limitations.

4.5 Conclusion

In conclusion, this study provides valuable insights into the cost-effectiveness of different RA treatment options compared to csDMARDs. The results indicated that TNF-alpha inhibitors, B-cell inhibitors, and JAK inhibitors were not cost-effective compared to csDMARDs for RA at the current price considering a willingness-to-pay threshold of one GDP per capita for India. It also indicates that the cost-effectiveness of b/tDMARDs was sensitive to changes in drug pricing. Scenario analyses showed that 75% cost reductions for b/tDMARDs could potentially make some interventions cost-effective. Nevertheless, all evaluated interventions exhibited negative net monetary benefits. Despite the study limitations, the study provides valuable insights for healthcare decision-makers in optimizing resource allocation for improving RA patient outcomes. Future research could benefit from incorporating real-world data and conducting long-term follow-up studies to refine cost-effectiveness estimates and inform RA management more effectively.

STUDY RECOMMENDATIONS

Consideration of Conventional, Biologic and Targeted Synthetic DMARDs:

- At the current drug price for RA patients who have failed methotrexate, TNF-alpha, B-cell, and JAK inhibitors are not cost-effective compared to csDMARDs and hence not recommended.

- Given the negative net benefits of all evaluated interventions compared to csDMARDs, it is crucial to prioritize csDMARDs for RA treatment in India.

Affordability and Accessibility:

- Policy efforts should focus on improving the affordability and accessibility of csDMARDs, as they remain the standard of care and offer a reasonable balance between cost and clinical efficacy.

- Cost-effectiveness of b/tDMARDs was sensitive to changes in drug pricing in sensitivity analysis. Therefore, It is recommended to engage in price negotiations with pharmaceutical companies to reduce drug price of TNF-alpha, B-cell and JAK inhibitors when considering their inclusion in the publicly funded healthcare program for RA in India.

- To alleviate the burden due to RA, it is crucial to develop comprehensive approaches to ensure financial risk protection for RA patients in India.

- Healthcare providers should be trained to offer evidence-based treatment options to improve the health-related quality of life, particularly focusing on pain and anxiety management to enhance overall health outcomes.

SUMMARY OF RECOMMENDATIONS FROM EXISTING INTERNATIONAL GUIDELINES FOR RA TREATMENT

First-Line Treatment

- Methotrexate is strongly recommended as the first-line DMARD for DMARD-naive patients with moderate-to-high disease activity. It is preferred over hydroxychloroquine, sulfasalazine, and leflunomide. [273-281]
- If methotrexate is contraindicated or not tolerated, leflunomide or sulfasalazine may be considered as alternatives for first-line treatment. [273-281]
- For patients with low disease activity, hydroxychloroquine is conditionally recommended as the first-line csDMARD [273-281].

Consideration of Biologic and Targeted Synthetic DMARDs

- In patients with high disease activity, combination csDMARD therapy should be considered, with close monitoring of therapy-related toxicities.[275, 276]
- If the treatment target is not achieved with the first csDMARD strategy, other csDMARDs should be considered, particularly in patients with poor prognostic features.[275, 276, 278]
- Biologic DMARDs (bDMARDs) and targeted synthetic DMARDs (tsDMARDs) can be used in combination with methotrexate for patients who have had an inadequate response to csDMARDs. [275, 276, 279, 282-285]
- A treat-to-target approach is strongly recommended over usual care for patients who have not been previously treated with bDMARDs or tsDMARDs and conditionally recommended for patients who have had an inadequate response to bDMARDs or tsDMARDs.[276]

- For patients not at target, addition of a bDMARD or tsDMARD is conditionally recommended over triple therapy (sulfasalazine and hydroxychloroquine) for patients taking maximally tolerated doses of methotrexate.[276, 282, 285]
- Switching to a bDMARD or tsDMARD of a different class is conditionally recommended over switching to a bDMARD or tsDMARD belonging to the same class for patients taking a bDMARD or tsDMARD who are not at target.[276, 285]

Tapering/Discontinuing DMARDs

- Continuation of all DMARDs at their current dose is conditionally recommended over a dose reduction of a DMARD, dose reduction is conditionally recommended over gradual discontinuation of a DMARD, and gradual discontinuation is conditionally recommended over abrupt discontinuation of a DMARD for patients who are at target for at least 6 months.[276]
- Gradual discontinuation of sulfasalazine is conditionally recommended over gradual discontinuation of hydroxychloroquine for patients taking triple therapy who wish to discontinue a DMARD. [276]
- Gradual discontinuation of methotrexate is conditionally recommended over gradual discontinuation of the bDMARD or tsDMARD for patients taking methotrexate plus a bDMARD or tsDMARD who wish to discontinue a DMARD. [276]

PUBLICATIONS FROM THE STUDY

- Kumar SS, Bagepally BS, Sasidharan A. Cost Effectiveness of Rituximab Therapy for Rheumatoid Arthritis: A Systematic Review and Meta-Analysis of Cost-Utility Studies. Clin Drug Investig. 2023 Feb;43(2):97-108. doi: 10.1007/s40261-022-01238-3. Epub 2023 Jan 9. PMID: 36624250.
- Kumar SS, Haridoss M, Venkataraman K, Bagepally BS. Cost-effectiveness of janus kinase inhibitors for rheumatoid arthritis: A systematic review and meta-analysis of cost-utility studies. Front Pharmacol. 2022 Dec 13;13:1090361. doi: 10.3389/fphar.2022.1090361. PMID: 36582538; PMCID: PMC9792993.
- Sajith kumar S., Bagepally BS. (2023) "Cost-effectiveness of Tumour Necrosis Factor-alpha inhibitors: A systematic review and meta-analysis of cost-utility studies" (Under Review in Expert Review of Pharmacoeconomics & Outcomes Research)
- Haridoss M, Bagepally BS, Venkataraman K, Purushothaman SR. Health-related quality of life and its association with disease activity/functional status in Rheumatoid arthritis: A cross-sectional study (Manuscript under review in Plos one)
- Bagepally BS , Kumar SS, Sasidharan A, Haridoss M, Venkataraman K. Household Catastrophic Health Expenditures for Rheumatoid Arthritis in South India (Manuscript under review in Scientific Reports)

APPENDICES

Appendix 2.1.1 Search Strategy for Systematic review of cost-utility studies on TNF-a, B-cell and JAK inhibitors

PICOS	PUBMED search terms	Hits on date 12th Feb 2021	Hits on date 5th May 2022
P	"arthritis, rheumatoid"[MeSH Terms] OR rheumatoid arthritis	153,377	161,308
I	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
O	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 5th May 2022		90

PICOS	**Embase Search terms**	Hits on date 12th Feb 2021	Hits on date 5th May 2022
P	'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

I	'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 '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 'eticovo' OR 'infinitam' OR 'lifmior' OR 'nepexto' OR 'opinercept' OR 'recombinant tumor necrosis factor receptor fc fusion protein' OR 'recombinant tumour necrosis factor receptor fc fusion protein' OR 'tumor necrosis factor receptor fc fusion protein' OR 'tumour necrosis factor receptor fc fusion protein' OR 'tunex' OR 'tofacitinib'/exp OR 'tasocitinib' OR 'tasocitinib citrate' OR 'tofacitinib' OR 'tofacitinib citrate' OR 'xeljanz' OR 'xeljanz xr' OR 'adalimumab'/exp OR 'ctp17' OR 'cyltezo' OR 'exemptia' 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 n10 methylpteroylglutamic acid' OR 'mtx' OR 'amethopterin' OR 'amethopterine' OR 'canceren' OR 'farmotrex' OR 'folex' OR 'imeth' OR 'metex' OR 'methotrexat' OR 'methotrexate' OR 'methrotrexate' OR 'methylaminopterin' OR 'meticil' OR 'metothrexate' OR 'metotrexat' OR 'metotrexate' OR 'metrex' OR 'r 9985' OR 'rheumatrex' OR 'texate' OR 'trexall' OR 'xatmep' OR 'xaken' OR 'rituximab'/exp OR 'mabthera' OR 'reditux' OR 'ritemvia' OR 'ritumax' OR 'rituxan' OR 'rituximab' OR 'rituxin' OR 'rituzena' OR 'rixathon' OR 'riximyo' OR 'ruxience' OR 'tuxella' OR 'truxima' OR 'ocrelizumab'/exp OR 'ocrelizumab' OR 'ocrevus' OR 'ofatumumab'/exp OR 'arzerra' OR 'humaxcd20' OR 'ofatumumab' OR 'kesimpta' OR 'ublituximab'/exp OR 'utuxin' OR 'ublituximab' OR 'dmard'	356,629	396,592
O	'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	877,755	970,430

	efficiency analysis' OR 'willingness to pay' OR 'cost utility analysis'/exp OR 'cost utility' OR 'cost utility analysis'		
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 till date		157
PICOS	**Scopus search terms**	Hits on date 12th Feb 2021	Hits on date 5th May 2022
P	"Rheumatoid arthritis" OR rheumatoid	560,511 results	611,784 results
I	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
O	"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	1,542 results	1,716 results

	life years" OR qaly OR ly OR "life year$" OR daly OR "disability adjusted" OR "incremental cost effective ratio" OR "ICER" OR "incremental net benefit" OR inb OR "benefit ratio" OR 'cost AND benefit' OR 'cost AND minimi?ation' OR "cost-effectiveness" OR "cost effectiveness ratio" OR "cost efficiency analys?s" OR "cost utility") AND (LIMIT-TO (DOCTYPE , "ar")) AND (LIMIT-TO (SRCTYPE , "j"))		
	From 2021 to 5th May 2022 TITLE-ABS-KEY ("Rheumatoid arthritis" OR rheumatoid) AND (tnf OR "Tumor Necrosis Factor" OR "JAK inhibitor" OR "JAK inhibitors" OR "Janus kinase inhibitor" OR dmard OR "disease modifying anti-rheumatic drugs" OR biologics OR upadacitinib OR rinvoq OR baricitinib OR olumiant OR simponi OR "Simponi Aria" OR golimumab OR "certolizumab pegol" OR certolizumab OR inflectra OR infliximab-dyyb OR infliximab OR remicade OR etanercept-szzs OR erelzi OR etanercept OR enbrel OR adalimumab-atto OR amjevita OR adalimumab OR humira OR cyltezo OR hyrimoz OR cimzia OR methotrexate OR amethopterin OR mtx OR otrexup OR trexall OR rheumatrex OR rasuvo OR tofacitinib OR xeljanz OR rituximab OR rituxan OR truxima OR mabthera OR ocrelizumab OR ofatumumab OR ublituximab) AND ("cost effectiv*" OR "cost utility" OR "cost benefit" OR "cost-benefit" OR "quality adjusted life years" OR qaly OR ly OR "life year$" 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))		171 results

Appendix 3.1.1 STROBE Statement—Checklist (HRQoL in RA)

	Item No.	Recommendation	Page No.
Title and abstract	1	(*a*) Indicate the study's design with a commonly used term in the title or the abstract	Yes
		(*b*) Provide in the abstract an informative and balanced summary of what was done and what was found	Yes
Introduction			
Background/rationale	2	Explain the scientific background and rationale for the investigation being reported	Yes
Objectives	3	State specific objectives, including any prespecified hypotheses	Yes
Methods			
Study design	4	Present key elements of study design early in the paper	Yes
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection	Yes
Participants	6	(*a*) *Cross-sectional study*—Give the eligibility criteria, and the sources and methods of selection of participants	Yes
		(*b*) *Cohort study*—For matched studies, give matching criteria and number of exposed and unexposed *Case-control study*—For matched studies, give matching criteria and the number of controls per case	
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable	Yes
Data sources/ measurement	8*	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group	Yes
Bias	9	Describe any efforts to address potential sources of bias	Yes
Study size	10	Explain how the study size was arrived at	Yes

Appendix 3.2.1 CHEERS 2022 Checklist

Topic	No.	Item	Location where item is reported
	1	Identify the study as an economic evaluation and specify the interventions being compared.	NA
	2	Provide a structured summary that highlights context, key methods, results, and alternative analyses.	NA
Introduction			
Background and objectives	3	Give the context for the study, the study question, and its practical relevance for decision making in policy or practice.	Yes
Methods			
Health economic analysis plan	4	Indicate whether a health economic analysis plan was developed and where available.	Yes
Study population	5	Describe characteristics of the study population (such as age range, demographics, socioeconomic, or clinical characteristics).	Yes
Setting and location	6	Provide relevant contextual information that may influence findings.	Yes
Comparators	7	Describe the interventions or strategies being compared and why chosen.	NA
Perspective	8	State the perspective(s) adopted by the study and why chosen.	Yes
Time horizon	9	State the time horizon for the study and why appropriate.	Yes
Discount rate	10	Report the discount rate(s) and reason chosen.	NA
Selection of outcomes	11	Describe what outcomes were used as the measure(s) of benefit(s) and harm(s).	Yes
Measurement of outcomes	12	Describe how outcomes used to capture benefit(s) and harm(s) were measured.	Yes
Valuation of outcomes	13	Describe the population and methods used to measure and value outcomes.	Yes
Measurement and valuation of resources and costs	14	Describe how costs were valued.	Yes
Currency, price date, and conversion	15	Report the dates of the estimated resource quantities and unit costs, plus the currency and year of conversion.	Yes
Rationale and description of model	16	If modelling is used, describe in detail and why used. Report if the model is publicly available and where it can be accessed.	NA
Analytics and assumptions	17	Describe any methods for analysing or statistically transforming data, any extrapolation methods, and approaches for validating any model used.	NA
Characterising heterogeneity	18	Describe any methods used for estimating how the results of the study vary for subgroups.	Yes
Characterising distributional effects	19	Describe how impacts are distributed across different individuals or adjustments made to reflect priority populations.	Yes
Characterising uncertainty	20	Describe methods to characterise any sources of uncertainty in the analysis.	NA
Approach to engagement with patients and others affected by the study	21	Describe any approaches to engage patients or service recipients, the general public, communities, or stakeholders (such as clinicians or payers) in the design of the study.	Yes
Results			
Study parameters	22	Report all analytic inputs (such as values, ranges, references) including uncertainty or distributional assumptions.	Yes
Summary of main results	23	Report the mean values for the main categories of costs and outcomes of interest and summarise them in the most appropriate overall measure.	Yes
Effect of uncertainty	24	Describe how uncertainty about analytic judgments, inputs, or projections affect findings. Report the effect of choice of discount rate and time horizon, if applicable.	Yes
Effect of engagement with patients and others affected by the study	25	Report on any difference patient/service recipient, general public, community, or stakeholder involvement made to the approach or findings of the study	NA
Discussion			
Study findings, limitations, generalisability, and current knowledge	26	Report key findings, limitations, ethical or equity considerations not captured, and how these could affect patients, policy, or practice.	Yes
Other relevant information			
Source of funding	27	Describe how the study was funded and any role of the funder in the identification, design, conduct, and reporting of the analysis	Yes

Topic	No.	Item	Location where item is reported
Conflicts of interest	28	Report authors conflicts of interest according to journal or International Committee of Medical Journal Editors requirements.	Yes

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Appendix 3.2.2 STROBE Statement—Checklist (Assessment of OOPES in RA)

	Item No	Recommendation	Page No
Title and abstract	1	(*a*) Indicate the study's design with a commonly used term in the title or the abstract	Yes
		(*b*) Provide in the abstract an informative and balanced summary of what was done and what was found	Yes
Introduction			
Background/rationale	2	Explain the scientific background and rationale for the investigation being reported	Yes
Objectives	3	State specific objectives, including any prespecified hypotheses	Yes
Methods			
Study design	4	Present key elements of study design early in the paper	Yes
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection	Yes
Participants	6	(*a*) Give the eligibility criteria, and the sources and methods of selection of participants	Yes
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable	Yes
Data sources/ measurement	8*	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group	Yes
Bias	9	Describe any efforts to address potential sources of bias	NA
Study size	10	Explain how the study size was arrived at	Yes
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why	Yes
Statistical methods	12	(*a*) Describe all statistical methods, including those used to control for confounding	Yes
		(*b*) Describe any methods used to examine subgroups and interactions	Yes
		(*c*) Explain how missing data were addressed	Yes
		(*d*) If applicable, describe analytical methods taking account of sampling strategy	NA
		(*e*) Describe any sensitivity analyses	Yes
Results			
Participants	13*	(a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed	Yes
		(b) Give reasons for non-participation at each stage	NA
		(c) Consider use of a flow diagram	
Descriptive data	14*	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders	Yes
		(b) Indicate number of participants with missing data for each variable of interest	NA
Outcome data	15*	Report numbers of outcome events or summary measures	Yes
Main results	16	(*a*) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included	Yes
		(*b*) Report category boundaries when continuous variables were categorized	Yes
		(*c*) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period	Yes
Other analyses	17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses	Yes
Discussion			
Key results	18	Summarise key results with reference to study objectives	Yes
Limitations	19	Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias	Yes
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and	Yes

		other relevant evidence	
Generalisability	21	Discuss the generalisability (external validity) of the study results	Yes
Other information			
Funding	22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based	Yes

*Give information separately for exposed and unexposed groups.

The STROBE checklist is best used in conjunction with this article (freely available on the Web sites of PLoS Medicine at http://www.plosmedicine.org/, Annals of Internal Medicine at http://www.annals.org/, and Epidemiology at http://www.epidem.com/). Information on the STROBE Initiative is available at www.strobe-statement.org.

Appendix 4.1 CHEERS 2022 Checklist (Model-based economic evaluation of RA interventions)

Topic	No.	Item	Location where item is reported
	1	Identify the study as an economic evaluation and specify the interventions being compared.	Yes
	2	Provide a structured summary that highlights context, key methods, results, and alternative analyses.	NA
Introduction			
Background and objectives	3	Give the context for the study, the study question, and its practical relevance for decision making in policy or practice.	Yes
Methods			
Health economic analysis plan	4	Indicate whether a health economic analysis plan was developed and where available.	Yes
Study population	5	Describe characteristics of the study population (such as age range, demographics, socioeconomic, or clinical characteristics).	Yes
Setting and location	6	Provide relevant contextual information that may influence findings.	Yes
Comparators	7	Describe the interventions or strategies being compared and why chosen.	Yes
Perspective	8	State the perspective(s) adopted by the study and why chosen.	Yes
Time horizon	9	State the time horizon for the study and why appropriate.	Yes
Discount rate	10	Report the discount rate(s) and reason chosen.	Yes
Selection of outcomes	11	Describe what outcomes were used as the measure(s) of benefit(s) and harm(s).	Yes
Measurement of outcomes	12	Describe how outcomes used to capture benefit(s) and harm(s) were measured.	Yes
Valuation of outcomes	13	Describe the population and methods used to measure and value outcomes.	Yes
Measurement and valuation of resources and costs	14	Describe how costs were valued.	Yes
Currency, price date, and conversion	15	Report the dates of the estimated resource quantities and unit costs, plus the currency and year of conversion.	Yes
Rationale and description of model	16	If modelling is used, describe in detail and why used. Report if the model is publicly available and where it can be accessed.	Yes
Analytics and assumptions	17	Describe any methods for analysing or statistically transforming data, any extrapolation methods, and approaches for validating any model used.	Yes
Characterising heterogeneity	18	Describe any methods used for estimating how the results of the study vary for subgroups.	Yes
Characterising distributional effects	19	Describe how impacts are distributed across different individuals or adjustments made to reflect priority populations.	Yes
Characterising uncertainty	20	Describe methods to characterize any sources of uncertainty in the analysis.	Yes
Approach to engagement with patients and others affected by the study	21	Describe any approaches to engage patients or service recipients, the general public, communities, or stakeholders (such as clinicians or payers) in the design of the study.	Yes
Results			
Study parameters	22	Report all analytic inputs (such as values, ranges, references) including uncertainty or distributional assumptions.	Yes
Summary of main results	23	Report the mean values for the main categories of costs and outcomes of interest and summarise them in the most appropriate overall measure.	Yes
Effect of uncertainty	24	Describe how uncertainty about analytic judgments, inputs, or projections affect findings. Report the effect of choice of discount rate and time horizon, if applicable.	Yes
Effect of engagement with patients and others affected by the study	25	Report on any difference patient/service recipient, general public, community, or stakeholder involvement made to the approach or findings of the study	Yes
Discussion			

Topic	No.	Item	Location where item is reported
Study findings, limitations, generalisability, and current knowledge	26	Report key findings, limitations, ethical or equity considerations not captured, and how these could affect patients, policy, or practice.	Yes
Other relevant information			
Source of funding	27	Describe how the study was funded and any role of the funder in the identification, design, conduct, and reporting of the analysis	NA
Conflicts of interest	28	Report authors conflicts of interest according to journal or International Committee of Medical Journal Editors requirements.	NA

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