Project: Cost Effectiveness of Targeted Immune Modulators for Rheumatoid Arthritis

Modeling Analysis Plan

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Version 1.0

The Cost-Effectiveness of Targeted Immune Modulators for Rheumatoid Arthritis: Modeling Analysis Plan

Background

Rheumatoid arthritis (RA) is the most common autoimmune inflammatory arthritis in adults, affecting between 1.3 and 1.8 million Americans.[1,2] RA is more common in women and may occur at any age, with peak incidence occurring at ages 50 to 60 years.[3] RA is typically characterized by morning stiffness and symmetrical joint swelling of the feet, hands, and knees, although any joint (and in some cases, internal organs) may be involved.[3] RA is considered a clinical syndrome that encompasses several disease subsets, each of which involves a distinct inflammatory cascade that can lead to joint damage, deformity, and organ dysfunction.[4] The course of RA may be complicated by cardiac, hematologic, and other extra-articular manifestations.[3] Historically, RA was associated with both progressive disability and a shortened lifespan, although improvements in diagnosis as well as aggressive use of disease-modifying anti-rheumatic drugs (DMARDs) have greatly improved prognosis in the past 20 years.[5]

The chemotherapeutic agent methotrexate is the most widely used conventional DMARD; it is considered an "anchor drug" because of its effectiveness and tolerability as well as its potential to enhance the effectiveness of biologic and non-biologic drugs that are targeted at certain mediators of inflammation in RA, known collectively as "targeted immune modulators" (TIMs).[3] However, only about 50% of patients treated with methotrexate alone will receive sufficient reduction in disease activity or remission of symptoms. Over the past 18 years, the introduction of TIMs has greatly improved prognosis for many RA patients. Agents with indications for RA include inhibitors or antagonists of multiple mediators of the inflammatory cascade, including tumor necrosis factor (TNF), the B-lymphocyte CD20 antigen, interleukin (IL) 1 and 6, Janus kinase (JAK), and T cells. Agents with anti-IL-6 and anti-JAK activity are also currently under regulatory review for an RA indication. Guidelines from the American College of Rheumatology recommend use of TIMs in patients with moderate-to-severe disease activity despite use of conventional DMARDs.[6] However, TIMs for moderate-to-severe RA are expensive, and there is evidence that both their prices and the proportion of those costs paid by patients have increased substantially in recent years.[7] Uncertainty remains in whether or not the price and administration of these drugs is justified by improved prognosis for RA patients.

Approach

The primary aim of this analysis is to estimate the cost-effectiveness of TIMs for moderately-to-severely active RA patients. We will develop a sequential treatment cohort model to assess the cost-effectiveness of each of the TIMs detailed below relative to conventional DMARDs as well as against the TIM market leader. The target population will consist of adult patients with moderately-to-severely active RA who have an inadequate response to prior therapy. Alternative strategies will be evaluated pending available evidence, including (1) use of TIMs in TIM-naïve patients with an inadequate response to conventional DMARDs; and (2) use of TIMS in patients with an inadequate response to their first TIM therapy.

Population

The population for the cost-effectiveness analysis will include adults aged 18 years and older with moderately-to-severely active RA and inadequate response to or intolerance to conventional DMARDs. The model will simulate a hypothetical homogenous cohort of patients, with baseline characteristics

similar to United States RA registries as summarized by Curtis and colleagues.[8] Two different cohorts of patients will be modeled, including (1) patients who are TIM-naïve and have had an inadequate response to conventional DMARDs; and (2) patients who are starting a second TIM after having an inadequate response to initial TIM therapy. Table 1 depicts the model characteristics for each cohort.

Table 1. Model Cohort Characteristics

	Value	Primary Source
TIM-Naïve Patients		
Mean age	55 years (range 50 to 60 years old)	Curtis et al., 2010[8]
Female	79% (range 73%,86%)	Curtis et al., 2010[8]
Caucasian	84%	Curtis et al., 2010[8]
Mean Weight	170 pounds	National Health and Nutrition Examination Survey data[9]
Baseline HAQ	1.5 (range: 1.1 to 2.1)	Curtis et al., 2010[8]
Baseline TSS	54 (SD: 64)	Lillegraven et al., 2011[10]
Number of Previous DMARDs (non-TIM)	2	Curtis et al., 2010[8]
TIM-Experienced Patients		
Mean age	55 years (range 50 to 60 years old)	Curtis et al., 2010[8]
Female	79% (range 73%,86%)	Curtis et al., 2010[8]
Caucasian	84%	Curtis et al., 2010[8]
Mean Weight	170 pounds	National Health and Nutrition Examination Survey data[9]
Baseline HAQ	1.5 (range: 1.1 to 2.1)	Curtis et al., 2010[8]
Baseline TSS	54 (SD: 64)	Lillegraven et al., 2011[10]
Number of Previous TIMS	1	Model evaluation

HAQ=Health Assessment Questionnaire for Rheumatoid Arthritis Disability Index
TSS=Total Sharp Score

Of these model cohort characteristics, age and gender will be used to calculate the risk of mortality. The mean weight will be used to calculate average dosing for TIMS administered intravenously, and the baseline HAQ score will serve as the starting point for the model-simulated HAQ score.

Interventions

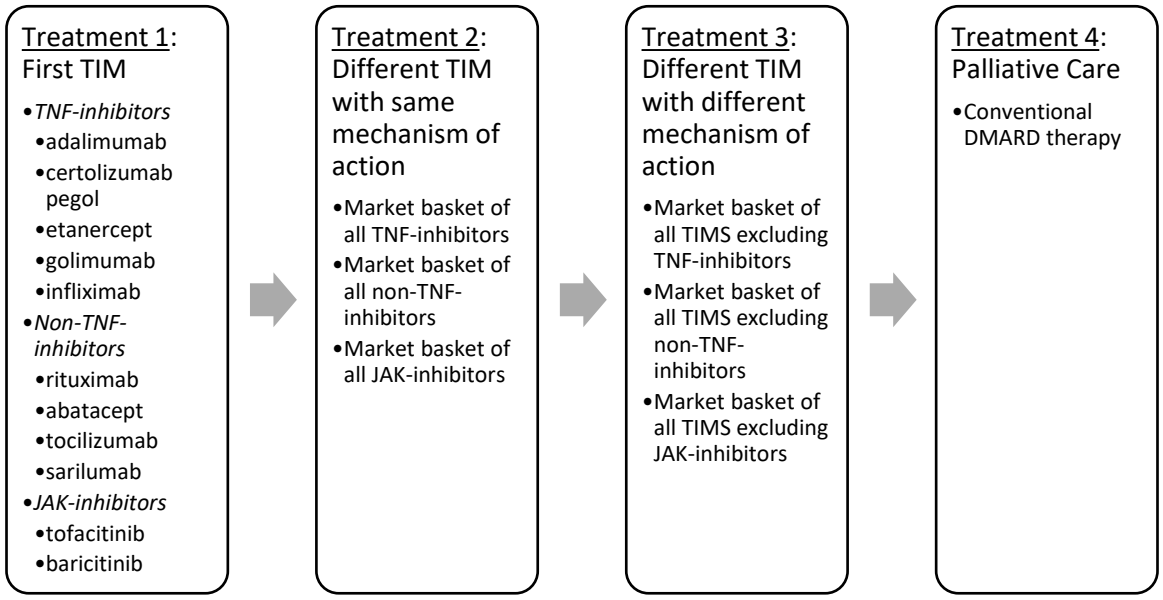
A comprehensive list of TIMS with FDA indications for RA, as well as two investigational therapies currently undergoing FDA review, will be considered. The interventions of interest, listed by class, include:

- TNF inhibitors (adalimumab, certolizumab pegol, etanercept, golimumab, infliximab)
- CD20-directed cytolytic antibody (rituximab)

- T-cell inhibitor (abatacept)
- IL-6 inhibitors (tocilizumab, sarilumab [investigational])
- JAK inhibitors (tofacitinib, baricitinib [investigational])

In the clinical setting, it is not uncommon for patients to cycle through multiple therapies before finding a treatment option to which they best respond and tolerate. To account for this, the model will allow patients who withdraw from a TIM (due to lack/loss of effectiveness and/or adverse events) to switch therapy up to three times. The first switch will be to an agent with a similar mechanism of action; the second will be to an agent with a different mechanism of action; and the third and final switch will be to a palliative care state that involves conventional DMARD therapy. A scenario analysis will be conducted where Treatment 4 will consist of a market basket of all TIMS instead of conventional DMARD therapy. Patients will stay on the market basket of TIMs for the duration of their treatment. The model's sequential treatment pattern is consistent with the ACR 2015 Guidelines for the treatment of RA and is presented in Figure 1.[6]

Figure 1. Model Sequential Treatment Pattern



According to Figure 1, the TIM-naïve cohort will enter the model with Treatment 1, while the TIM-experienced cohort will enter the model with Treatment 2, assuming they previously failed Treatment 1.

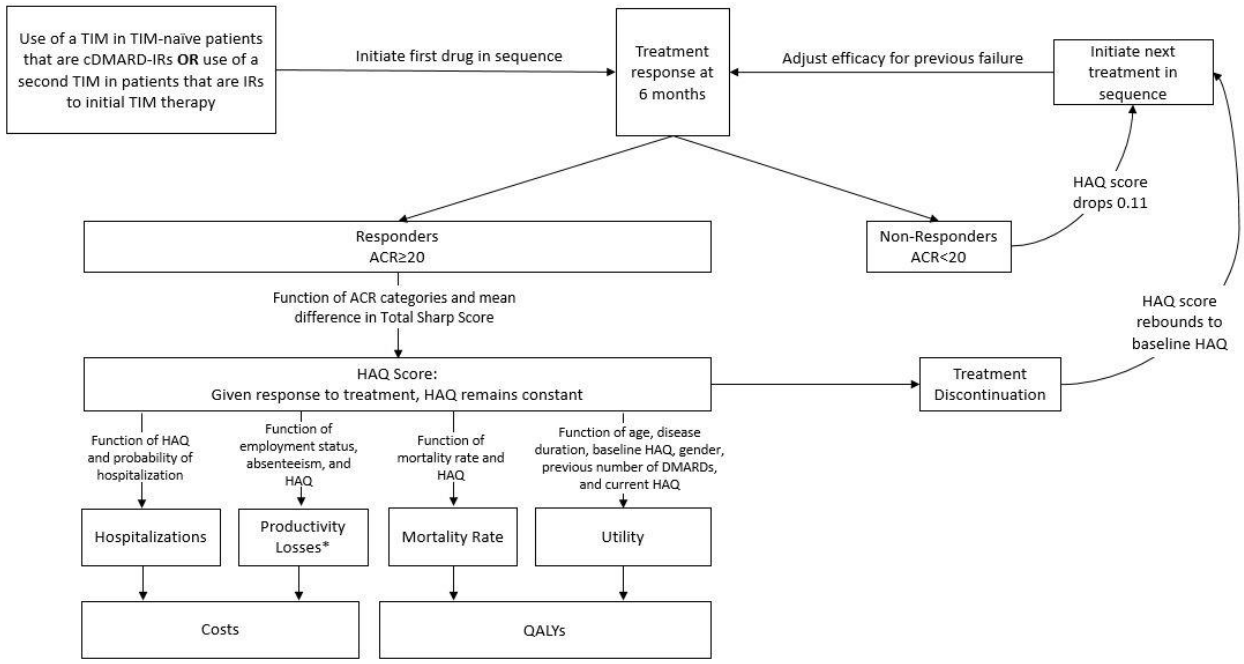
Because we expect most available clinical trials of TIMS will involve comparisons to conventional agents for regulatory approval, the primary comparator will be conventional DMARDs (i.e. methotrexate or alternative conventional DMARDs for those who cannot tolerate methotrexate). However, comparisons will also be made against the TIM market leader (adalimumab).

Model Overview

Model Structure

The sequential treatment cohort model will simulate a hypothetical homogenous cohort of patients from the initiation of a TIM until death, and therefore a lifetime time horizon will be used to reflect the chronic nature of RA. The model framework is depicted in Figure 2. After starting a TIM, the model will relate the American College of Rheumatology (ACR) response to the Health Assessment Questionnaire for Rheumatoid Arthritis Disability Index (HAQ) after six months of therapy (consistent with other US peer-reviewed models).[11-15] In addition to relating ACR response to HAQ, this model framework will also accommodate the association of joint damage, as measured through Total Sharp Score, with HAQ.[14] The HAQ score will then be linked to utility, mortality, hospitalizations, and productivity. The simulated utility score and mortality will be used to calculate the quality-adjusted life years (QALYs) gained, and the hospitalization rate will factor into the total costs from the payer perspective. The model will continue to simulate the long-term HAQ score every six months until withdrawal from the treatment or death. Patients can withdraw from a TIM due to lack/loss of effectiveness and/or adverse events. Upon withdrawal, the model simulates the patient switching therapy up to three different times. A cycle length of six months will be used to reflect the time needed to conclude a treatment's efficacy.[12] All future costs and outcomes will be discounted 3% per year.

Figure 2. Model Framework



*Productivity losses will be investigated in a scenario analysis.
ACR=American College of Rheumatology improvement criteria
cDMARD=conventional disease-modifying antirheumatic drug
DMARD=disease-modifying antirheumatic drug
HAQ=Health Assessment Questionnaire
IR= inadequate responder
QALYs=quality-adjusted life years

The economic evaluation will primarily be from a health-system perspective, and will thus largely focus on direct medical and pharmacy costs. We will conduct a separate analysis to attempt to extend the

perspective to a societal one in order to include the indirect costs due to potential productivity gains.[16] We will develop the model in Microsoft Excel®.

Key Model Choices and Assumptions

A number of assumptions will be made to inform our model. These assumptions are detailed below.

- Patients can discontinue treatment for three reasons: (1) lack of effectiveness, (2) loss of effectiveness, and (3) occurrence of adverse event.
- A treatment is tested for at least six months before a decision to discontinue is made.
- Those that discontinue treatment move to the next treatment in the sequence.
- After three different TIM failures, a patient goes back to palliative care and stays with that therapy for the rest of his/her life. A scenario analysis will consider a market basket of all TIMS (instead of palliative care) as the fourth and final treatment strategy.
- Those patients who have an ACR score less than 20 are assumed to not respond to therapy.[15]
- Cost of treatment for those that do not respond will be the full length of the cycle (six months). Sensitivity analyses will consider other time periods for treatment non-response (i.e. three months).
- Responders experience a constant probability of discontinuation for treatment cycles 2 and above.[15]
- Given response to treatment, the HAQ remains constant.[15]
- At the half-way point in a cycle resulting in discontinuation, HAQ rebounds to the HAQ at treatment initiation.[15]
- Oral treatments are assumed to have zero administration costs. Self-administered subcutaneous treatments will include a one-time office visit cost for training on the self-administration. Administration costs for an office-administered subcutaneous treatment will include the cost of an office visit per administration. The administration cost for treatments administered intravenously will include the cost for an intravenous infusion.

Model Inputs: Model-Wide Inputs

Model-Wide Clinical Inputs

Model-wide clinical inputs and functions are detailed in Table 2.

Table 2. Model-Wide Clinical Inputs and Functions

Input	Value	Source
HAQ Score relationship with ACR score/categories	ACR70→HAQ score drop of 1.07 ACR50→HAQ score drop of 0.76 ACR20→HAQ score drop of 0.44 subACR20→HAQ score drop of 0.11	Carlson et al., 2015[15] Gabay et al., 2013[17]
HAQ Score relationship with Total Sharp Score	**E(HAQ) on treatment**= exp(-1.73+0.02(baseline TSS+TSS mean difference)) / 1 + exp(-1.73+0.02(baseline TSS+TSS mean difference))*3	Stephens et al., 2015[14]

	E(HAQ) at baseline= exp(-1.73+0.02baseline TSS) / 1+exp(-1.73+0.02baseline TSS)*3 **Change in HAQ**=E(HAQ) on treatment – E(HAQ) at baseline	
Mortality rate relationship with HAQ score	RA-specific mortality rate = Mortality from life table*1.33^{HAQ}	US national statistics to create life table. Carlson et al., 2015[15] Wolfe et al., 2003[18]
Utility score relationship with HAQ score	EQ-5D=2.0734 + 0.0058age + 0.0023disease duration – 0.2004baseline HAQ – 0.2914male + 0.0249previous DMARDs – 0.8647current HAQ	Wailoo et al., 2008[11]
Hospital days relationship with HAQ score	**P(hospitalization)**=exp(3.616-0.786*HAQ) / (1+ exp(3.616-0.786*HAQ)) Number hospital days given hospitalization, **H** =2.4898+0.0497*HAQ Expected value of hospital days = **P(hospitalization) * H**	Stephens et al., 2015[14]
Baseline missed worked days per month due to RA	4 days	Emery et al., 2015[19]
Days missed from work relationship with HAQ score	Responders: 1.93 fewer missed work days per month ACR nonresponders: 0.71 more missed work days per month	Osterhaus et al., 2009[20]
Unemployment relationship with HAQ score	A 0.25 increase in HAQ is associated with a 30% increased likelihood for unemployed status (OR=1.30, 95% CI=1.22, 1.39). Baseline unemployment: 3.8% for all ages ≥ 55 years old.	Han et al., 2015[21] US Bureau of Labor and Statistics[22]
Efficacy of secondary/tertiary DMARDs after insufficient response to previous treatment	HR: 0.84	Carlson et al., 2015[15] Karlsson et al., 2008[23]

Model-Wide Cost Inputs

Model-wide cost inputs are detailed in Table 3.

Table 3. Model-Wide Cost Inputs

Input	Value	Source
Cost of intravenous treatment administration (per hour)	$105	Carlson et al., 2015[15] Centers for Medicare and Medicaid Services[24]
Cost per hospital day	$1251	Carlson et al., 2015[15] Centers for Medicare and Medicaid Services[24]
Cost per office visit	$55	Carlson et al., 2015[15] Centers for Medicare and Medicaid Services[24]
Average hourly wage	$23.23	US Buerau of Labor Statistics[25]
Drug monitoring cost*	$250	Assumption

*For drug monitoring costs, we are assuming that frequency of monitoring will drive the cost and that cost per monitoring is approximately equal across TIMs.
All costs will be adjusted to 2015 USD.

Model Inputs: Treatment-Specific Inputs

Drug Response

Drug response will be measured by ACR score. The **proportion of patients** in each ACR response category (subACR20, ACR20, ACR50, and ACR70) will be used in the model to measure response and improvement due to therapy. These categories are mutually exclusive and exhaustive. Given that the trial evidence is generally limited to shorter follow-up duration, the proportion who are in the subACR20 category will be assumed to discontinue treatment at the end of the first model treatment cycle. If the trials also report on treatment discontinuation due to lack/loss of effectiveness or adverse events, this information will be used in the model for treatment cycles beyond the first treatment cycle. Additional literature will be used to support how discontinuation rates are estimated for time cycles over the lifetime horizon. These inputs are detailed in Table 4.

Table 4. Drug Response Inputs

Input	Value	Source
Conventional DMARDs		Evidence Review
subACR20	TBD	
ACR20	TBD	
ACR50	TBD	
ACR70	TBD	
adalimumab		Evidence Review
subACR20	TBD	
ACR20	TBD	
ACR50	TBD	
ACR70	TBD	
Discontinuation rate due to lack/lossed effectiveness	TBD	

Discontinuation rate due to adverse events	TBD	
TSS Mean Difference	TBD	
certolizumab pegol		Evidence Review
subACR20	TBD	
ACR20	TBD	
ACR50	TBD	
ACR70	TBD	
Discontinuation rate due to lack/lossed effectiveness	TBD	
Discontinuation rate due to adverse events	TBD	
TSS Mean Difference	TBD	
etanercept		Evidence Review
subACR20	TBD	
ACR20	TBD	
ACR50	TBD	
ACR70	TBD	
Discontinuation rate due to lack/lossed effectiveness	TBD	
Discontinuation rate due to adverse events	TBD	
TSS Mean Difference	TBD	
golimumab		Evidence Review
subACR20	TBD	
ACR20	TBD	
ACR50	TBD	
ACR70	TBD	
Discontinuation rate due to lack/lossed effectiveness	TBD	
Discontinuation rate due to adverse events	TBD	
TSS Mean Difference	TBD	
infliximab		Evidence Review
subACR20	TBD	
ACR20	TBD	
ACR50	TBD	
ACR70	TBD	
Discontinuation rate due to lack/lossed effectiveness	TBD	
Discontinuation rate due to adverse events	TBD	
TSS Mean Difference	TBD	
rituximab		Evidence Review
subACR20	TBD	
ACR20	TBD	
ACR50	TBD	

ACR70	TBD	
Discontinuation rate due to lack/lossed effectiveness	TBD	
Discontinuation rate due to adverse events	TBD	
TSS Mean Difference	TBD	
abatacept		Evidence Review
subACR20	TBD	
ACR20	TBD	
ACR50	TBD	
ACR70	TBD	
Discontinuation rate due to lack/lossed effectiveness	TBD	
Discontinuation rate due to adverse events	TBD	
TSS Mean Difference	TBD	
tocilizumab		Evidence Review
subACR20	TBD	
ACR20	TBD	
ACR50	TBD	
ACR70	TBD	
Discontinuation rate due to lack/lossed effectiveness	TBD	
Discontinuation rate due to adverse events	TBD	
TSS Mean Difference	TBD	
sarilumab		Evidence Review
subACR20	TBD	
ACR20	TBD	
ACR50	TBD	
ACR70	TBD	
Discontinuation rate due to lack/lossed effectiveness	TBD	
Discontinuation rate due to adverse events	TBD	
TSS Mean Difference	TBD	
tofacitinib		Evidence Review
subACR20	TBD	
ACR20	TBD	
ACR50	TBD	
ACR70	TBD	
Discontinuation rate due to lack/lossed effectiveness	TBD	
Discontinuation rate due to adverse events	TBD	
TSS Mean Difference	TBD	
baricitinib		Evidence Review

subACR20	TBD	
ACR20	TBD	
ACR50	TBD	
ACR70	TBD	
Discontinuation rate due to lack/lossed effectiveness	TBD	
Discontinuation rate due to adverse events	TBD	
TSS Mean Difference	TBD	

The efficacy of each intervention will be adjusted for the efficacy of secondary/tertiary DMARDs after insufficient response to primary treatment.

Drug Utilization and Monitoring

Drug utilization will be estimated from the following data:

- Average dose
- Dosing schedule
- Dose intensity
- Administration
- Patient characteristics

Drug monitoring will be estimated from the following data:

- Type of procedures and tests
- Frequency of procedures and tests
- Timing of procedures and tests

Drug Cost

The drug cost will be adjusted for drug utilization characteristics that are consistent with the clinical evidence review as well as the Food and Drug Administration labeled indication. The Wholesale Acquisition Cost less a class-level or TIM-level average rebate will be used to approximate the six-month drug cost for each cycle. Table 5 details these inputs.

Table 5. Drug Cost Inputs

Intervention	Class	Recommended Dose (mg)	Frequency of Administration	Route of Administration	Drug Monitoring Schedule	Patent Expiration Date	Cost (WAC in September 2016)
adalimumab	TNF	40mg	every other week	Subcutaneous (Self-injection or in office administration)	TB and Infection: at beginning of therapy and annually	2016	$2046.50 for a 40mg syringe

certolizumab pegol	TNF	400mg initially and at weeks 2 and 4, followed by 200mg for duration	every other week	Subcutaneous (Self-injection or in office administration)	Liver function test: if used with methotrexate (every 3 months for 12 months) Monitoring of hepatic enzymes and blood counts.	2020	$3510.15 for a 200mg syringe
etanercept	TNF	50mg	weekly	Subcutaneous (Self-injection or in office administration)		2028	$512.22 for a 50mg syringe
Golimumab	TNF	50mg	monthly	Subcutaneous (Self-injection or in office administration)		2024	$3811.18 for a 50mg syringe
infliximab	TNF	3mg/kg at initially and at weeks 2 and 6. followed by 3mg/kg for every 8 weeks	baseline, week 2, week 6, and then every 8 weeks	Intravenous		2018	$1071.48 for a 100mg
rituximab	Non-TNF	two-1000mg IV infusions	every 24 weeks	Intravenous	Complete blood count: every 2-4 months Platelet count: prior to therapy PML to monitor neurologic function	2016	$803.1/1000mg (10 vials @ 10mg/1mL)
abatacept	Non-TNF	IV=weight [<60kg 500mg,	baseline, week 2, week 6, and	Intravenous or Subcutaneous	TB and Infection: at	2017	$931.16/250mg (IV) or

		60-100kg 750mg, >100kg 1000mg] SC=125mg	then every 4 weeks (IV) or weekly (SC)		beginning of therapy and annually Liver function test: if used with methotrexate (every 3 months for 12 months) Monitoring of hepatic enzymes and blood counts.		$902.97/125mg (SC)
tocilizumab	Non-TNF	Start at 4mg/kg and titrate by dose response up to 8mg/kg	every 4 weeks	Intravenous	TB and Infection: at beginning of therapy and annually Liver function test: if used with methotrexate (every 3 months for 12 months) Monitoring of hepatic enzymes and blood counts: 4-8 weeks after treatment initiation and every 6 months after	2015	$90.53/20mg
sarilumab*	Non-TNF	150mg-200mg	every other week	Subcutaneous Injection		2028	
tofacitinib	JAK	5mg	twice daily	Oral	Monitoring of hepatic enzymes and	2020	$57.81 per tablet

					blood counts: at baseline, 4-8 weeks after treatment initiation and every 3 months after Liver function test: at treatment initiation		
baricitinib*	JAK	4mg-8mg	once daily	Oral		2029	

All costs will be adjusted to 2015 USD.

Adverse Events

Table 6 details the adverse event inputs.

Table 6. Adverse Event Inputs

Input	**Value**	**Source**
Probability of type of adverse events	TBD	Evidence Review
Cost of adverse events	TBD	Literature Review
Utility decrement due to adverse events	TBD	Literature Review

Model Outcomes

The model will estimate the health and economic outcomes of each intervention in terms of responses achieved, life-years, and QALYs. Relevant pairwise comparisons will be made between treatment

pathways, and results will be expressed in terms of the marginal cost per QALY gained, cost per life-year gained, and cost per response or remission achieved.

Model outcomes of interest for each intervention will include:

- Quality adjusted life expectancy (discounted)
- Life expectancy (discounted)
- Average proportion of patients who achieve at least ACR50 and at least ACR70 (not-discounted)
- Incremental cost-effectiveness ratios for each intervention versus the primary comparator, in pairwise comparisons
- Incremental cost-effectiveness ratios for each intervention versus the secondary comparator, in pairwise comparisons

Sensitivity Analyses

The model programming will allow for flexible and comprehensive sensitivity analyses. A one-way sensitivity analysis will use the low and high bounds from 95% confidence intervals for key model inputs where available. For inputs where 95% confidence intervals are not available, uncertainty will be based on plausible values from literature. A tornado diagram will be used to display the results of the one-way sensitivity analysis.

Multiple scenario analyses will be conducted based on feedback from stakeholders: 1) other treatment assessment durations by assigning only three months of treatment cost to those who fail in a given cycle, 2) treatment adherence, 3) price changes over time, 4) HAQ score over time, 5) having a market basket of all TIMS as the fourth treatment in the sequential treatment pattern rather than palliative care, and 6) extending the perspective to a societal one in order to include the indirect costs due to potential reduced absenteeism and unemployment.

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