Long-term Comparative Effectiveness of Rheumatoid Arthritis Treatment Strategies

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Dedication

To my mother, Parween.

Abstract

Rheumatoid arthritis (RA) is a chronic debilitating disease characterized by progressive joint damage, reduced quality of life, loss of productivity and premature death. It affects 1% of the adult US population, and is one of the most demanding diseases on our healthcare resources. Biologic disease modifiers are new drugs that provide hope to improve the course of RA; however, biologics are among the most expensive specialty drugs. Although the treatment costs of RA have recently increased with the introduction of biologics, most of the economic and societal impacts are due to consequences of RA rather than direct treatment costs. Thus, the cost-effectiveness of biologics in RA is of high priority as recognized by many agencies including the National Institute of Health.

This thesis focuses on three limitations of the current cost-effectiveness analyses (CEA) of biologics in RA. First, Most CEAs are based on randomized clinical trials (RCT) that are rarely applicable to real-life clinical practice. This thesis examines the long-term comparative clinical- and cost-effectiveness of biologics using clinical practice data from a large registry of RA patients (The National Data-Bank of Rheumatic Diseases). Second, we lack a meta-analytical approach specific to CEAs, and previous tools are deemed inappropriate. This thesis presents a novel approach of meta-analysis specific to CEAs. Using this tool we examine if prior CEAs of biologics in RA are consistent. Third, due to the biologics' high costs, RA treatment guidelines often recommend biologics as second line agents after nonbiologics. However, early aggressive treatment is crucial to avoid permanent joint damage. In this thesis we use Markov decision processes (MDP) as an innovative approach to identify the optimal timing of biologics in RA.

The results from this analysis have significant policy, clinical and methodological implications. This work provides important insights into the comparative effectiveness of biologics in RA from a US societal perspective, which can influence health policy and medical insurance coverage decisions. Methodologically, the proposed meta-analytical approach can be applied to other conditions, and have the potential to reconcile the inconsistencies in published CEAs and improve the quality of future studies.

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Chapter 1

Introduction

Rheumatoid arthritis (RA) is a chronic debilitating disease affecting 1% of the adult US population. RA manifestation may vary, but it generally affects the synovial membrane of joints and causes progressive pain, swelling, lower quality of life, disability and premature death.

RA is one of the most demanding diseases on our healthcare resources. This disease may significantly lower the productivity of the patients and their caregivers. As a result, the economic impact of RA on society is estimated to approach that of coronary heart disease.[1] Although the treatment costs of RA have recently increased dramatically, the indirect cost (e.g., due to productivity loss) is estimated to be two to three times higher than the direct treatment costs. Therefore, most of the economic impact of RA is expected to be due to consequences of RA rather than treatment costs.

Diseases-modifying anti-rheumatic drugs (DMARDs) are the mainstay for slowing RA joint damage, improving the prognosis and RA patients and their quality of life. These drugs are generally categorized into nonbiologic (synthetic) and biologics DMARDs. Nonbiologic DMARDs include a wide class of synthetic medications such as methotrexate, sulfasalazine, hydroxychloroquine and corticosteroids. Biologic DMARDs, such as infliximab, etanercept and adalimumab, are complex compounds that

target the inflammatory mediators involved in RA. Biologics are newer and generally more effective than nonbiologics. Thus, biologics are an integral part in treating RA patients. However, biologics are significantly more expensive than nonbiologic DMARDs. The average annual cost of biologics is about $25,000 per patient compared to a small fraction of this amount for nonbiologic agents. Cost consideration is an important limiting factor of biologics use, and guidelines often recommend their use after failure of nonbiologic DMARDs.[2, 3]

This combination of marked benefits and high costs brings a challenging dilemma in terms of the appropriate allocation of limited healthcare resources. As demand for these new costly drugs rises, it is important to understand the long-term comparative clinical- and cost-effectiveness of these agents. The cost-effectiveness of biologics in treating RA is widely recognized by many agencies, including the National Institute of Health, as a high priority research area.[4]

Most prior cost-effectiveness analyses (CEAs) that compare biologic to nonbiologic DMARDs are based on randomized controlled trial (RCT) data.[4] However, most RCTs are shown to inflate the benefit of biologics compared to clinical practice.[5, 6, 7, 8] Two important causes for this bias are RCT eligibility and the Hawthorne Effect. To be eligible to participate in an RCT, RA participants must exceed certain disease activity thresholds that exclude the majority of biologic eligible patients.[7] One study have shown that on average, 90% of individuals in two large clinical RA cohorts were not eligible to participate in biologics RCTs.[9] In addition, another study showed that RCT-eligible patients are consistently more responsive to biologics than those ineligible to participate.[7] A third study have shown that half of the improvement observed during an RCT period disappeared immediately after the trial terminated due to the Hawthorne effect.[10] Consequently, CEAs that are based on RCTs may favor biologics compared to what is observed in real-life clinical practice.[8]

Chapter 2 discusses the cost-effectiveness analysis of biologics in RA from a US societal perspective using a National Data Bank for Rheumatic Diseases (NDB). This analysis proposes to narrow the gap between clinical practice and comparative effectiveness evidence by using a large database of real-life RA patients. The NDB consists of detailed self-reported semiannual questionnaires from 28,960 community RA patients from around the US.[11]

In Chapter 3, we develop a novel technique of meta-analysis specific to CEAs, we implement this approach to RCT-based CEAs that compare biologics to nonbiologics, and we investigate the impact of using NDB parameter estimates on the findings of the RCT-based CEAs. Prior CEAs of biologics are inconsistent.[4] Studies sponsored by the pharmaceutical industry often report favorable outcomes.[12] It is unclear if this inconsistency is due to the parameter values used as inputs, or if these studies are structurally dissimilar. Traditional meta-analytic approaches used to summarize the findings from RCTs are deemed inappropriate for CEAs due to the large variation in the study population and parameter estimates.[13] Thus, our approach provides the first attempt to conduct meta-analysis on CEA and economic evaluations.

In Chapter 4, we use Markov decision processes (MDP) as an innovative approach to understand if there is a window of opportunity for biologics in early RA. Specifically, this chapter investigates the relative cost-effectiveness of biologics in early versus late RA. MDP is an operational tool that have been successfully utilized in recommending liver transplant in treating chronic liver diseases and HIV treatment sequences.[14, 15]. MDP is a natural choice for RA treatment strategies due to the chronic nature of this disease and the frequent change of medications. The practice of early diagnosis and treatment in the first few months after RA disease process starts is crucial to prevent permanent joint damage and deformity. Rheumatologists recognize the importance of this window of opportunity in improving quality of life, reducing work disability,

and preventing premature death.[16, 17] However, due to cost considerations, guideline often recommend biologics when remission or low disease activity are not achievable with nonbiologics.[18, 19, 20, 2, 3] In addition, the pharmaceutical industry presses to expand biologics utilization and increase their market share to early RA arguing that the increased benefit through improved quality of life and reduced work disability can offset the high short-term biologics costs. Nonetheless, our understanding of the optimal timing of biologics is limited because all CEAs are conducted with traditional tools that are inappropriate to investigate the best time to initiate biologics. The current analysis is the first that implements MDP in RA treatment strategies.

In summary, the **specific aims** of this thesis are to investigate:

1. if biologics are utilized cost-effectively in clinical practice in the US,
2. if using clinical practice effectiveness alters the findings of prior RCT-based CEAs, and
3. if there exists a window of opportunity during which biologics are most cost-effective in early RA.

Comparative effectiveness of biologics in RA is recognized as one of the highest priorities of the National Institute of Health (NIH) in the US. The work conducted in this thesis has important clinical, policy, and methodological implications. First, medical insurance coverage can be updated to suggest treatment choices that are best for RA patients and that can lower societal costs. Second, this analysis can improve upon the clinical guidelines by incorporating both long-term individual benefits and societal costs. Third, this thesis addresses health services research issues critical to priority populations. RA is most prevalent among women and is an important cause of disability. In addition, this thesis incorporates advanced methodological tools from operations research into the clinical practice of RA treatment strategies. This thesis provides the first methodological attempt to conduct meta-analysis specific to CEAs.

This approach can be easily extended and tested in other conditions and diseases to reveal sources of inconsistency in prior CEAs, and help improve the quality of future analyses. In addition, this thesis is the first to utilize MDP to model the sequential decisions involved in RA treatment strategies over the long-term nature of this disease.

Chapter 2

Are Anti-TNFs Cost-Effective? Analysis Based on the Real-Life Experience of Patients with Rheumatoid Arthritis

Background. Previous cost-effectiveness analyses (CEAs) of biologics for patients with rheumatoid arthritis (RA) based on randomized controlled trials (RCTs) are limited by their short time horizon and lack of generalizability to real-world effectiveness. Objective: To conduct a CEA of biologics in real-life RA patients using data from an observational study.

Methods. We developed a Markov simulation model to estimate quality-adjusted life years (QALYs) and costs associated with several treatment strategies for RA patients over the lifespan. We evaluated strategies based on different sequences of 5 biologics (etanercept, infliximab, adalimumab, abatacept, and rituximab) compared to conventional non-biologic DMARDs. We modeled the discontinuation rate of each biologic as well as the reason (i.e. serious AE, cost of medication, or ineffectiveness). Those who discontinued because of ineffectiveness were allowed to transition to the next biologic in the sequence based on the probability of switching biologics in an observational study

(the National Data Bank [NDB]). Those who discontinued because of the other reasons switched to nonbiologics. Markov health states were defined by Health Assessment Questionnaire (HAQ) scores and the types of medication the patients received. Transition probabilities, effectiveness measures (i.e., HAQ score improvements), AE rates, quality of life weights, and discontinuation rates were estimated from the NDB. Direct and indirect costs (2009 US dollars) were obtained from the literature. Both costs and effectiveness are discounted by 3% annually.

Results. In the base-case analysis, biologics were generally more effective than nonbiologics. The most cost-effective sequence of biologics was EtanerceptInfliximabAdalimumab (EIA), with an incremental lifetime effectiveness of 0.3 QALYs compared to nonbiologics. The EIA strategy had an incremental lifetime cost of about $170,000 yielding an ICER of nearly 0.5M/QALY, which is well above willingness to pay (WTP) thresholds considered acceptable. Our findings were robust to one-way sensitivity analyses. In a series of what-if scenarios, an immediate and sustainable improvement in HAQ, faster HAQ progressions, and reduced biologics costs lowered ICERs below $100K/QALY.

Conclusion. Using observational data, we were unable to observe the cost-effectiveness reported by RCT-based CEAs. The primary reasons for this discrepancy relate to a lower incremental effectiveness of biologics in real-life patients compared to those enrolled in RCTs.

2.1 Background

There are several biological therapies available to treat patients with rheumatoid arthritis (RA), all of which are generally more effective than nonbiologic disease-modifying antirheumatic drugs (DMARDs) but cost $17,800 to $24,900 annually. This combination of marked benefits and high costs brings a challenging dilemma in terms of the appropriate allocation of limited resources. As demand for these new costly drugs rises, it is important to understand the long-term clinical effectiveness and cost-effectiveness of these agents. Most cost-effectiveness analyses (CEAs) that compare biologic to nonbiologic DMARDs were based on randomized controlled trial (RCT) data.[4] In these analyses, estimates of RCT efficacy were used directly as clinical effectiveness. However, trial-based efficacy of biologics has been shown to be significantly greater than real-life effectiveness.[7, 5, 8] This difference is attributed to RCT eligibility criteria and the timing of measuring drug effects. Vashisht et al. found that, on average, 90% of individuals in two large clinical RA cohorts would not have been eligible for any of the RCTs used for the nine biologics currently approved by the US Food and Drug Administration (FDA).[9] Furthermore, Kievit et al. showed that RCT-eligible patients have a 44% higher response than RCT-ineligible patients.[7] The timing of receiving biologics and measuring their effect may introduce additional bias. Specifically, disease activity observed at RCT baseline may be artificially elevated if participants abstain from their medications before the trial starts as per protocol.[21, 22, 23] RCT-based CEAs that ignore this timing effect overestimate the effectiveness of biologics. Accordingly, we developed a simulation model to conduct a CEA of biologics using effectiveness data from real-life patients in a large RA registry in the US (the national Data Bank for Rheumatic Diseases [NDB]), supplemented with data from the medical literature.[11]

2.2 Methods

2.2.1 Model

We developed a microsimulation model to simulate the lifetime experience of one million hypothetical RA patients similar to those in the NDB (Figure 2.1). The model computes the clinical benefits, measured as gains in quality-adjusted life years (QALYs), and lifetime costs associated with biologic and nonbiologic treatment strategies. The comparison strategy of non-biologic DMARDs represents the experience of the average biologic-nave RA patients as observed in the NDB. We evaluated the outcomes for five different biologics: etanercept, infliximab, adalimumab, abatacept and rituximab. We found these five biologics to be the most frequently prescribed in the NDB from 1998 through 2011. In the biologic strategies, we allowed patients to receive a maximum of three different biologics in a sequence, depending on observed discontinuation rates and reason for discontinuation. Thus, the resulting number of unique biologic strategies was 60 (five biologics as first choice four biologics as second choice three biologics as the third choice).

We used the Health Assessment Questionnaire Disability Index (HAQ) to represent disease severity. HAQ correlates well with patient outcomes such as health-related quality of life (HRQoL), cost and mortality.[24, 25, 26, 10] In addition, HAQ is a well-validated instrument and is the most commonly used instrument to define health status in RA CEAs.[27, 28] Each simulated patient was assigned a baseline age and HAQ, drawn from a joint distributions that reflect biologic-nave RA patient characteristics in the NDB at the time they started biologics. Each 6-month cycle, a simulated patient may experience a change in their HAQ status (i.e., disease progression), which in turn affects their HRQoL, cost, and disease-specific mortality. In addition, they face a risk of experiencing an adverse event, depending on the drug they are receiving, as well

as a risk of discontinuing their current biologic. We considered three possible reasons for discontinuation as recorded by patients in the NDB: (1) ineffectiveness, (2) serious adverse event, or (3) high out-of-pocket cost or other personal decision making factors. If a biologic becomes ineffective, we allowed the patient to switch to the next biologic in the sequence (to a maximum of three). A 6-month cycle length was chosen to be consistent with other RA CEA models and because it corresponds well to the suggested decision points in the American College of Rheumatology (ACR) guidelines.[20]

For each of the 61 strategies we calculated discounted QALYs and discounted lifetime costs, using a discount rate of 3% per year. To calculate QALYs and lifetime costs, we assigned a HRQoL weight and cost, respectively, to each 6-month cycle based on a simulated patients HAQ score and the presence of any adverse events. All statistical analyses were conducted in Stata (StataCorp. 2011. Stata Statistical Software: Release 12. College Station, TX: StataCorp LP.) and all model development and analyses were conducted using TreeAge Pro (TreeAge Software, Inc., Williamstown, MA) and Visual Basic for Applications in Microsoft Excel.

2.2.2 Data

The NDB consists of detailed self-reported semiannual questionnaires from 28,960 community RA patients from around the US. Details of this databank are described elsewhere. [11] All parameters were derived from the NDB when possible; otherwise, they were derived from the medical literature. We followed three steps to derive our parameter estimates. First, we reviewed published NDB studies for existing estimates. For example, the clinical benefits of biologics were obtained directly from a recent NDB publication[29] that provides the adjusted annual disability progression rates for nonbiologics and three of the biologics: infliximab, etanercept, and adalimumab. Second, we

conducted necessary analyses for parameters that were not readily available. For example, we repeated the aforementioned published analysis of the NDB to obtain estimates for abatacept and rituximab. Finally, we conducted a literature search to obtain some of the cost and HRQoL estimates. Model parameter values are listed in Table 2.1.

2.2.3 Benefits

Treatment effectiveness was modeled through changes in HAQ and the subsequent effect on HRQoL and mortality. As previously noted, we used published annual progression rates derived from an analysis of the NDB,[29]and repeated the analysis for biologics not included in the original study. For example, the annual progression rate for nonbiologic therapy was 0.018, indicating that on average HAQ increases by 0.018 per year for RA patients on nonbiologics. The estimated progression rates for biologics were all slower than that for nonbiologics (see Table 2.1). In the base-case analysis, we assumed no immediate improvement in the baseline HAQ separate from the progression rates. In a sensitivity analysis, we tested the effect of immediate improvement in the baseline HAQ. We modeled mortality as a function of age and HAQ. The age-specific mortality was derived from the US life tables,[30] and the additional mortality due to RA was modeled as a function of HAQ score. For example, a patient with a HAQ score of 2 experiences an excess RA-specific death rate of 0.0018 (Table 2.1).[26] We assumed an additive approach to calculate an overall mortality rate from the age-specific and RA-specific rates.[31]

2.2.4 Harms

We derived 6-month probabilities of adverse events related to treatment from a published systematic review.[32] Adverse events were categorized as serious infection, nonmelanoma skin cancer, and minor side effects. We assumed that all adverse events were

short-term in that they were associated with a 6-month decrease in HRQoL, a 6-month increase in cost, and serious infections were associated with a case fatality rate.[33, 34] We assumed that all biologics were associated with the same risk of adverse events, which were higher than the risks for nonbiologic therapy. Although there is evidence that lymphoma is also associated with biologics,[35, 36] the evidence is weak and we did not include this adverse event in our base-case analysis. However, we did include this long-term adverse event and its associated mortality[37] in a sensitivity analysis.

2.2.5 Outcomes

Health-related Quality of Life(HRQoL)

Health outcome was measured in QALYs, which combines HRQoL and life expectancy. To estimate QALYs we identified HRQoL weights (i.e., utilities) to assign to simulated patients for every 6-month cycle. Weights of 1 represent perfect health and weights of 0 represent death. We conducted an analysis of the NDB to estimate a linear relationship between HAQ score and EQ-5D preference weight (slope and intercept reported in Table 2.1). For example, the utility for a HAQ score of 2 is 0.567, compared to 0.739 for a HAQ score of 1. The EQ-5D is a validated scale that allows one to map a health state into a utility and this measure was collected from NDB patients. For adverse events we used HRQoL weights derived from the medical literature.[38, 39, 40]

Costs

Direct and indirect costs were obtained from the literature and are reported in 2009 US dollars (Table 2.1). We used the medical care component of the Consumer Price Index to adjust for inflation in medical costs.[41] We adopted a US societal perspective and calculated total cost as direct cost plus indirect cost. In addition, direct cost was assumed to have two components: drug-related and-disability related.

We estimated the semi-annual cost for nonbiologic therapy from previous analyses.[42, 43] We used a weighted average approach to aggregate individual nonbiologic costs into a single estimate. The weights were calculated from the NDB drug utilization patterns. The costs of biologics costs were estimated from the Red Book.[44] We accounted for the medication and administration costs. Costs of medications were based on the medication unit cost, dose and frequency of administration. Similarly, administrations of an intravenous biologic were based on infusion frequency. We assumed that the dosages of etanercept, adalimumab, and rituximab were constant over time. However, those of infliximab and abatacept were allowed to increase.

In addition to medication costs, each unit increase in HAQ was associated with $1,500 increase in direct cost relative to a HAQ score of 0.[24] In addition, we assigned a short-term cost to serious infection,[38] non-melanoma skin cancer,[45] and a minor adverse event. In sensitivity analysis, we incorporated the treatment costs associated with lymphoma.[40]

Indirect costs were also included as productivity loss for those patients 65 years or younger. We calculated the indirect cost as a function of HAQ based on a previous approach.[46] We estimated the indirect cost using this formula: indirect cost = change in work capacity x average wage. Where change in work capacity = 0.21 x change in HAQ [47] A six-month average wage was derived from 2009 annual average wages from the Department of Labor Statistics.[48]

2.2.6 Sensitivity Analysis

In the base-case analysis, we compared the incremental cost-effectiveness ratio (ICER) of each of the 60 biologic strategies to the same nonbiologic base-case strategy. Next, we conducted one-way sensitivity analysis by varying the model parameters between their lower and upper confidence bounds. We performed additional what-if analyses on

three key parameters in the model: biologics initial benefit, HAQ progression rate for biologics and nonbiologics, and biologic costs.

2.3 Results

We found that, on average, treatment with biologics resulted in 0.01 to 0.34 QALYs greater than treatment with nonbiologics, depending on the biologic sequence. The most effective sequence of biologics was a strategy starting with etanercept, followed by infliximab, then adalimumab (EIA) (0.34 QALYs). The incremental lifetime cost of biologics ranges from about $130K to $250K compared with nonbiologics. All biologic sequences were similar in terms of their cost-effectiveness. Biologic strategies starting with older biologics (e.g., etanercept and infliximab) were slightly more effective than strategies starting with newer biologics (e.g., rituximab and abatacept). The sequence with the lowest ICER compared with nonbiologics was the EIA strategy at $0.5 million per QALY, a value that is well above willingness to pay (WTP) thresholds considered acceptable.

Table 2.2 presents the one-way sensitivity analyses of the models input parameters. Our base-case results were robust to all sensitivity analyses scenarios. In all of these scenarios, the ICER of EIA was greater than 0.3 million/QALY.

We conducted further analyses on three key parameters in the model: the initial HAQ improvement following biologics, HAQ progression rate for both biologics and nonbiologics, and the cost of biologics. For our base-case analysis we assumed that the progression rates estimated from the NDB reflected both the short- and long-term effects of treatment. However, many RCT-based CEAs incorporate a short-term benefit in addition to long-term delay of disease progression. Figure 2.2(a) shows a representation of our base-case assumption, where the average HAQ progression for simulated patients all starting at HAQ 1.2 is shown under two scenarios: nonbiologics compared to the

EIA biologic strategy. Figure 2.2(b) illustrates the mean HAQ over time under the assumption of a 0.25 absolute initial HAQ improvement, whereas Figure 2.2(c) shows the average HAQ over time under the assumption that the HAQ progression rates are twice that of our base-case assumption. The area between the curves is proportional to the incremental effectiveness of biologics relative to nonbiologics.

In a two-way sensitivity analysis, we investigated the impact of reducing the utility/HAQ conversion from -0.172 to -0.234, and assuming no HAQ progression while on biologics. Reducing the HAQ/utility conversion factor reduced the ICER from \$0.5M/QALY to \$0.4M/QALY while assuming no HAQ progression during biologics use reduced the ICER to \$0.3M/QALY, and reducing both parameters resulted in an ICER of \$0.2M/QALY.

Figure 2.3(a) presents the sensitivity analysis as we varied the initial benefit of biologics from 0 to 1. If the initial benefit were increased to 0.25 HAQ, the ICER drops rapidly and EIA becomes cost-effective at a WTP threshold of \$100K/QALY. Figure 2.3(b) illustrates the impact of a long-term assumption on the sensitivity of ICER of the EIA strategy. Here, we increased HAQ progression rates for both biologics and nonbiologics by the same factor. Most RCT-based CEA include a HAQ progression rate that is generally higher than observed in the NDB. As HAQ progresses at a faster rate for both biologics and nonbiologics, the ICER of EIA drops dramatically. This is likely due to nonbiologics having a higher base-case progression rate; multiplying the HAQ progression rates for both biologics and nonbiologics by the same factor widens the absolute difference between the two, as illustrated in 2.3(c).

In Figure 2.3(c) we examined the ICER sensitivity due to reduction in the cost of biologics. The relationship between ICER and biologics cost reduction is illustrated. As the biologics cost decreased relative to the base-case cost, the ICER of EIA decreases rapidly. At around 70% of their base-case costs, biologics start to become cost-effective

at a WTP threshold of $100K/QALY. At around 85% reduction, EIA appears cost saving.

2.4 Discussion

Based on real-life RA patient experience, we simulated the long-term cost-effectiveness of biologics compared to nonbiologics from a US societal perspective. To mimic current biologic administration patterns, we relied primarily on the NDB as the main data source. We utilized published estimates and conducted further analyses of the NDB in order to obtain parameter estimates that were difficult to locate. We were able to compare a large number of the most frequently used biologics, take into account discontinuation patterns of these drugs, and their potential adverse events. Using these data, we found biologics strategies to be slightly more effective and significantly more expensive than nonbiologics. As a result we observed very high ICERs for biologic strategies. We investigated varying sequences of the five most prescribed biologics: infliximab, etanercept, adalimumab, abatacept and rituximab.

Most biologic sequences that we investigated were similar in their lifetime costs and benefits. However, we found that strategies starting with rituximab or abatacept were generally less effective than those starting with infliximab or etanercept. This effect may partly be due to data limitation since rituximab and abatacept are relatively newer and less likely to be the first biologic a patient uses. More patients who have already failed the older biologics may switch to these newer biologics causing them to appear less efficacious in the NDB. Further investigation is required when more biologic nave patients receive these newer biologics as the first line of therapy.

Using long-term data from real-life practices, we were unable to observe the ICERs reported by most RCT-based CEAs. While we found the lifetime incremental costs similar to those reported in the RCT-based CEAs, we found the incremental health

benefits of biologics to be significantly less than those reported in most studies. We believe that the difference in health benefit between our study and RCT-based CEAs has two components. The first was previously explained by Wolfe and colleagues,[5] who showed that HAQ score improvement from RCTs were much greater than those from observational studies. The reason for this was later explained to be due to RCT eligibility criteria and the timing of the measurement.[27] The second component, and perhaps the more important one, is how disability is converted to QALY in a trial setting. Most trial-based CEAs measure QALY as the difference between the HRQoL measurement at the beginning of a trial and the first measurement. Thus, these analyses extrapolate the initial trial flare to be lasting an entire model cycle length, generally six months. However, it is known that HAQ worsening in trials corresponds to a temporary flare in disease severity. The six-month cycle may be significantly longer than the duration of the temporary flare. Thus, the calculated QALY in RCTs can be potentially many folds larger than the actual real-life improvement.

Since we focused on long-term outcomes, we assumed that a pooled estimate of HAQ progression rate over a twelve year window in the NDB is sufficient to capture all biologic and nonbiologics benefits (including short-term and long-term benefits). Therefore, in this analysis we used HAQ progression rate solely to reflect biologic and nonbiologic benefits. This is a major difference between our approach and prior CEAs, particularly those based on RCTs. The RCT analyses are based on short-term data and often assume that biologic and nonbiologic benefits have an immediate and long-lasting HAQ improvement (short-term benefit), and the second component is through a slower disease progression for those who receive biologics (long-term benefit). In a sensitivity analysis we investigated the impact of incorporating short-term benefits and altering long-term benefits similar to these RCT-based analyses. As expected, most of the difference between our results and those from RCT-based CEAs disappeared.

Since our analysis reflects the differential HAQ progression rates among biologics and nonbiologics users, our results may bias against biologics. To account for this bias, we investigated the cost-effectiveness of biologics under increased biologics benefit. In a what-if scenario, we investigated the sensitivity of ICER while increasing biologics short-term benefit. Although, this change caused biologics to be cost-effective, the immediate benefit of biologics had to be relatively high for biologics to be cost-effective.

Long-term data on newer biologics, e.g.: abatacept and rituximab are limited. We found treatment strategies that start with these newer biologics to be less cost-effective. This can perhaps be explained due to some of those who take the newer biologics may have already tried, and failed, the older biologics making them more prone to be unresponsive to other agents.

Another limitation of the basecase analysis is that we assumed that HAQ progression is independent from discontinuation due to inefficacy. In a sensitivity analysis, we build a correlation between biologics discontinuation and HAQ progression. We allowed 50% increase in the likelihood of discontinuing due to inefficacy if the progression on biologics was higher than nonbiologics, and 50% decrease otherwise. As a result, the incremental benefit increased from 0.30 to 0.35, and the ICER decreased from about \$0.5 to \$0.45 Million per QALY. Thus, building this correlation had a small impact on the results. This is because less than 4% of patients who are on biologics discontinue due to inefficacy in the NDB.

Since our analysis was based on observational data, it is difficult to eliminate selection bias (i.e. the sicker patients may receive biologics). The original analysis that we based our study on controlled for baseline characteristics that are likely to confound the effect of treatment [29]. However, this may not be complete and there may still exist other confounder or unobservable variables that may influence these results. To account for selection bias, in a sensitivity analysis we assumed the best case scenario

that biologics can stop HAQ progression. The ICER was still significantly above ranges often considered acceptable by many health-care agencies.

Observational data may not be devoid of measurement timing bias. RA patients in the NDB complete the questionnaire voluntarily. Although the questionnaire is sent at regular six months intervals, the timing of the response (measurement timing) may not be uncorrelated with receiving the biologics (decision timing). For example, those who suffer a flare may be unable to fill the questionnaire until after they received the biologic. As a result, these patients may report a lower HAQ score than what they have experienced when they received the questionnaire.

We were unable to conclude that biologics were cost-effective in patients with RA from a US societal perspective. Our results were robust to extensive sensitivity analyses. Although biologics may be cost-effective in RCT settings, in real-life they may not have been restricted to patients that fulfill the RCT eligibility criteria. These eligibility criteria and several short-term and long-term assumptions made in RCT-based CEAs may cause biologics to appear more cost-effective than they observed in real-life settings.

2.5 Tables

Table 2.1: Parameter Estimates Used in the Model

Parameter	**Value**	**Range**	**Source**
Starting age (year)	N(47,14)[a]	18 – 80	[b]
Starting HAQ	N(1.2,0.76)[c]	0 – 3	[b]
Annual HAQ progression rates (HAQ/year)			[29], [b]
Nonbiologics	N(0.018,0.010)	0 - 0.038	
Etanercept	N(0.007,0.0055)	0 - 0.018	
Infliximab	N(0.006,0.0055)	0 - 0.012	
Adalimumab	N(0.01,0.0085)	0 - 0.027	
Abatacept	N(0.015,0.008)	0 - 0.031	
Rituximab	N(0.012,0.010)	0 - 0.032	
Excess HAQ-related annual mortality rates relative to HAQ 0 (per 1000)			[26]
HAQ [1, 2, 3]	[0.5, 1.8, 5.5]		
Six-month probability of adverse events			
Serious infections NB	0.017	Reference	[32]
Serious infection Biologics	0.034	0.022 − 0.051	[32]
Nonmelanoma skin cancer NB	0.002	Reference	[32]

Parameter	Value	Range	Source
Nonmelanoma skin cancer B	0.007	0.003 − 0.019	[32]
Minor adverse events - B	0.01	0.005 − 0.02	Assumed
Case fatality rate due to serious infection	0.36	0.225 − 0.377	[33, 34]
Conditional probabilities of discontinuation by cause			[a]
Inefficacy	0.415		
Major adverse event	0.206		
Out-of-pocket cost/other	0.379		
Health-related quality of life (utility) weights, timeframe			
Intercept, utility = f(HAQ)	0.911	0.77 - 0.911	[a]
Slope, utility = f(HAQ)	−0.172	−0.234 – (−0.172)	[a]
Serious Infection	0.42	0.4 – 0.8	[38]
Nonmelanoma skin cancer	0.996	0.984 – 1.0	[39]
Lymphoma	0.83	0.30 − 1.0	[40]
Minor AE HRQoL weight	0.99	0.98 – 1.0	Assumed
Six-month cost of treatment (2009 US Dollars)			
Nonbiologics	$1,203		[42]
Etanercept	$11,371		
Infliximab	$12,946	10,004 - 17,067	[43]

Parameter	Value	Range	Source
Adalimumab	$11,371		
Abatacept	$15,652	14,323 - 18,730	
Rituximab	$13,173		
Six-month cost of adverse events			
Serious infection	$5,780	$9,000– $18,400	[38, 49]
Non-melanoma skin cancer	$1,200	$992 – $1,460	[45]
Minor adverse event	$100	$50 – $200	Assumed
Indirect Cost			
Slope, HAQ and work capacity	−0.21	−0.2515 – (−0.0838)	[47]
Median wage in 2009	$22,776		[48]

Notes: NB = nonbiologics; B = biologics; HRQoL = health-related quality of life; [a] = Age restricted between 18 and 80 years.; [b] = NDB analysis; [c] = HAQ restricted between 0 and 3.

Table 2.2: One way sensitivity analysis

	Scenario	Parameter Change	ΔCost	ΔQALY	ICER
Base case		-	170,300	0.34	500,900
Intercept, utility = f(HAQ)	LB	0.77	170,300	0.31	549,300
Slope, utility = f(HAQ)	LB	-0.234	167,200	0.45	371,500
Utility skin cancer	LB	0.984	170,300	0.35	486,500
Utility - severe infection	UB	0.8	170,300	0.31	549,300
Risk of skin cancer on biologics	LB	0.003	171,200	0.35	489,000
Risk of skin cancer on biologics	UB	0.019	168,300	0.34	495,000
Risk of serious infection on biologics	LB	0.022	171,700	0.35	490,500
Risk of serious infection on biologics	UB	0.051	167,500	0.33	507,700
Risk of lymphoma on biologics	UB	0.0006	166,900	0.25	667,800
Risk of minor adverse events	LB	0	170,200	0.51	333,700
Risk of minor adverse events	UB	0.01	170,400	0.3	568,000
Slope of wage function	LB	-0.25	169,400	0.34	498,300
Slope of wage function	UB	-0.17	171,200	0.34	503,400
Cost of skin cancer treatment	UB	1,460	170,300	0.34	500,800
Cost of serious infection treatment	LB	9,000	169,500	0.34	498,600

	Scenario	Parameter Change	ΔCost	ΔQALY	ICER
Cost of serious infection treatment	UB	18,400	167,300	0.34	492,100
Cost of minor adverse event treatment	LB	50	170,300	0.34	500,700
Cost of minor adverse event treatment	UB	200	170,400	0.34	501,100

ΔCost = incremental cost; ΔQALY = incremental effectiveness; ICER = incremental cost-effectiveness ratio; LB = lower bound of parameter value; UB = upper bound.

2.6 Figures

Figure 2.1: A simplified outline of the decision tree.

The model compares biologic strategies to a base-case nonbiologic strategy. A hypothetical patient is simulated through all strategies simultaneously. In the base-case nonbiologic strategy, the patient continues to receive nonbiologics treatment. In the biologic arm, the patient starts with the first biologic, and continues if there is a minor adverse event (AE). In case of a serious AE or high out-of-pocket cost, the patient discontinues the biologic. In case of inefficacy, the patient switches to the next biologic in the sequence. These alternatives repeat while on the second and third biologics. The patient discontinues biologics if the third biologic is ineffective.

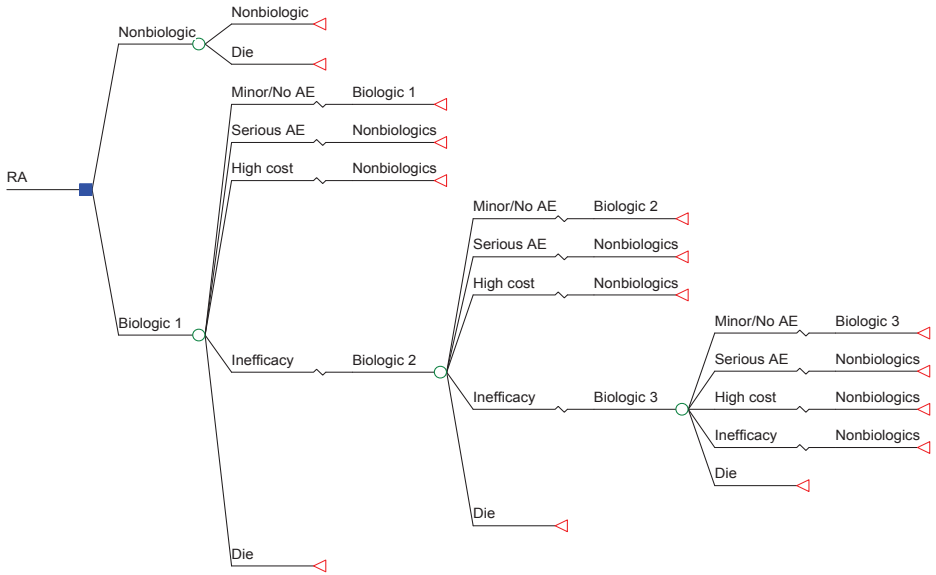


Figure 2.2: HAQ progression for a biologic (EIA) and nonbiologic (base-case) strategies. HAQ is plotted on the y-axis and time since biologic decision is plotted on the x-axis. (A) represents the basecase analysis. An immediate improvement in HAQ was introduced in (B), and HAQ progression rates were doubled in (C).

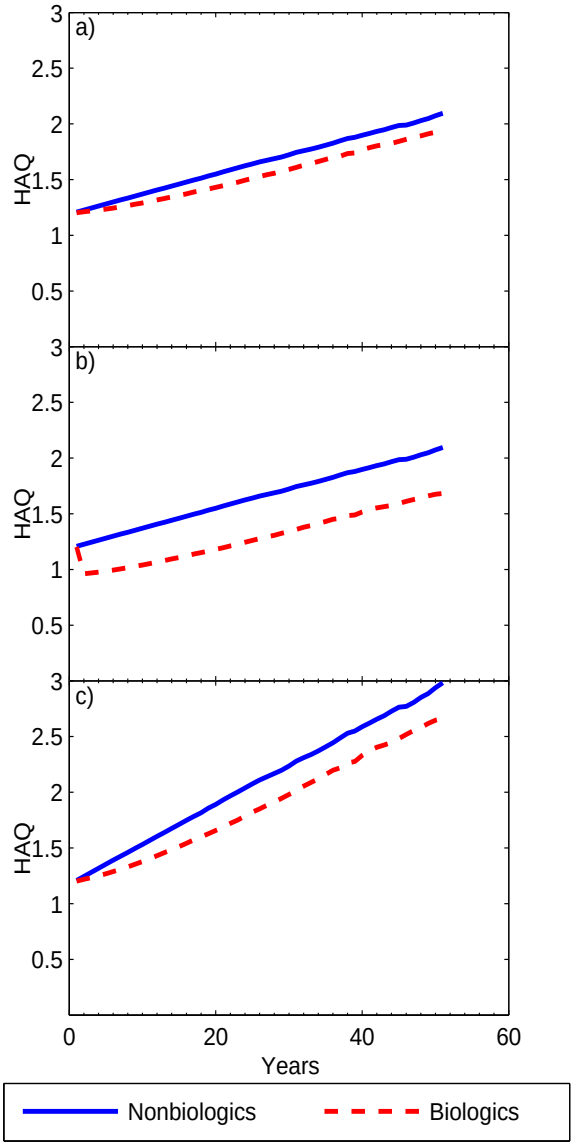
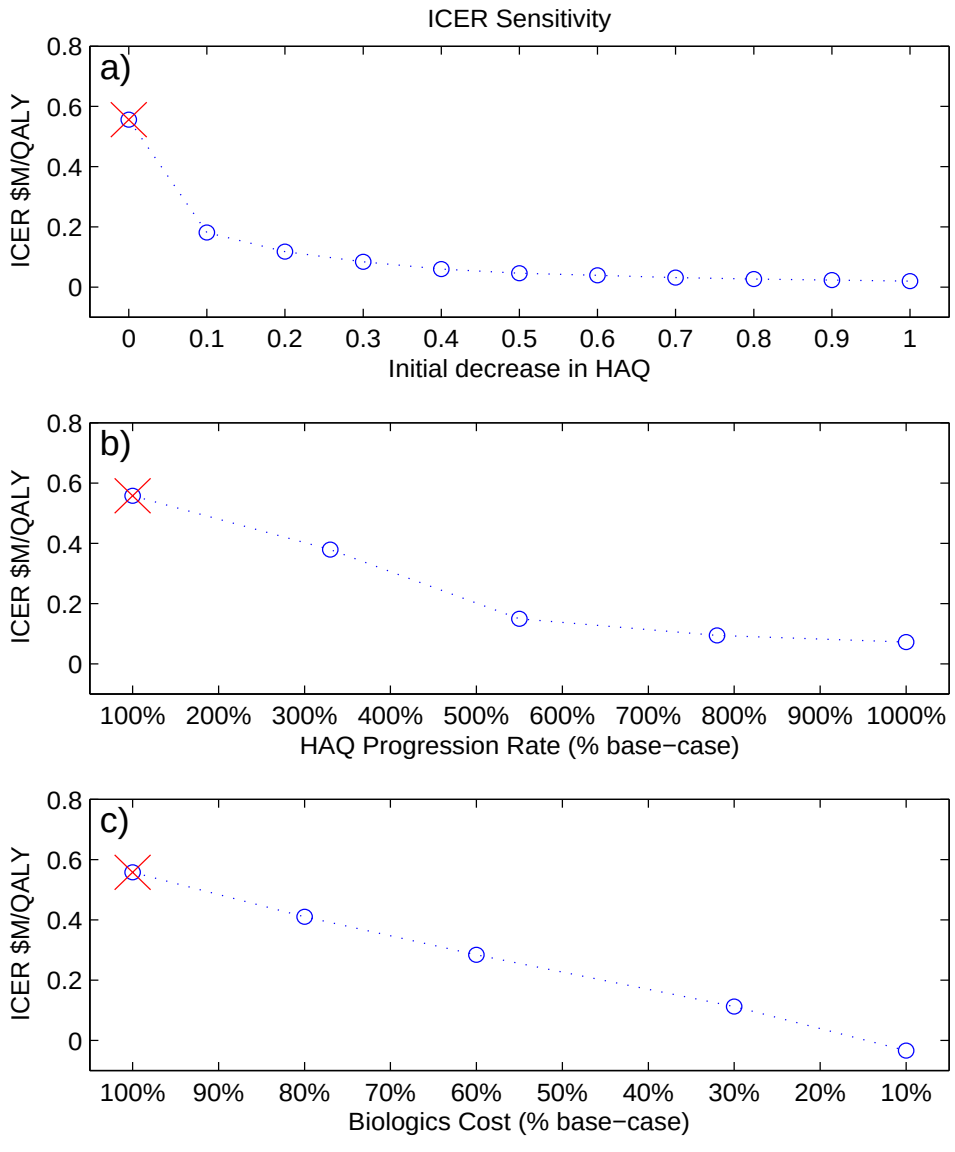


Figure 2.3: ICER sensitivity.

Incremental cost-effectiveness ratio (ICER) Sensitivity is shown for (A) initial HAQ improvement, (B) HAQ progression rates, and (C) biologics cost. In all plots, ICER is plotted on the y-axis. The x-axes represent the initial decrease in HAQ, percent increase in the HAQ progression rate, and biologics cost percentage in A, B, and C, respectively. The base-case values for each parameter is indicated with an $\times$. In the base-case analysis we assumed no immediate improvement in HAQ (A), biologics and nonbiologics progression as reported in Table 1 (B), and biologics full cost (C). An immediate and sustainable HAQ improvement of more than 0.25, a HAQ progression rates of 8 folds higher than the base-case, or a reduction in biologics cost by 30% can reduce the basecase ICER to \$100K/QALY. Biologics became cost-saving when at 85% of their original costs.



Chapter 3

Implications of Using Effectiveness Instead of Efficacy on the Cost-Effectiveness of Biologics in Rheumatoid Arthritis: A Novel Meta-analytic Approach

Background. Systematic reviews of the cost-effectiveness of biologics in rheumatoid arthritis (RA) are limited to a description of the models and their findings. These reviews do not analyze the information presented in the sensitivity analyses which provide important insights into these models.

Purpose. To systematically review prior cost-effectiveness analyses (CEA)s of biologics compared to nonbiologics in RA, and study the implications of using clinical practice data instead of randomized clinical trial (RCT) on the results of RCT-based CEAs.

Methods. We reviewed the literature for CEA in adult-onset RA. We investigated the association between the funding source and the ICER and developed a meta-analytical

approach that utilizes the published sensitivity analysis results from these CEAs. In addition, we obtained parameter estimates from the National Data Bank for Rheumatic Diseases (NDB) for the six most commonly reported model parameters, and tested the implications of using these estimates on the results of RCT-based CEAs.

Results. Of the 15 CEAs that were sponsorship by the industry, only one produced unfavorable results compared to 5 out of 11 non-industry sponsored studies. In addition, using the NDB estimates doubled the ICER form RCT-based CEAs. Overall, the most important input parameter was the initial Health Assessment Questionnaire (HAQ) improvement following biologics. This parameters estimate was 71% lower in the NDB compared to the mean estimates from the RCT-based CEAs. Using the NDB estimate for this parameter increased the average ICER by 139%. The second most influential factor was the background HAQ progression rate. NDB estimate of this parameter resulted in 34% increase in the ICER. Among all parameters analyzed, only the HAQ progression of biologics in the NDB reduced the ICER all other parameters increased the ICER.

Conclusion. Funding sources and data sources have important implications on RCT-based CEA analyses. This study is the first that utilizes published sensitivity analyses results to reveal the characteristics of CEA and uses this information to investigate the impact of data source on the findings.

3.1 Background

Rheumatoid arthritis (RA) is a chronic debilitating condition that affects 1% of the adult US population. RAs presentation may vary, but it generally affects the synovial membrane of joints and causes progressive pain, swelling, lower quality of life and premature death. In addition, RA has an important implication on the society from direct resource use and indirectly through productivity loss and caregiver costs.

Diseases modifying anti-rheumatic drugs (DMARDs) greatly improved the prognosis of RA by slowing joint damage and improving the quality of life. DMARDs include a wide class of medications such as methotrexate, sulfasalazine, hydroxychloroquine and corticosteroids. Biologic DMARDs may even provide the best improvement in the quality of life and decelerating the joint damage. However, biologics are significantly more expensive than nonbiologic DMARDs. As a result, guidelines often recommend their use after failure of nonbiologic DMARDs.[2, 3]

Cost-effectiveness of biologics in treating RA is widely recognized by many agencies (e.g., National Institute of Health) as a high research priority area.[4] Cost-effectiveness analyses (CEA) investigate whether biologics benefit through improving quality of life, increased productivity, and extending life can offset the direct drug cost through mathematical modeling. However, the results from these studies are largely controversial because they are mostly funded by the industry and use short-term RCT efficacy data instead of clinical practice effectiveness.[50] In a previous meta-analysis of the CEAs of biologics, all studies that were supported by industry reported favorable outcomes.[4] In addition, an analysis of the Tufts CEA Registry database (available online at http://tufts-nemc.org/cearegistry) found an increased likelihood of reporting favorable outcomes in industry sponsored CEAs.[12] Another study found no unfavorable conclusion for studies that were sponsored by the pharmaceutical industry which formed nearly 70% of the published analyses.[51] However, neither of these reviews were specific for RA. In this

study we analyze the association between industry sponsorship on CEA of biologics in RA.

Furthermore, randomized controlled trials (RCT) show greater efficacy for biologics in RA compared to clinical practice effectiveness from observational studies.[5, 6] The initial health states of RCT participants may not represent the health states of patients in clinical practice. To be eligible to participate in an RCT, RA participants must meet certain disease activity that exclude the majority of biologic eligible patients.[7] Therefore, RCT show a larger improvement in disability following biologics administration. In addition, participation in RCT has shown to temporarily improve the health status of the participants due to the Hawthorne effect.[10] In a study, half of the improvement observed during the RCT period disappeared immediately after the trial terminated.[10] Therefore, the results from RCT-based CEAs are believed to cause biologics to appear more cost-effective than they are in clinical practice.[8]

Because these models are essentially black-boxes, it is challenging to test how their findings change using updated clinical practice data without access to the original models. Even with the access to these models, it is challenging to reconcile their parameters and their results. In order to understand the implication of using observational data in RCT-based cost-effectiveness analyses (CEA), we needed a meta-analytical approach capable of combining information from multiple RCT-based CEAs. The task of combining information from multiple CEAs is of particular importance to policy and decision makers.[52, 13] However, there is no meta-analysis study that involves statistical analysis of different CEAs. Studies that provide descriptive analysis of CEAs are rather systematic reviews rather than meta-analyses.[52] Most CEAs provide important insight into the models through sensitivity analysis tables and figures (e.g., tornado diagrams). However, this information in a row format is of limited use, since most studies use different parameter values.[13] As a result these meta-analyses are often limited to a

descriptive comparison of the sensitivity analyses, including a recent systematic review of biologics CEAs in RA.[4]

In this study, we adopted a metamodeling approach that utilizes the published sensitivity analyses to reveal the underlying dynamics of these models. Our metamodeling approach was a linear approximation of the relationship between the model input parameters and the ICERs. Metamodeling is widely used as add-on to simulation models because it removes the need for the simulation model.[53] To the extent of our knowledge, this analysis is the first that utilizes the important information provided in sensitivity analysis to compare CEAs analytically.

3.2 Methods

3.2.1 Literature search

We conducted an electronic search of the National Health Services Economic Evaluation Database (second quarter 2013) and the Tufts Medical Center Cost-Effectiveness Analysis Registry (1976 to June 2013). We identified 203 citations containing the phrase rheumatoid. 153 articles were excluded because (1) they compared other medication or interventions, (2) were not economic evaluations, (3) compared biologics to other biologic agents[28, 54, 55], (4) did not report cost per quality adjusted life years (QALY)[56, 47], or (5) were about juvenile arthritis, or other non-specific arthritis that did not include specific results for RA.

We retrieved the full-text of 31 CEAs that compared biologics to nonbiologics for RA patients. From each study, we retrieved study variables, such as currency type, currency year, ICER of a biologic vs. a nonbiologic and the studys funding source (Table 3.1).

The CEA Registry provides approximate ICERs, but exact ICERs were obtained from the articles directly. If a study provided ICER for more than one biologic strategy,

we included the ICER of the biologic sponsored through funding agency if applicable. If no such funding resource existed, we used the ICER of the first reported biologic. Similarly we included ICERs from societal perspective, but when unavailable we used the payers perspective. Furthermore, if ICERs over multiple time periods were provided, we used the ICER over the longest duration.

Next, we obtained the published sensitivity analysis results to reveal parameter importance. Among the 31 article, 17 reported one-way sensitivity analysis (OWSA) and used efficacy data from RCTs. OWSA is commonly reported in economic evaluations in which the model outcome is repeatedly re-evaluated while changing one parameter at a time. Thus, OWSA can provide important insight into the behavior of a model. These studies reported the OWSA either in a tabular format or as a tornado diagram. For each study, we retrieved the values of six parameters that were most commonly included in sensitivity analyses. These parameters were: (1) the initial Health Assessment Questionnaire Disability Index (HAQ) improvement following biologics, (2) HAQ/utility conversion factor for calculating HRQoL from HAQ score; (3) HAQ progression while on biologics, (4) background HAQ progression rate, (5) increased mortality rate for each unit increase in HAQ, and (6) the standardized mortality rate which measures the overall increase in risk of mortality due to RA compared to the general population. Most studies either reported SMR or RR of mortality by HAQ. One study[27] included both, which was considered double counting of the mortality effect by another study[42]. Not every study reported all input parameters, but for those reported, we retrieved the resulting ICER associated with each parameter value.

Most CEAs reported OWSA to illustrate the robustness of the results. As a result, they were less consistency among the type of inputs and input scales (relative or absolute) chosen in these analyses. For example, several studies reported the HAQ/utility conversion factor directly; others reported the HRQoL as a regression equation of

HRQoL on HAQ. In these regression equations, two parameters are changed simultaneously: the intercept and the slope of HAQ. For example, three of these regressions reported in many sensitivity analyses were HRQoL $= 0.77 - 0.17 \times$ HAQ in [57], HRQoL $= 1.12 - 0.19 \times$ HAQ in [58], and HRQoL $= 0.72 - 0.28 \times$ HAQ in [59]. To isolate the HAQ/utility conversion factor from these equations, we estimated the value of ICER while holding the intercept constant at its base-case value. Then, we recomputed the conversion factor while adjusting for the regression intercept. Other studies reported non-linear function between HAQ and HRQoL. For example, Soini and Hallinen used a non-linear function of EQ5D $= 0.82 - 0.1 \times$ HAQ $- 0.07 \times$ HAQ^2.[60] we transformed this function using the best fitting line over a HAQ range of 0-3, in the form HRQoL $= 0.9215 - 0.31 \times$ HAQ.

A number of analyses, especially those presenting the results as tornado diagrams were unspecific to whether the low value of an input was associated with the low value of ICER or vice versa. In these cases we made a decision of the direction of the association. We confirmed these relationships to make sure the direction of these associations were logical and consistent across studies.

3.2.2 Input effect size (IES)

We used the published sensitivity analysis results to calculate the input effect sizes (IES) in each study for the reported parameters of interest. We defined IES as the percent change in ICER due to one percent change in an input from its baseline (i.e., IES for an input x = % change in ICER / % change in x from its baseline value). Next, we calculated the average IES estimates for each input across all studies that reported the same parameter. The number of studies that examined each parameter varied from two (initial HAQ improvement) to seven (Background HAQ progression rates). (Appendix A presents the detailed calculation of the average input parameter

values and the associated IES for the selected parameters from the RCT-based CEAs). Some studies only reported the relative changes from the parameters baselines without providing the base-case values. In these cases, we were able to compute the IES values.

In order to examine the impact of replacing RCT efficacy with observational effectiveness in these models, we replaced the model parameter estimates with those obtained from the National Data Bank for Rheumatic Diseases (NDB). We calculated percent deviation of the NDB estimates from the mean parameter estimates from the RCT-based CEAs. Then, we computed the predicted percent change in ICER when observational estimates are used as the produce of IES and NDBs percent deviation.

3.3 Results

Figure 3.2 compares the reported ICER by the CEAs funding sources. The results are presented in US dollars using an average exchange rate and updated to 2013 US dollars using the 2013 Consumer Price Index Data.[61] The original currency type and year are also presented. Fifteen studies were funded by industry, ten indicated a non-industry source, and the funding sources were not reported in five studies. Among all industry sponsored studies, only two studies[62, 63] reported unfavorable ICERs, and only one[62] had unfavorable conclusion compared to 8 that reported unfavorable ICERs among 10 non-industry funded studies. All studies with unknown funding reported favorable ICERs.

Table 3.2 presents the impact of replacing parameters used in these studies with NDB-based estimates. Overall, the IES and RCT-based inputs values were similar across all RCT-based CEAs except for the parameters representing mortality [the relative risk of mortality for each unit increase in HAQ (IES mean = +0.04 and IES standard deviation = 0.23), and RA specific mortality (IES mean = +0.32 and standard deviation = 0.88). See appendix A].

The most influential input parameter was the initial HAQ improvement with an IES of -1.96, indicating that ICER decreases by about 2% for each 1% increase in HAQ improvement from the baseline. The second most influential factor was the background HAQ progression with an IES of -0.5. This is an important finding since background HAQ progression is not directly related to biologics treatment and thus not expected to change the ICER dramatically.[50] This table also presents the NDB-based estimates for these model parameters. The largest deviation of NDB estimate versus the RCT-based CEA estimates was the Mortality RR for each unit increase in HAQ with a % deviation (%D) of 79% indicating NDB-based estimate was, on average, about 80% higher than the values used in RCT based studies. However the IES of this input was relatively small, and the overall estimated ICER change was about +3% if NDB-based estimate was used instead of the mean estimate from the RCT-based studies. The NDB values for the initial HAQ improvement, Background HAQ progression and biologics HAQ progression were all about 70% less than the values used in the RCT-based CEAs. Overall, using NDB estimates instead of RCT-based CEA sources resulted in nearly tripling the ICERs reported by these studies (an increase of +99%).

Figure 3.3 presents the IES for the six selected input parameters. The IES varies significantly from one study to another, indicating a high degree of structural inconsistencies among these CEAs. For example, the IES for the background HAQ progression rate varied between -200% to 0%. This trend is also visible for the other parameters. However, the IES directions were all similar, except for the IES of the mortality relative risk per unit HAQ which was positive for some studies and negative for others.

3.4 Discussion

We reviewed the literature for published CEAs of biologics compared to nonbiologics, and developed a novel approach of meta-analysis of CEAs. We investigated the impact

of funding source on the CEA results and the implications of using real-life clinical data instead of RCT efficacy in these analyses. We found a large variation in the reported ICERs of biologics relative to nonbiologics. Analyses sponsored by industry were more likely to report favorable ICERs than non-industry sponsored studies. These findings confirmed the results of a prior analysis of the CEA Registry which also found indications for publication bias.[12] The current analysis is the first study that systematically compares the impact of funding source of biologics in RA. Although a recent meta-analysis specific to RA presented the funding source of these studies, it did not make the connection between the funding source and the ICERs reported.[4]

We further investigated the parameter importance in the RCT-based CEAs and the implications of using clinical practice effectiveness data instead of RCT efficacy as sources of parameter estimates in these CEAs. We used the published sensitivity analyses results that reported ICER sensitivity to six parameters related to short-term HAQ improvement, long-term HAQ progression, HAQ/utility conversion factor and RA related mortalities. Furthermore, we obtained estimates for these parameters from clinical practices as observed from the NDB and used these estimates to predict the impact of using clinical practice data on the results of RCT-based CEAs.

We defined IES as a new measure of CEA sensitivity. Because IES measures the relative change in ICER, it can be compared across studies that use different currencies or were conducted in different calendar years. IES also captures relative change in the model parameters. Therefore, it can be used for studies that only report relative sensitivity analysis (e.g., +/- 50% change from baseline) instead of absolute changes.

The initial HAQ improvement following biologics administration was overall the most influential parameter. This parameter is also the most criticized in the literature because it is directly related to the treatments and observational studies generally report smaller improvements than RCTs. As a result, previous studies have questioned the

generalizability of RCT-based CEAs to clinical practice.[7, 5] In addition, one study found that the ICER almost doubled when using clinical practice effectiveness instead of RCT efficacy data.[63]

The initial HAQ improvement only captures the short-term model assumptions. The second most influential input was the background HAQ progression. This is an important finding because background HAQ progression is not directly related to biologic treatment and is generally equally applied to both the treatment arms in the CEAs. In addition, we lack accurate estimates simply because long-term data do not exist.[5] The NDB estimates were generally three times higher than the estimates used in the RCT-based CEA. However this impact was partially offset by the HAQ progression while on biologics. This is because the NDB estimate of this parameter was also about 70% less than that reported in the RCT-based CEAs. Higher rates of progression reported in RCT-based CEA may be due to the trials flare design and the regression to the mean phenomenon.[29]

The HAQ/utility conversion factor also influenced the reported ICER significantly. Our findings confirm a study conducted by Marra et al where the authors found that different HRQoL instrument can significantly alter the conclusion of cost-effectiveness analyses.[64] The authors compared the impact of using EQ5D, SF6D, and HUI3. SF6D resulted in the largest ICER, while SF6D produced the lowest.[64] It is noteworthy to mention that the HAQ/utility conversion factors reported by these authors were -0.29 and -0.13 when using the SF6D and HUI3, respectively. Our results confirm these findings, because we used a conversion factor of -0.11 from the NDB compared to the RCT-based CEAs which used an average conversion factor of -0.26 as a result the ICER increased by 27%.

Unlike the other parameters, the HAQ-related mortality was contradictory among the RCT-based CEAs. The base-case value for this parameter in RCT-based CEAs was

(1.33-1.77), while the IES range was (-0.74-0.96), indicating that increased mortality relative risk by HAQ were not consistent among studies. Although it is expected that higher HAQ related mortality should decrease ICER due to higher QALYs, it is also expected to increase the survivor cost during the gained years of life.

This approach has several important limitations. First, the accuracy of our results is determined by the accuracy and consistency of sensitivity analysis reporting. Sensitivity analysis is an approach to demonstrate the robustness of the results to parameter uncertainty. As a result, current analyses do not adhere to a specific set of inputs to incorporate and report in the sensitivity analyses.[13] Several CEAs only reported relative change in parameters without referring to the base-case values. Although, we were able to calculate the IES, we were unable to incorporate the base-case values in our analysis. In addition, several studies especially those used tornado diagrams did not indicate the direction of ICER change relative to the input change. We believe that we overcome some of these limitations and hope that future analyses will report on a minimal set of parameters.

Second, since we relied on published OWSA, we are unable to capture the additional effect of parameter interaction in these models. Interactions occur in multilinear models when the parameters are located on the same decision branch. In addition, several studies reported probabilistic sensitivity analyses only. IES cannot be computed from PSA directly without some measure of parameter importance, such as the expected value of partial perfect information (EVPPI).

Third, due to the small sample, we did not adjust for study populations in the CEA. Several CEAs are specific by disease severity, duration, or prior DMARD failure, and these factors are important in influencing ICERs. Although the study population may impact the base-line ICER, we believe by measuring the relative change in ICER, we control for most of the impact of study population. In addition, by aggregating all the

results we are more likely capture an effect that can be generalizable to clinical practice.

3.5 Conclusion

This study sheds light on two important aspects of our current understanding of CEA of biologics in RA: the association of funding source with the findings of these study and the implications of using clinical practice data instead on the RCT-based CEAs through a novel meta-analytic approach.

We found that using observational-based estimates for several common inputs in RCT-based CEAs tripled the ICERs reported by these studies, causing biologics to appear less cost-effective than originally thought. To our knowledge, this is the first attempt to systematically reconcile the impact of using observational data instead of RCT results on the CEA of biologics in RA.

As more long-term data becomes available and the quality of CEAs improves, we become more certain on the true cost-effectiveness of these agents. We recommend establishing a minimal set of required parameters that will help future analysts to compare CEAs on the input level and better summarize their findings, and reconcile their differences.

3.6 Tables

Table 3.1: Summary Characteristics of Cost-Effectiveness Studies.

Author, year [ref.]	**Country**	**Horizon**	**Perspective**	**Discounting**	**Currency**	**Data source**
Bansback, 2005 [65]	Sweden	Lifetime	Payer	3%, 3%	EUR, 2001	RCT
Barbieri, 2005 [66]	United Kingdom	Lifetime	Payer	6%, 1.5%	GBP, 2000	RCT
Barton, 2004 [67]	United States	Lifetime	Payer	6%, 1.5%	GBP, 2000	RCT
Benucci, 2010 [68]	Italy	1 Year	Payer	N/A	EUR, 2008	OBS
Brennan, 2004 [27]	United Kingdom	Lifetime	Payer	6%, 1.5%	GBP, 2000	RCT
Brennan, 2007 [69]	United Kingdom	Lifetime	Payer	6%, 1.5%	GBP, 2003	RCT
Chen, 2006 [42]	United States	Lifetime	Payer	6%, 1.5%	GBP, 2004	RCT
Coyle, 2006 [70]	Canada	5 Years	Payer	5%, 5%	CAD, 2004	RCT
Davies, 2009 [71]	United States	Lifetime	Societal	3%, 3%	USD, 2007	RCT
Farahani, 2006 [63]	Canada	1 Year	Payer	N/A	CAD, 2003	OBS+RCT
Finckh, 2009 [72]	United States	Lifetime	Payer	3%, 3%	USD, 2007	OBS
Jobanputra, 2002 [73]	United States	Lifetime	Payer	6%, 1.5%	GBP, 2000	RCT
Kielhorn, 2008 [74]	United Kingdom	Lifetime	Societal	3.5%, 3.5%	GBP, 2006	RCT
Kobelt, 2003 [57]	Sweden	10 Years	Societal	3%, 3%	EUR, 2001	RCT
Kobelt, 2004 [75]	Sweden	1 Years	Societal	N/A	EUR, 2002	OBS

Author, year [ref.]	Country	Horizon	Perspective	Discounting	Currency	Data source
Kobelt, 2005 [76]	Sweden	10 Years	Societal	3%, 3%	EUR, 2004	RCT
Kobelt, 2011 [77]	Sweden	10 Years	Societal	3%, 3%	EUR, 2008	RCT
Lekander, 2010 [78]	Sweden	Lifetime	Societal	3%, 3%	EUR, 2007	RCT
Marra, 2007 [64]	Canada	10 Years	Societal	3%, 3%	CAD, 2002	OBS
Merkesdal, 2009 [79]	Germany	Lifetime	Societal	3.5%, 3.5%	EUR, 2008	RCT
Schipper, 2011 [62]	Netherlands	5 Years	Societal	4%, 4%	EUR, 2009	OBS
Soini, 2012 [60]	Finland	Lifetime	Societal	3%, 3%	EUR, 2010	RCT
Spalding, 2004 [80]	United States	Lifetime	Payer	3%, 3%	USD, 2005	RCT
Tanno, 2006 [81]	Japan	Lifetime	Societal	6%, 1.5%	GBP, 2005	RCT
van den Hout, 2009 [82]	Netherlands	2 Years	Societal	3%, 3%	EUR, 2008	OBS
Vera-Llonch, 2008 [83]	United States	Lifetime	Payer	3%, 3%	USD, 2006	RCT
Virkki, 2008 [84]	Finland	NA	Payer	N/A	EUR, 2006	OBS
Welsing, 2004 [85]	Netherlands	5 Years	N/R	4%, 4%	EUR, 2002	RCT
Wong, 2002 [86]	Canada	Lifetime	Societal	3%, 3%	USD, 1998	RCT
Yuan, 2009 [87]	United States	Lifetime	Payer	3%, 3%	USD, 2007	RCT

Discounting is presenting for cost and effectiveness, respectively; QALY=quality-adjusted life-year; RCT = randomized clinical trial; OBS = observational data; EUR = Euro; GBP = Great Britain Pound Sterling; CAD = Canadian dollar; USD = US dollar.

Table 3.2: Change in incremental cost-effectiveness ratio (ICER).

Screened Parameters	**IES**			**Input Est.**		**D**	**ΔICER**	**Data sources**	
	Mean	**s**	**n**	**R**	**O**	**(O-R)/R**	**IES * D**	**NDB**	**RCT CEAs**
Initial HAQ change	-0.77	0.07	3	-0.89	-0.26	-71%	55%	[8]	[27, 81]
Annual Background HAQ progression	-0.5	0.03	7	0.07	0.023	-69%	34%	[29]	[42, 27, 1, 71, 74, 83, 87]
HAQ/utility conversion	-0.48	0.06	5	-0.26	-0.11	-57%	27%	[a]	[27, 60, 1, 74, 79]
Annual HAQ progression for biologics	0.37	0.01	5	0.03	0.008	-69%	-26%	[29]	[42, 27, 1, 74, 76]
Mortality RR per HAQ	0.04	0.23	6	1.52	2.71	79%	3%	[26]	[42, 27, 83, 87, 86, 66]
RA-Specific Mortality	0.32	0.88	4	1.98	2.26	14%	5%	[88]	[27, 1, 79, 77]
Total change							**99%**		

Notes: IES = input effect size; s = standard deviation; n = number of studies; RCT = randomized clinical trail; R = RCT data source; O = observational data source; D = observational deviation from RCT; ΔICER = change in ICER due to using observational data; NDB = National Data Bank for Rheumatic Diseases; HAQ = Health Assessment Questionnaire; RR = relative risk; RA = rheumatoid arthritis; [a]=regression analysis of EQ5D on HAQ.

3.7 Figures

Figure 3.1: Flow chart of study selection.

CEA = Cost-effectiveness analysis; NHS EED = National Health Services Economic Evaluation Database.

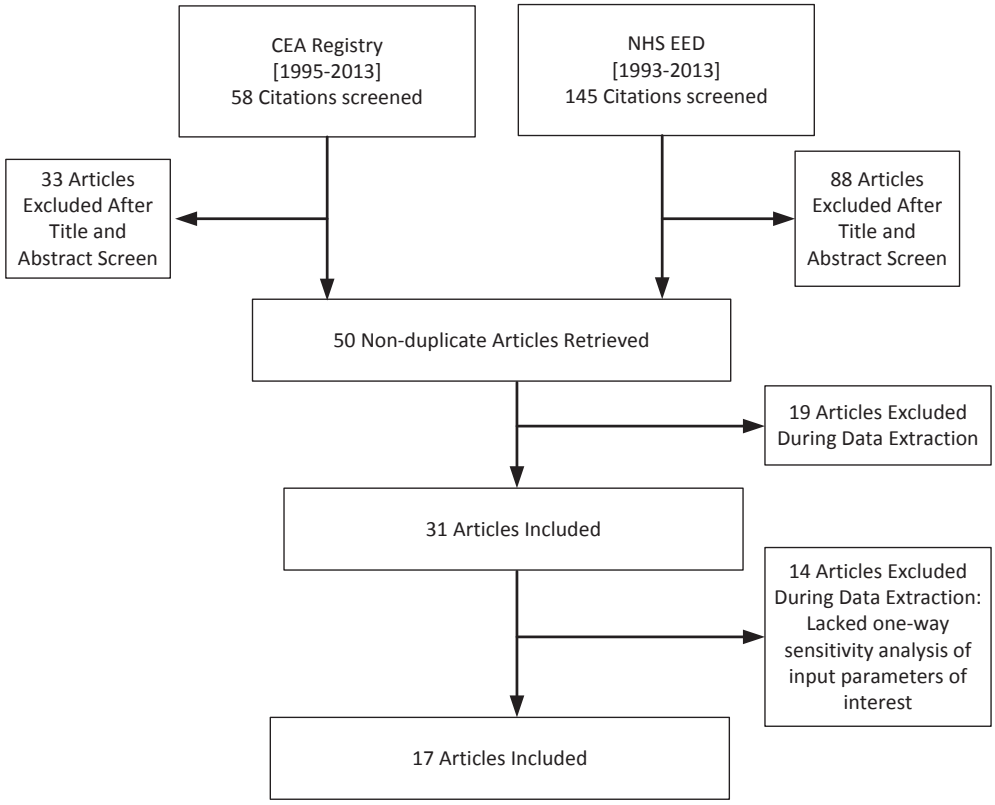


Figure 3.2: Distribution of incremental cost-effectiveness ratios (ICER) by funding source.

NICE = Application for the National Institute for Health and Care Excellence; N/R = not reported; CAD = Canadian Dollar; EUR = Euro; GBP = UK Pound Sterling; USD = US Dollar; ICER = Incremental Cost-Effectiveness Ratio.

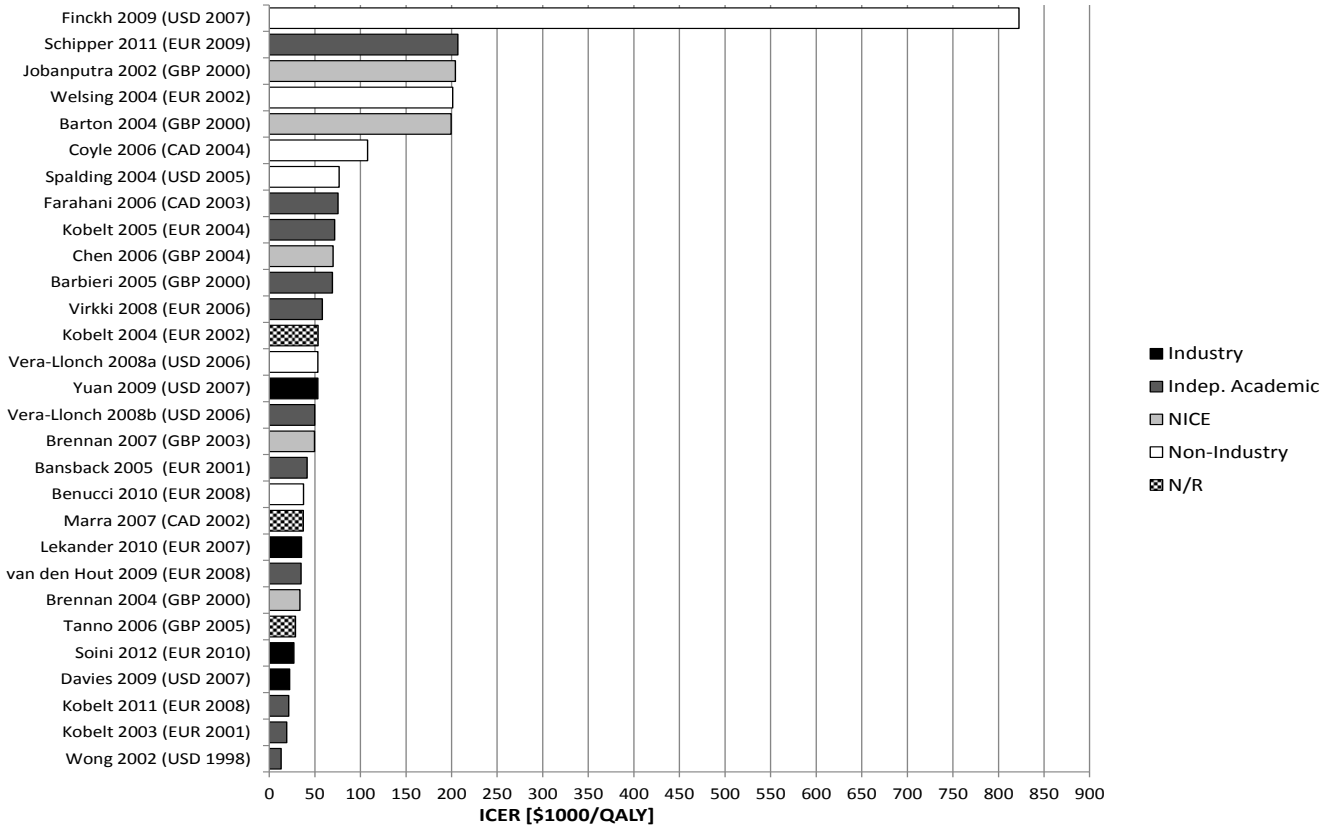
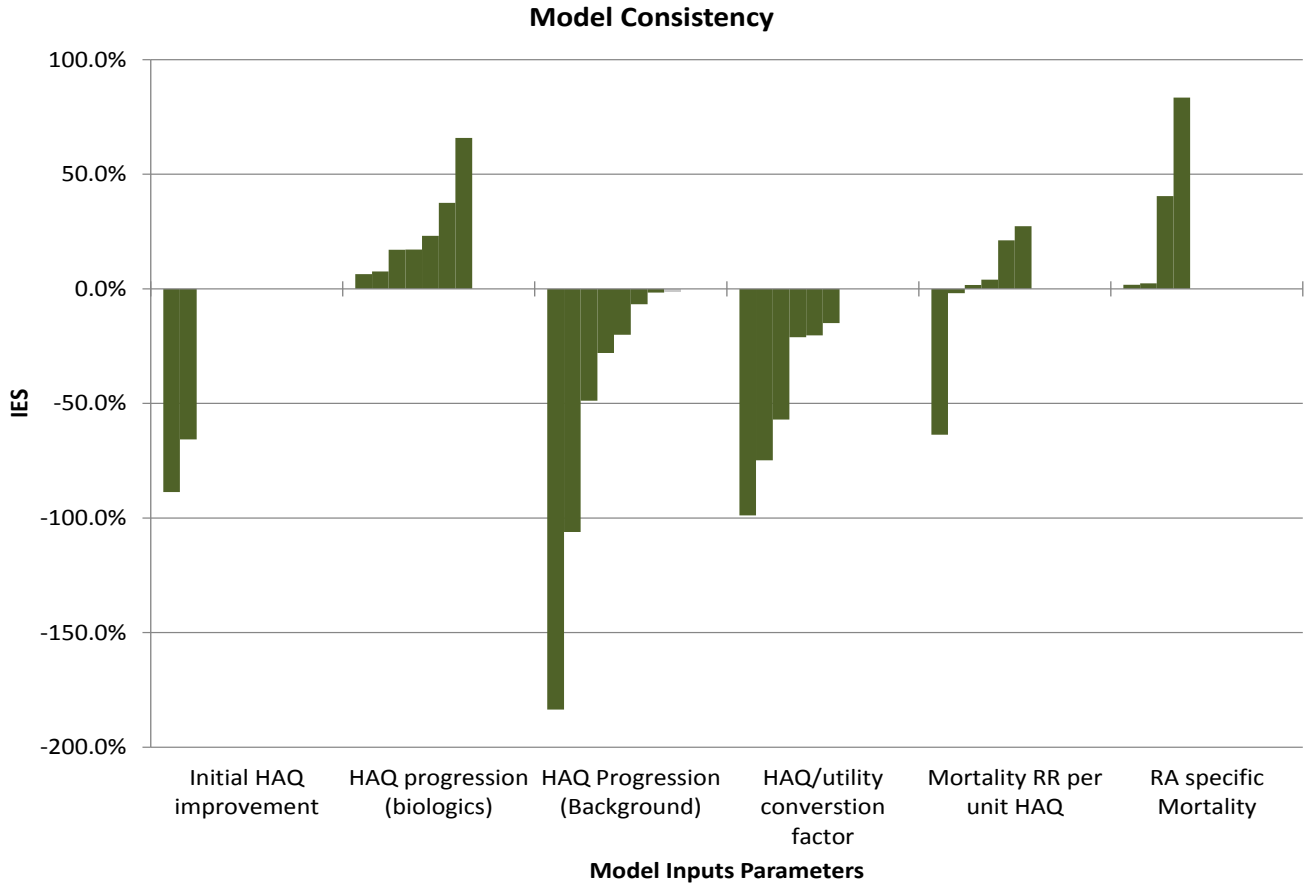


Figure 3.3: Model Consistency among RCT-based CEAs

IES = Input effect size; HAQ = Health Assessment Questionnaire; RR = relative risk; RA = rheumatoid arthritis.



Chapter 4

Is there a Window of Opportunity for Biologics in Early Rheumatoid Arthritis? A Cost-Effectiveness Analysis

Background. Although the concept of a window of opportunity for early treatment of rheumatoid arthritis (RA) is widely recognized among rheumatologists, it is unclear if biologics are cost-effective during this period.

Methods. We used a Markov decision process (MDP) to identify the optimal sequencing of biologics and nonbiologics for a hypothetical cohort of newly diagnosed 45-year-old RA patients. RA health states were defined by the Health Assessment Questionnaire (HAQ) quintiles. We identified transition probabilities for biologics and nonbiologics in early RA (duration<3years) and established RA (duration> 3 years) from the National Data Bank for Rheumatic Diseases (NDB). Health-related quality of life, RA-specific mortality, and work disability were estimated as functions of the HAQ and were estimated from the NDB and the literature. Model outcomes were quality-adjusted life expectancy and lifetime costs. We assumed a 6-month Markov cycle length and used 3% discount rate for all costs and benefits.

Results. In the base-case analysis, biologics were not cost-effective at a willingness-to-pay (WTP) threshold of $100,000/QALY and at biologics at their full cost. At 40% of the cost, biologics were cost-effective in early RA with HAQ scores 1.0. In addition, at this reduced cost, biologics were cost-effective for established RA with HAQ 1.875. When biologic costs were further reduced by 75%, biologics became cost-effective for early and established RA with HAQ 1.875.

Conclusion. We adopted a novel approach that combines operations research theory and real-life RA treatment practices to investigate the most-cost effective timing of biologics. The findings from this study suggests that (1) biologics are not cost-effective at their full cost as observed in real-life practices in the US compared to WTP thresholds often considered acceptable, and (2) that at reduced cost, biologics are more cost-effective in early RA than later in the course of the disease. These results have important practice and policy implications.

4.1 Background.

Modern management of rheumatoid arthritis (RA) patients aims toward slowing disease progression through timely diagnosis and treatment with the goal of complete remission.[18] Early diagnosis and treatment in the first few months after the disease process starts are crucial to prevent permanent joint damage and deformity. Even though this window of opportunity in early RA is not clearly defined[89], rheumatologists recognize its importance in improving quality of life, reducing work disability, and preventing premature death.[16, 17] In one study, biologics were more effective in slowing disease progression in early RA patients compared to established cases. The disability improvement in both groups were rapid and sustained, but it was superior in early RA.[90]

The American College of Rheumatologists (ACR) and the European League Against Rheumatism (EULAR) continuously update the RA treatment guidelines to more effectively target this window by promoting early diagnosis and treatment.[91, 19, 20, 2] In these guidelines, synthetic (nonbiologic) disease modifying anti-rheumatic drugs (DMARDs) such as methotrexate (MTX) are often recommended as first-line agents. Biologic DMARDs are only indicated when remission or low disease activity are not achieved with nonbiologics, or when patients have features of poor prognosis (See Appendix B).[18, 19, 20, 2, 3]

The main issue with biologics is their high price tag which is at the maximum of the markets tolerance.[92] Meanwhile, providers are under constant pressure to provide biologics in early arthritis.[92] The high cost of biologics are argued to be offset by the long-term improvement in quality of life, physical function, clinical and radiographical outcomes, increased productivity, and reduced work disability.[93, 94, 95] For example during the first 2-3 years of RA,. 20-30% of the patients were work disabled

and within 10 years 50% of them were unable to work.[96, 97] However, the comparative clinical and cost-effectiveness of biologics relative to nonbiologics in early arthritis is controversial.[18] Current cost-effectiveness analyses (CEAs) are based on standard decision trees that are incapable of handling a large number of possible treatment sequences and are mostly based on clinical trial data. For example Chen et al found the incremental cost to effectiveness ratio of biologics compared to nonbiologics in early arthritis to be four times higher in early arthritis compared to established arthritis.[42] Another study based on observational data, concluded that biologics were cost-effective only in a scenario in which all parameters were in favor of biologics and the biologics costs were reduced by 75%.[72] However, these studies are based on standard decision trees which compare a limited number of treatment sequences, and are inherently incapable of identifying an optimal starting time for biologics if such timing exists.

This study aims at identifying the optimal timing of biologics from a societal perspective in real-life settings. Specifically, is there a window of opportunity during which biologics are most cost-effective in early RA? To properly address this question, we adopted an innovative approach by using tool from operations research, Markov Decision Processes (MDP), instead of a standard decision tree and we used the National Data-Bank for Rheumatic Diseases (NDB) as the primary source of model inputs. The NDB consists of detailed self-reported semiannual questionnaires from 28,960 community RA patients from around the US.[11]

The main advantage of MDP is its ability to model sequential decisions. MDP has been successfully used in recommending the optimal timing of liver transplantation in treating chronic liver diseases and in the optimal timing of HIV treatment strategies.[15, 14] Despite its clinical relevance, powerful properties, and successful implementation, this tool remains underutilized in clinical settings.[98] To the best of our knowledge, this is the first study that uses MDP to identify the most cost-effective timing of biologics

in RA.

4.2 Methods

We used an MDP approach to identify the optimal timing of biologics for a cohort of newly diagnosed 45-year-old RA patients. Specifically, the MDP identifies the biologic-nonbiologic sequence that maximizes the net health benefit[1] (NHB) among all possible sequences. MDP uses backward induction, which simply indicates that the MDP computes the NHB from the last set of decisions (age 99.5 to 100), and determines which decision resulted in the maximum NHB for every state. The algorithm then moves backwards to the decisions at prior ages (99 to 99.5, 98.5 to 99, and so forth until age 45). During each cycle the MDP records the optimal decision at each state. At the end of the simulation, the MDP outputs the optimal sequence of decisions for each state and RA duration, starting at age 45.

Figure 1 outlines the structure of the MDP, which consists of a set of health states, the decision of biologics versus nonbiologics, a set of transition probabilities among the states, and a set of rewards (not shown). The MDP simulates the lifetime experience of a cohort of newly diagnosed 45-year-old RA patients. We used six-month Markov cycles for a total of 110 cycles. In each cycle, the patients in the cohort transition among the various states. These transitions are dependent on the RA duration and the biologics versus nonbiologic decision.

The health states in the MDP were defined by the Health Assessment Questionnaire Disability-Index (HAQ) score (Table 1). The HAQ measures the upper and lower limb functions relative to difficulty in performing daily tasks. HAQ is the primary RA clinical outcome measure in most cost-effectiveness analyses because it correlates well with

[1]NHB is an alternative to incremental cost-effectiveness ratio (ICER). NHB measures the difference between the actual benefit gained investing in an intervention and what could have been gained if we instead invested in a marginally cost-effective strategy at the willingness to pay threshold.[99]

mortality and both direct and indirect costs.[1] We defined six health states in the MDP defined by the five HAQ quintiles observed in the NDB (higher quintiles indicate worse disability) and an additional state for death.

Transitions among various health states were estimated from the number of RA patients who transitioned among the HAQ quintiles in the NDB. To account for potential confounding by indication, we restricted our sample to 28,209 newly diagnosed RA patients who were biologic nave when they entered the NDB, but eventually received biologics during the NDBs observation time. Table 2 shows the number of NDB observations used to estimate the transitions among various HAQ quintiles. We used an arbitrary cutoff of 3 years to distinguish disease progression in early arthritis from established disease because disability in early RA is most likely due to acute inflammation rather than joint deformity which occur later in the disease process. There were fewer available data to infer the transition probabilities in early RA patients compared to established RA patients. In addition, there was more information on biologics use versus nonbiologics use because of censoring those patients who never received biologics. We used the HAQ scores of these patients prior to and after initiating biologics to infer their HAQ transitions during nonbiologic and biologic use, respectively (Table 3). In addition, we used patient-specific cubic splines to correct for irregularities in NDB response timing.[15]

Model estimates for health-related quality of life, costs, and RA-specific mortality are shown in Table 1. Health-related quality-of-life weights were estimated from a regression analysis of EQ5D (a measure of health status from the EuroQoL Group) on HAQ and age from the NDB. Direct medical costs were obtained from the literature. Indirect costs were calculated as the product of three terms: the increase in productivity loss due to each unit increase in HAQ (0.2), the median wage for a full-time employee (estimated at $22,770) [48], and the mean HAQ in each quintile. All costs were inflated

to 2013 US dollars using the medical care component of the Consumer Price Index to adjust for inflation in medical costs.[61] Both costs and benefits were discounted by 3% annually. Death was modeled as an additional state. Background age-specific mortality was obtained from the US life tables.[30] RA-specific mortality was obtained from the literature and varied by HAQ.[26]

4.3 Results

Table 4 presents the optimal strategy by RA duration and HAQ quintile for early versus established RA at various biologics cost assumptions. In the base-case analysis, we used biologics full cost. At this cost, nonbiologics were the optimal choice regardless of the RA durations or the HAQ quintile, indicating that the marginal benefits from biologics were insufficient to offset their high costs as observed in real-life patients. At 40% cost, biologics appeared cost-effective in early RA for the more disabled patients (HAQ 1.0). At this cost, biologics were also cost-effective for established RA with HAQ 1.875. When biologics costs were further reduced to 25%, biologics appeared cost-effective for early and established RA with HAQ 1.0. These results indicate that the marginal cost to benefit ratio of biologics compared to nonbiologics may be higher in early RA compared to established RA later in the disease process. For example, nonbiologic would be the most cost-effective strategy for a patient who stays in quintile 2 during early RA. However, if this patient transitions to quintile 3 during late RA, biologics become the most cost-effective choice. In a benefit-only analysis, nonbiologics were still more effective than biologics for established RA with HAQ <1.0. For all other cases, biologics were more effective than nonbiologics.

Table 5 presents the simulated outcomes of the most cost-effective strategy for a cohort of 45-year-old RA patients. The results are shown at full biologics cost, as well as reduced costs of 40% and 25%. Those who start at higher HAQ quintiles tend to

spend more time at higher disability levels as shown in Figure 2 which illustrates the cohorts dynamic at ages 45, 48, 60, 80 and 100 years in the various health states. At age 45, the cohort is equally distributed among the HAQ quintiles. At age 48, the majority of the cohort (35%) resides in the first quintile, which may partly be caused by regression to the mean.[29] Later in life the cohort resumes a more uniform distribution among various states. Meanwhile, as the simulation progresses, an increased proportion of the original cohort dies and by age 100, the majority of the cohort will be in the dead state. As a result of this cohort dynamic, the lifetime benefits are lower and the costs are higher in the higher quintiles. Because in the base-case analysis biologics were not optimal, the higher costs associated with the high HAQ scores are due to non-drug costs and indirect costs rather than drug costs. Reducing biologics cost decreases the lifetime costs of the optimal strategies. These cost reductions are relatively larger in the higher HAQ scores. At reduced biologics costs, the biologic costs explain part of the difference in the lifetime costs among the HAQ quintiles because more patients in these states receive biologics compared to the lower quintiles.

In another sensitivity analysis, we examined the cohorts outcome while varying the starting age between 35 and 55 years. Our findings were robust to these changes. Nonbiologics were the optimal choice in early and established RA and for all HAQ quintiles. At reduced biologics costs, biologics were more cost-effective in early arthritis compared to established RA.

We also varied the cutoff time point that distinguishes early versus established RA from 2 to 5 years. This analysis allowed us to examine the impact of this arbitrary cutoff value on the cost-effectiveness of biologics. For example, biologics were cost-effective in early RA at reduced costs of 50%, 45%, 40% and 20% when using 2, 3, 4 and 5 years as cutoff values, respectively. Cutoffs values beyond 5 years were unable to capture a different cost-effectiveness value of biologics in early arthritis. These results indicate

that the RA progression during early arthritis is different than established arthritis and biologics modify these progressions at different rates than nonbiologics.

4.4 Discussion

Although the concept of a window of opportunity for early treatment is widely recognized among rheumatologists, it is unclear if there is a window of opportunity during which biologics are most cost-effective in early RA. More often clinicians are faced with the decision whether to start biologics in early arthritis or wait until the nonbiologics were tried and failed. To identify the most cost-effective timing of biologics, we adopted a novel approach that combines operations research theory and real-life RA treatment practices. In the base-case analysis, we found (1) that biologics were not cost-effective at their full cost compared to WTP thresholds generally considered acceptable, and (2) that biologics were marginally more cost-effective in early RA rather than later in the course of the disease. These results directly address the cost considerations involved in initiating biologics in early arthritis. Our base-case analysis was robust to variations in WTP thresholds between $100K-250K/QALY.

Our approach improves upon prior CEAs in two important ways. First, we used observational data to represent real-life RA patient transitions among various HAQ states. Most prior CEAs of biologics in RA are based on efficacy from clinical trials instead of real-life effectiveness. The effectiveness of biologics in real-life practices is lower than the efficacy observed in clinical trials.[8, 7] Wolfe et al. (2004) summarizes the problems of estimating efficacy from RCT data as:[8] (1) patients experiencing temporary worsening of symptoms may be overrepresented in RCTs due to eligibility criteria, (2) the treatment options compared in RCTs are rarely applicable to clinical settings, and (3) RCT duration is typically shorter than the duration of RA observed in real-life.

Second, we used MDP as a natural and realistic approach to examine the optimal timing of biologics in RA. Prior CEAs are limited because they reduce the complexity of treatment sequences to a manageable set of treatment scenarios that are incapable of capturing the optimal timing of biologics. For example, a standard decision tree comparable to the MDP must evaluate 2 to the power of 500 treatment scenarios! Such complexity is neither practical nor necessary. In the current study, we modeled the first MDP to address the importance of the optimal timing of biologics.

We calculated different HAQ progressions for the first 3 years of RA (early RA) and after the third year (established RA). We hypothesized that HAQ progression in early RA may be more reflective of acute inflammatory disease and that would be different than later on in the disease where HAQ progression may be more reflective of joint deformity with acute exacerbations. As we reduced the duration of early arthritis from 5 to 2 years, biologics appeared marginally more cost-effective in the early arthritis. This finding supports the theory of a window of opportunity that biologics are marginally more cost-effective. Due to sample limitations we were unable to estimate HAQ progressions for very early RA (i.e., first 3 months). Based on the results from a previous CEA biologics were not cost-effective compared to nonbiologics in this period.[72] In addition, two recent clinical trials also concluded comparable benefits of biologics and nonbiologics in early arthritis.[100, 101]

Because we relied on observational data to estimate biologics and nonbiologics effectiveness, confounding was a potential limitation. Specifically, those who received biologics in the NDB might have been at greater disability than those who received nonbiologics. To address this issue, we restricted our analysis to those who were biologics nave when entered the DNB but eventually received biologics at some point during their NDBs observation period. In addition, we estimated transitional probabilities that adjust for the baseline HAQ scores for each 6-month period. Our analysis remains

limited by other confounding variables that are not correlated with the base-line HAQ score.

Our findings are in agreement with other published studies.[72, 42] Similar to our analysis Finckh et al. found that biologics were not cost-effective at their full cost and that biologics were marginally more cost-effective in early RA than established RA. Similarly, Chen et al. found that using early RA data showed favorable results for biologics compared to established RA. In Chens analysis, using biologics among patients with established RA increased the incremental cost-effectiveness ratio of biologics compared to nonbiologics by four-fold and well above acceptable WTP thresholds.

Timing of biologics and nonbiologics may impose a threat to the validity of our results. By design, our analysis used data for patients who received biologics after nonbiologics. As a result, in the data biologics were taken when the patients were older and with higher number of comorbidities, both of which are shown to be associated with higher HAQ scores. To address the potential impact of increased age and comorbidities on HAQ progression, we conducted a separate analysis in which we used adjusted HAQ scores by age and comorbidities in a multivariate regression analysis to define the health states. These adjusted HAQ scores were highly correlated with the unadjusted scores (correlation coefficient = 0.93) and the MDP results were robust to the adjusted scores.

An important limitation of the MDP is that past events cannot account for future decisions. This is because the MDP computes the optimal decisions by simulating a patients experience backwards in time starting at the end of life. As such, the MDP is inherently incapable of capturing events that occur in the future. For example, we were unable to incorporate drug discontinuations in our analysis. As a result, we assumed that both biologics and nonbiologics can be continued indefinitely. For the same reason, we were unable to incorporate the risk of adverse events (e.g., serious infection and

malignancy) in the model. These adverse events are important consideration in biologics recommendations. However, the evidence surrounding them is controversial. A meta-analysis of clinical trials found 2 folds increase in the risk of serious infection and 3.3 folds increase in the risk of malignancy for biologics compared to placebo.[32] However, increased risks of serious infections and malignancy is not definite in observational data.[94]

Finally, our analysis does not account for radiographic improvements. Two clinical trial showed slower radiographic changes associated with receiving biologics compared to nonbiologics.[100, 101] However these changes were very small in both trials and significant in only one of them.[101] Even though we did not incorporate radiographical changes in our model directly, these changes are found to be highly correlated with HAQ scores especially over lengthier disease durations.[95]

4.5 Conclusion

Even though we found biologics not to be cost-effective as observed in real-life US practices, we found strong indications that they are marginally more cost-effectiveness in early versus established arthritis. Thus, a window of opportunity seems to exist in early RA during which biologics are more beneficial in terms of improved health-related quality of life and reduced productivity loss. However, biologics were only cost-effective at significantly reduced prices.

4.6 Tables

Table 4.1: The HAQ quintiles and associated health-related quality of life (QoL) weights, direct and indirect costs, and RA specific mortality rates.

HAQ			**QoL**	**Cost**	
Quintile	**Mean**	**Ranges**		**Direct**	**Indirect**
1	0.23	(0-0.375)	0.87	$349	$1113
2	0.7	(0.5-0.875)	0.81	$1044	$3331
3	1.13	(1-1.375)	0.74	$1702	$5427
4	1.52	(1.5-1.75)	0.67	$2275	$7253
5	2.02	(1.875-3)	0.57	$3026	$9649

Table 4.2: Transition probabilities among HAQ quintiles by drug category and RA duration (early vs. established).

			Nonbiologics						Biologics					
			HAQ Quintile						HAQ Quintile					
	From\To		1	2	3	4	5	Death	1	2	3	4	5	Death
Early	HAQ Quintile	1	0.749	0.15	0.05	0.013	0.037	0.002	0.706	0.2	0.057	0.029	0.007	0.002
		2	0.343	0.425	0.18	0.033	0.016	0.003	0.295	0.455	0.208	0.024	0.016	0.003
		3	0.037	0.277	0.369	0.221	0.092	0.004	0.055	0.277	0.461	0.166	0.037	0.004
		4	0.029	0.059	0.292	0.439	0.175	0.006	0.018	0.145	0.271	0.343	0.217	0.006
		5	0.041	0.041	0.124	0.206	0.578	0.01	0.071	0.047	0.141	0.165	0.566	0.01
	Death		0	0	0	0	0	1	0	0	0	0	0	1
Established	HAQ Quintile	1	0.688	0.135	0.028	0.008	0.008	0.134	0.682	0.14	0.029	0.008	0.008	0.134
		2	0.145	0.446	0.172	0.028	0.006	0.204	0.152	0.423	0.187	0.027	0.009	0.204
		3	0.018	0.12	0.408	0.124	0.032	0.298	0.022	0.14	0.386	0.127	0.027	0.298
		4	0.005	0.016	0.12	0.335	0.12	0.404	0.006	0.021	0.144	0.303	0.122	0.404
		5	0.003	0.003	0.013	0.049	0.357	0.575	0.005	0.005	0.021	0.073	0.321	0.575
	Death		0	0	0	0	0	1	0	0	0	0	0	1

Table 4.3: Optimal strategy by HAQ quintile, duration of RA and biologics costs.

Biologics Cost	Duration	HAQ Quintiles				
		1	2	3	4	5
100%	Early	N	N	N	N	N
(Base-case)	Late	N	N	N	N	N
40%	Early	N	N	B	B	B
	Late	N	N	N	N	B
25%	Early	N	N	B	B	B
	Late	N	N	B	B	B
QALY only	Early	B	B	B	B	B
	Late	N	N	B	B	B

Table 4.4: Maximum net health benefit (NHB) by HAQ quintiles and biologics costs for a newly diagnosed 45-year-old RA cohort.

Biologics Cost	**Outcome**	**HAQ Quintiles**				
		1	**2**	**3**	**4**	**5**
100%	NHB	10.08	9.86	9.38	9.06	8.76
(Base-case)	QALYs	12.86	12.73	12.48	12.25	12.02
	Costs	277,860	286,530	310,510	318,590	325,710
	NHB	10.31	10.11	9.68	9.35	9.05
40%	QALYs	12.86	12.73	12.48	12.25	12.02
	Costs	254,900	262,080	280,260	290,180	297,050
	NHB	10.57	10.37	9.99	9.66	9.37
25%	QALYs	12.86	12.73	12.48	12.25	12.02
	Costs	229,410	235,690	249,480	258,410	264,630

Figure 4.1: Markov Decision Processes (MDP) outline.

HAQ Q1-HAQ Q5 corresond to the Health Assessment Questionnaire quintiles 1 through 5.

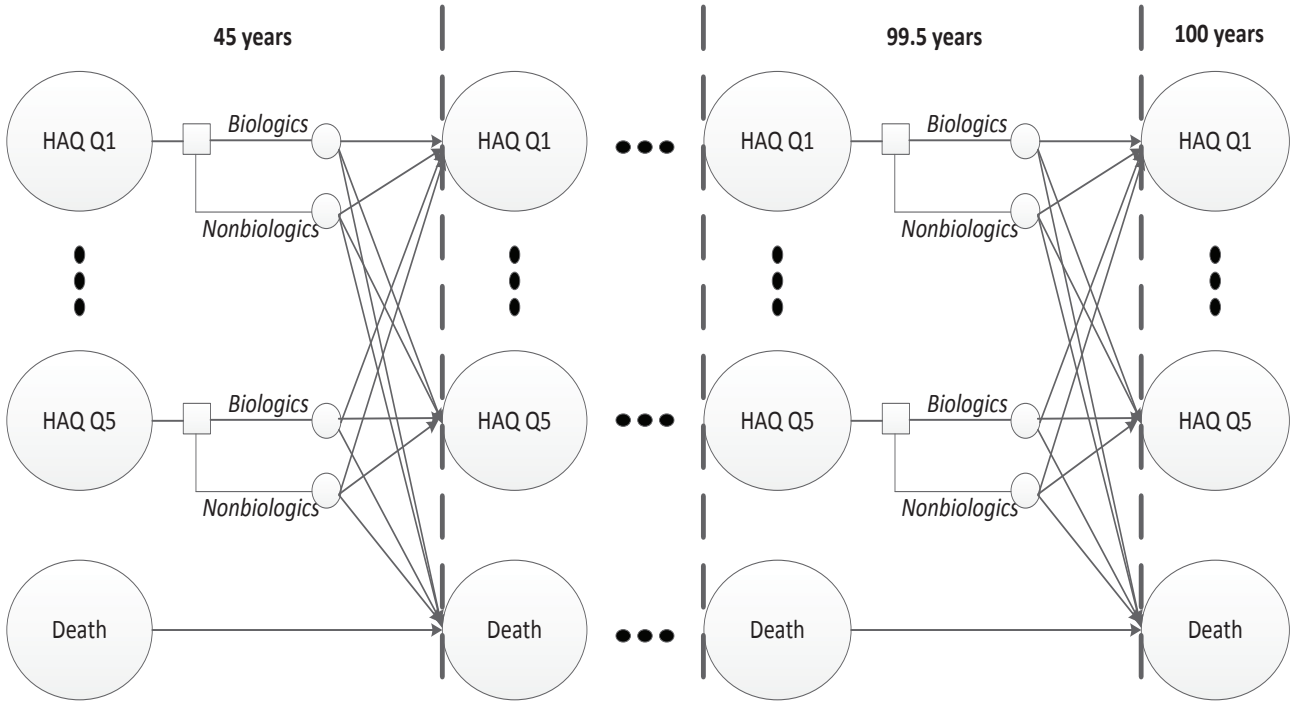
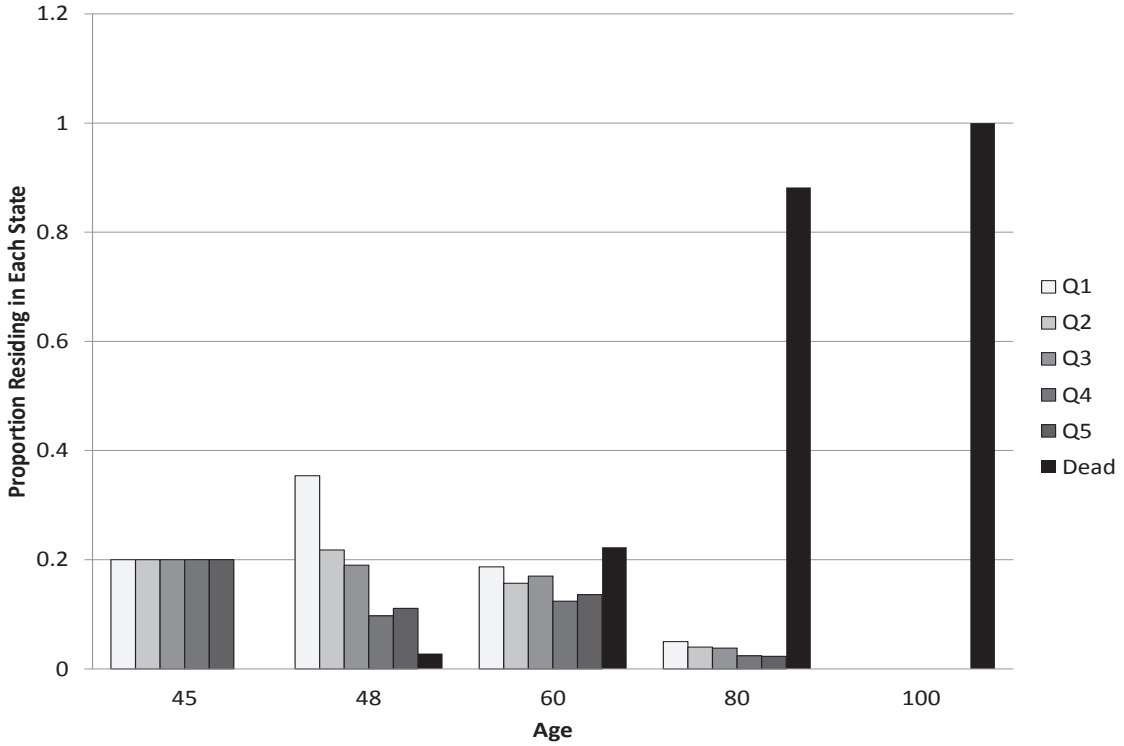


Figure 4.2: Proportions of the original RA cohort at each HAQ quintile and death for various ages. Q1-Q5 correspond to quintiles of the Health Assessment Questionnaire 1 through 5.



Chapter 5

Conclusion and Discussion

This thesis investigates various aspects of the cost-effectiveness of biologics in US clinical practice settings. In Chapter 2, we developed a simulation model to conduct a cost-effectiveness analysis (CEA) of biologics using clinical practice effectiveness data from a large RA registry in the US (The National Data Bank for Rheumatic Diseases [NDB]).[11] Based on real-life RA patient experiences, we simulated the long-term cost-effectiveness of biologics compared to nonbiologics from a US societal perspective. We were able to compare a large number of biologic sequences, take into account discontinuation patterns of these drugs, and their potential adverse events. Using clinical practice data as a source of model inputs, we found biologics strategies to be slightly more effective and significantly more expensive than nonbiologics. As a result we found the incremental cost-effectiveness ratio (ICER) of biologics compared to nonbiologics to be very high.

Our results were in conflict with the findings from most RCT-based CEAs. Although biologics may be cost-effective in RCT settings, most RA patients who receive biologics are not eligible to participate in these RCTs [9], and biologics efficacy for RCT eligible participants exceeds that of the ineligible participants [7]. Furthermore, RA treatment guidelines are generally less strict in the US than other countries that have universal

health insurance coverage and require strict adherence to guidelines for reimbursement purposes. As a result, fewer patients who receive biologics in the US may meet the RCT eligibility criteria. Consequently, the societal costs of biologics may far exceed their benefits given willingness to pay thresholds often considered acceptable by many healthcare agencies.

In Chapter 4, we attempted to reconcile the differences in the findings from our effectiveness-based CEA with those based on RCTs. Specifically, we investigated whether differences in the findings were due to the input parameter sources or from fundamental structural differences among CEAs. We reviewed the literature for published CEAs of biologics compared to nonbiologics, and developed a novel approach to meta-analyze these studies on their input levels using the published sensitivity analysis results. We investigated the implications of replacing RCT efficacy of biologics with effectiveness from clinical practice on the results of previously published RCT-based CEAs. We found that using clinical effectiveness can double the ICERs reported thus rendering biologics twice less cost-effective.

We also found that CEAs sponsored by the pharmaceutical industry were more likely to report favorable results than non-industry sponsored studies. These findings confirmed the results of a prior analysis of the CEA Registry (available online at http://tufts-nemc.org/cearegistry) which also found strong indications for publication bias in CEAs.[12]

In addition to reconciling the differences between our approach and prior analyses, this chapter also serves as the first meta-analysis effort specific to CEAs. Our approach utilized the information provided in sensitivity analyses results and did not require access the original models. This capability is of particular importance to policy and decision makers because it provides important insight into various assumptions adopted in these studies.[52, 13] Prior systematic reviews of CEAs have been limited to a descriptive

analysis entailing mere comparison and contrasting of these studies, including a recent systematic review of biologics CEAs in RA.[4] These systematic reviews were unable to summarize the information provided in the original CEAs.

In Chapter 4, we adopted Markov decision prcesses (MDP) as a novel approach to investigate the relative cost-effectiveness of biologics in early versus established RA. We examined if there exists a window of opportunity during which biologics are most cost-effective in RA. Although the concept of a window of opportunity for early diagnosis and treatment is widely recognized among rheumatologists, it is unclear if during this window biologics are also most cost-effective. Rheumatologists are often faced with the decision of whether to start biologics in early arthritis or wait until the nonbiologics were first tried and failed. In the base-case analysis, we found that (1) biologics were not cost-effective at their full costs compared to WTP thresholds generally considered acceptable, and (2) that biologics were marginally more cost-effective in early RA rather than later in the course of the disease. These results directly address the cost considerations involved in initiating biologics in early arthritis because guidelines recommend biologics as second line agents after the cheaper nonbiologics were tried thus ignoring the potential long-term benefits of these agents.

MDP is a natural choice for applications that investigate the optimal timing of a decision. In this particular type of research questions, it is superior to traditional CEAs, because it allows a large number of sequential decisions to be modeled efficiently. For example, MDP has been successfully implemented in recommending the optimal timing of liver transplantation and in treating chronic liver diseases and in the optimal timing of HIV treatment strategies.[15, 14] Despite its clinical relevance, powerful properties, and successful implementation, this tool remains underutilized in clinical settings.[98] This thesis is the first application of MDP being used in identifying the optimal timing to initiate biologics in rheumatoid arthritis.

In summary, although biologics may be cost-effective in the strict RCT settings, we found strong evidence that biologics are not utilized cost-effectively in clinical practice in the US. The difference between our results and those from RCT-based CEAs can be partially attributed to the input parameter estimates. Using parameter estimates from the NDB nearly doubled the ICERs reported from RCT-based CEAs. In addition, we found that at a reduced cost, biologics were marginally more cost-effective in early rather than established RA.

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Appendix A

Detailed Calculations of the Input Effect Sizes (IES)

The following tables present the detailed calculation of the mean parameter and mean input effect size (IES) for the six selected model parameters. These parameters are the initial HAQ improvement, annual HAQ progression for biologics, annual background HAQ progression, relative risk of mortality rate for each unit increase in HAQ, and the RA-specific mortality rates. The ICERs are in currency per QALY. The currency type and year vary from one study to another and is reported in Figure 3.2.

Table A.1: Initial HAQ Improvement.

Author	Year	Absolute Values						Percentage Change				IES
		Input			ICER			Input		ICER		
		Baseline	V1	V2	Baseline	V1	V2	V1	V2	V1	V2	
Brennan	2004	-0.842	-0.662	-1.023	16372	19121	14507	-0.2139	0.2148	0.167	-0.1139	-0.657
Tanno	2006	-0.94	-0.752	-1.128	2.5	2.975	2.088	-0.2	0.2	0.19	-0.165	-0.887
Mean		-0.891										-0.772
(S)		-0.069										0.162

Notes: ICER = incremental cost-effectiveness ratio; V1 = first input value; V2 = second input value; IES = Input effect size; S = standard deviation.

Table A.2: HAQ/Utility Conversion Factor.

Author	Year	Absolute Values						Percentage Change				IES
		Input			ICER			Input		ICER		
		Baseline	V1	V2	Baseline	V1	V2	V1	V2	V1	V2	
Brennan	2004	-0.2						-1				-0.57
Bansback	2005	-0.28	-0.173		34030	35970		-0.382		0.057		-0.149
Davies	2008	-0.28	-0.17		46946	65172		-0.392		0.388		-0.988
Kielhorn	2008	-0.28	-0.173		14683	18872		-0.381		0.285		-0.747
Merkesdal	2010	-0.173	-0.28		15564	13535		0.616		-0.13		-0.211
Soini	2012	-0.32	-0.173	-0.188	19113	20893	20713	-0.458	-0.412	0.093	0.083	-0.202
Mean		-0.255										-0.478
(S)		-0.056										0.34

Notes: ICER = incremental cost-effectiveness ratio; V1 = first input value; V2 = second input value; IES = Input effect size; S = standard deviation.

Table A.3: HAQ progression while on biologics.

Author	Year	Absolute Values						Percentage Change				IES
		Input			ICER			Input		ICER		
		Baseline	V1	V2	Baseline	V1	V2	V1	V2	V1	V2	
Brennan	2004	0.015		0.034	16372		19933		1.266		0.217	0.171
Bansback	2005	0.034	0		34030	28230		-1		-0.17		0.17
Chen(TNF@1)	2006	0.03	0		200956	32447		-1		-0.838		0.838
Chen(TNF@3early)	2006	0.03	0		30812	19264		-1		-0.374		0.374
Chen(TNF@3Late)	2006	0.03	0		88319	32045		-1		-0.637		0.637
Chen(TNF@last)	2006	0.03	0		31056	22203		-1		-0.285		0.285
Davies	2008	0.044	0		46847	36010		-1		-0.231		0.231
Kielhorn	2008	0.017	0		14684	5013		-1		-0.658		0.658
Vera-Iloch	2008	0.015		0.031	45979		49708		1.066		0.081	0.076
Yuan	2010	0.015		0.031	51041		54523		1.066		0.068	0.063
Mean		0.026										0.351
(S)		-0.01										0.27

Notes: ICER = incremental cost-effectiveness ratio; V1 = first input value; V2 = second input value; IES = Input effect size; S = standard deviation.

Table A.4: Background HAQ progression.

Author	Year	Absolute Values						Percentage Change				IES
		Input			ICER			Input		ICER		
		Baseline	V1	V2	Baseline	V1	V2	V1	V2	V1	V2	
Brennan	2004	0.13	0.065		16372	18661		-0.5		0.139		-0.279
Bansback	2005	0.132	0.107		34030	35320		-0.189		0.037		-0.2
Kobelt	2005	0.03	0	0.09	37331	38726	36779	-1	2	0.037	-0.014	-0.015
Chen(TNF@1)	2006	0.06	0.03		200956	206499		-0.5		0.027		-0.055
Chen(TNF@3early)	2006	0.06	0.03		30812	38334		-0.5		0.244		-0.488
Chen(TNF@last)	2006	0.06	0.03		31056	46659		-0.5		0.502		-1.004
Spalding	2006							-0.5	0.5	-0.035	-0.047	-0.012
Tanno	2006				2.5	2.548	2.481	-0.2	0.2	0.019	-0.007	-0.067
Kielhorn	2008	0.065	0.017		14684	34586		-0.738		1.355		-1.835
Lekander	2010	0.065	0.031		22780	35420		-0.523		0.554		-1.06
Mean		0.073										-0.501
(S)		-0.034										0.61

Notes: ICER = incremental cost-effectiveness ratio; V1 = first input value; V2 = second input value; IES = Input effect size; S = standard deviation.

Table A.5: Mortality relative risk by HAQ.

Author	Year	Absolute Values						Percentage Change				IES
		Input			ICER			Input		ICER		
		Baseline	V1	V2	Baseline	V1	V2	V1	V2	V1	V2	
Wong	2002	1.77			30689	19400		-1		-0.367		0.367
Barbieri	2005	1.77			33618	26510		-1		-0.211		0.211
Brennan	2004	1.375	1	1.75	16372	20112	14428	-0.272	0.272	0.228	-0.118	-0.636
Chen(TNF@1)	2006	1.33	0	2.73	200956	461453	150735	-1	1.052	1.296	-0.249	-0.748
Chen(TNF@3early)	2006	1.33	0	2.73	30812	29304	31817	-1	1.052	-0.048	0.032	0.039
Chen(TNF@3Late)	2006	1.33	0	2.73	88320	66332	239798	-1	1.052	-0.248	1.715	0.962
Chen(TNF@last)	2006	1.33	0	2.73	31056	31056	29581	-1	1.052	0	-0.047	-0.023
Vera-Iloch	2008	1.8	1.5	2	45979	45748	45948	-0.166	0.111	-0.005	-0.001	0.016
Yuan	2010	1.8	1	2	51041	51748	51343	-0.444	0.111	0.013	0.005	-0.019
Soini	2012	1.33	1		19113	17818		-0.248		-0.067		0.273
Mean		1.516										0.044
(S)		-0.231										0.48

Notes: ICER = incremental cost-effectiveness ratio; V1 = first input value; V2 = second input value; IES = Input effect size; S = standard deviation.

Table A.6: RA specific mortality.

Author	Year	Absolute Values						Percentage Change				IES
		Input			ICER			Input		ICER		
		Baseline	V1	V2	Baseline	V1	V2	V1	V2	V1	V2	
Brennan	2004	2.975	1	5.975	16372	16129	16790	-0.663	1.008	-0.014	0.025	0.024
Bansback	2005	1.63	1	1.9	34030	29190	36940	-0.386	0.165	-0.142	0.085	0.404
Kobelt	2005				37331	36655		-1		-0.018		0.018
Merkesdal	2010	1.33	1	2	15564	12937	22580	-0.248	0.503	-0.168	0.45	0.834
Average		1.978										0.32
(S)		-0.876										0.83

Notes: ICER = incremental cost-effectiveness ratio; V1 = first input value; V2 = second input value; IES = Input effect size; S = standard deviation.

Appendix B

Early RA Treatment Guidelines

The following diagrams are reproduced from the 2008 American College of Rheumatology (ACR) guidelines [20] for treating early cases of RA (duration < 3 months), and the updated version [2] of these guidelines published in 2012. In the 2008 guidelines, biologics are recommended in early RA if there is persistent disease activity despite nonbiologics therapy and features of poor prognosis. Because of cost consideration, in these guidelines, biologics are only recommended if there are no cost or insurance limitations. The 2012 update of these guidelines is similar, but the decision point related to biologics cost has been removed. Even though, biologics cost has is not directly addressed in the 2012 version, it still plays a key role in determining access to these drugs and an important limiting factor of biologics prescription in early RA.

Figure B.1: 2008 American College of Rheumatology (ACR) guidelins for treating early RA. Reproduced from [20].

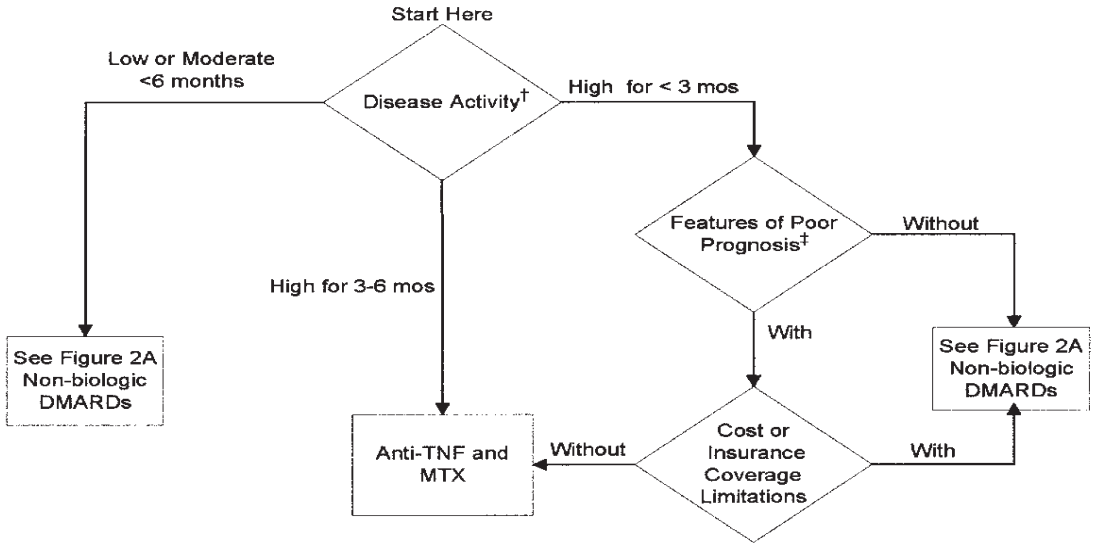
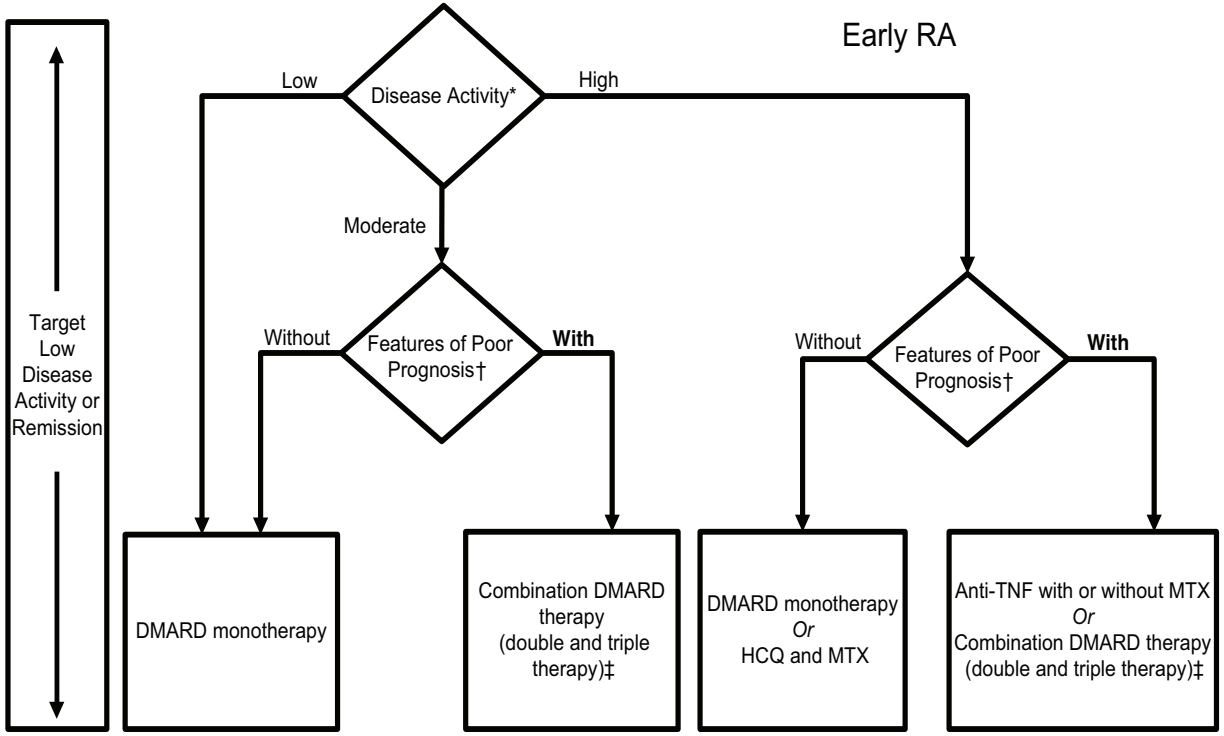


Figure B.2: 2012 Update 2008 American College of Rheumatology (ACR) guidelins for treating early RA. Reproduced from [2].



Appendix C

Markov Decision Processes

This section provides a detailed description of Markov Decision Processes (MDP). MDP originates from operational research. Since its conception, it has been successfully used in many applications, including medical decision making. For example, Alagoz and Schaefer provide a summary of several medical applications of MDP [98, 102]. Despite its clinical relevance, powerful properties, and successful implementation, this tool remains underutilized in medical decision making.[98]

The main advantage of MDP is the ability to model sequential decisions. Sequential decisions are important in clinical practice since most medical decisions tend to recur over time. It is theoretically possible to use standard decision models in these problems, but exhausting all possible sequences requires a very large number of decision branches. For example, in Chapter 4 if we tried to use a standard decision tree, we would have needed more than 10^{500} decision branches which can easily overrun the capability of the fastest computers. MDP is specifically designed to handle sequential decisions. Alagoz et al illustrates the advantage of using MDP to setup a sequential decision problem and the performace improvement gained with an MDP compared to a standard decision tree.[98]

Standard textbooks such as Markov Decision Processes by Martin Puterman [103]

are excellent resources for an in depth description of MDP. Although MDP and standard Markov models are very similar in concept, their algorithms are fundamentally different. While standard Markov decision trees use forward propagation in time, MDP utilizes a technique referred to as the Backward Induction Algorithm by Bellman.[104]

Chapter 4, used a finite-horizon discrete-time MDP. Finite-horizon (vs. infinite-horizon) indicates a limited duration because the model is limited by the patient's lifetime. Discrete-time (vs. continuous) indicates classification of time into a set of distinct periods. While all MDP flavors share a similar setup, their algorithms are somewhat different. We believe that the finite horizon discrete-time variety was the most appropriate in our case. In this section, we provide further detail into the setup and algorithm of this particular type of MDP. For further detail on the other types, please refer to Puterman's MDP textbook.[103]

C.1 MDP Setup

Figure C.1 illustrates the structure of a simple finite-horizon discrete-time MDP which consists of five elements [103]:

- A set of decision epochs or time periods (T)
- A set of health states (S)
- A set of actions (A)
- A set of state and action dependent rewards (r)
- A set of state and action dependent transition probabilities (p)

At each decision epoch (t) all patients must reside in one of the health states (s). A transitional probability (p) controls the flow of these patients among states over time. This transitional probability is dependent on the health state (s), decision epoch (t) and the action (a) chosen. A reward (r) accumulates as patients pass through the model. In Chapter 4 we used net health benefits to measure reward, but rewards can be in

the form of costs, or quality adjusted life years (QALYs), or any other type of relevant rewards. These rewards are dependent on the state (s), time (t) and selected action (a). This collection $\{T, S, A_s, p_t(.|s,a), r_t(s,a)\}$ forms the structure of the Markov Decision Process (MDP) [103].

Figure C.1 illustrates the setup of an MDP that consists of 3 decision epochs ($t = 3$), 3 health states ($s = 3$), and 4 actions ($a = 4$). Notice that no decision occurs in the last period but it is still considered a decision epoch for mathematical convenience. Thus, The number of decision epochs is always larger by one from the number of decisions points. In this diagram, the transitional probabilities are represented by the arrows pointing from the chance nodes to the health states in the next time period. Here we assume that transitions among all states are possible following every actions except for s_3 and a_4. We also assume that s_3 is an absorbing state (e.g. death) with arrows directing to it from all other states. Once a patient enters this state they will stay there for the rest of the simulation. These transitional probabilities are dependent on the originating state, the transitioning state, and the action taken. As a result of transitioning from one state to the next a reward (r) will accumulate. This reward is a function of both residing in the health state and the chosen action. Table C.1 the standard mathematical notation often used to describe MDP.

Figure C.1: MDP Setup

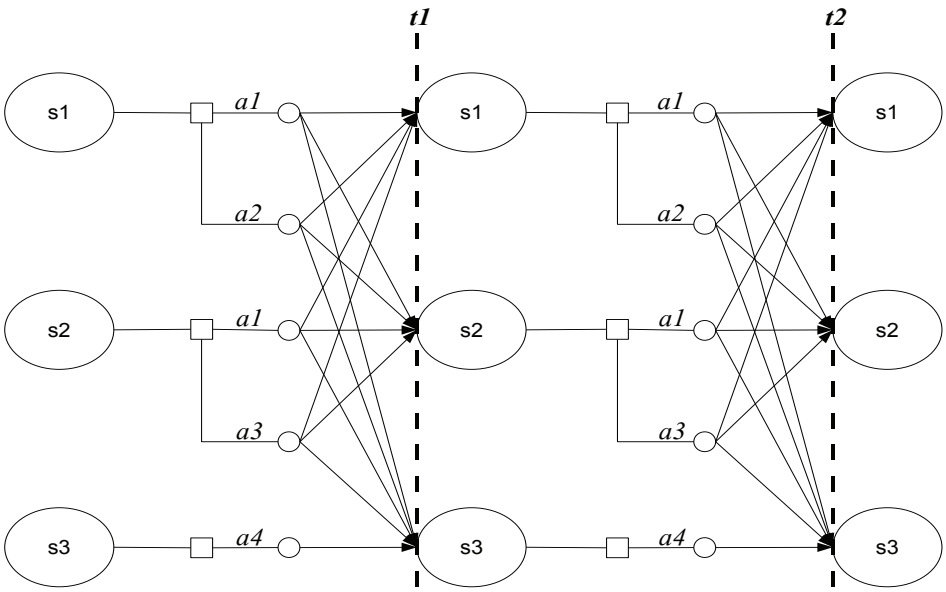


Table C.1: MDP Components

Parameter	**Values**	**Description**
T	$t \in T; t = 1, ..., N$	A set of decision epochs (time periods)
S	$s \in S$	A set of mutually exclusive and collectively exhaustible health states
A_s	$a \in A_s \subseteq A$	A set of actions available at state s. A represents the complete set of actions available for all states. Actions can also depend on time t.
$p_t(.\|s, a)$	$p \sim f(\mu, \sigma)$	Transitional probability distribution at decision epoch t following action a, conditional on being at state s
$r_t(s, a)$	Rewards	Reward at state s at time t following action a

Two key concepts in MDP that are decision rules (d) and policy (π). Decision rules are a set of rules that specify the relationship between actions, states and time. These rules defined the relationship between various actions, states and decision epochs. It is important to note that MDP is based on the "Markovian" principle and is therefore is memoryless. This means that the decision rule would be the same no matter the path or history that led to being in a certain state at a certain time. Thus, prior actions and states are irrelevant in MDP. That being said, modifications of the MDP exist that may account for history. Readers see [103] for additional detail.

C.2 The Backward Induction Algorithm

Finite-horizon discrete-time MDP utilizes an algorithm referred to as the Backward Induction Algorithm which finds the optimal policy (a sequence of decision rules) by iterating through this set of Bellman equations [104]:

Step 1:

$$u_N^*(s_i) = r_N(s_i) \tag{C.1}$$

Step $2, ..., N-1$:

$$u_t^*(s_i) = \max_{a \in A_s} \left\{ r_t(s_i, a) + (1-\alpha) \sum_{j \in S} p_t(j|s_i, a) u_{t+1}^*(j) \right\} \tag{C.2}$$

where $\forall s_i \in S$, $t = 1, ..., N-1$, $u_N^*(s_N)$ = health state specific maximum utility at the last decision period representing the optimal choice for each health state at the end of life, $r_N(s_N)$ = health state specific rewards at the last decision period (end of life), $u_t^*(s_t)$ = health state specific maximum utility at decision periods before the last period. Optimal choices at other years of life, α = discounting factor (e.g., 5%), u_{t+1}^* = state specific maximum utility and cumulative discounted future rewards at the next

decision period, i = residing state, and j = transitioning state.

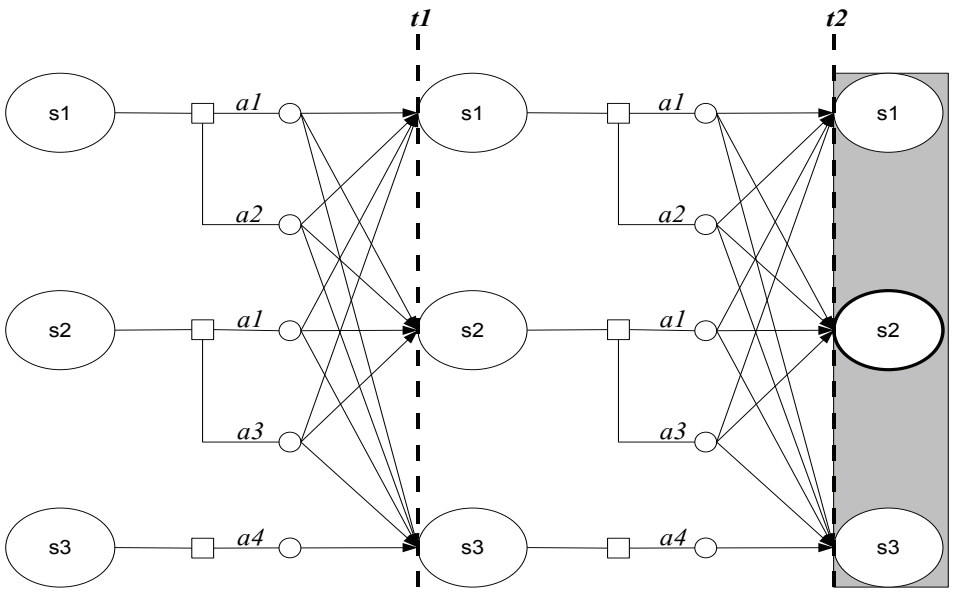
The objective of MDP is to find the optimal policy (π^*). This is accomplished by iterating from step 1 to $N-1$. At the end of these iterations, MDP finds the sequence of actions (medications) that maximizes the cumulative stage and period specific rewards.

MDP identifies the optimal solution using the Backward Induction Algorithm. This simply means starting the iterations from the end of the simulation instead of the beginning. This is useful because there are no future rewards in the last period because in this period, the optimal utility for each state $u_N^*(s_i)$ will simply be equal to the state specific rewards $r_N(s_i)$ at the end of life. This last decision epoch will act as the future rewards for all subsequent iterations. For example, the state specific reward for periods $N-1$ and N will be equal to the total of the state specific reward at $N-1$ summed with the discounted weighted average of future possible rewards $(1-\alpha)\sum_{j\in S} p_t(j|s_i,a)u_{t+1}^*(j)$. The weighted average of future rewards for a specific state is equal to the sum of the products of transitional probability and the state specific rewards at decision period N. At period $N-2$, the total state specific rewards at time $N-1$ will become the future rewards. Equation (7) will recursively iterate until it reaches the first decision period $t=1$. Figures C.2, C.3 and C.4 present a visual illustration of the MDP solution for this system of equations.

The shaded area represents the window that the MDP examines at each iteration. In the first step (Figure C.2), this window is limited to the last decision period at $(t=N=3)$. At this step no actions is chosen since the window does not cover any decision nodes. The optimal utility for each of the states at this period is simply the state specific reward at the last decision period (t_3). For the subsequent iterations, MDP extends the left margin of this shaded area until it stops when the last decision period is covered $(t=1)$. For each of these iterations $(t<N)$, the MDP recognizes the state specific actions (a) that maximizes the rewards accumulated in this window.

In each of these iterations, this area covers a new decision epoch. The system searches this last covered epoch for the optimal action (a). The optimal action maximizes the total of the state specific reward $r_t(s, a)$ and the discounted weighted average of future rewards. Both the action (a_t) and maximum reward (u_t^*) will be recorded. After the system finishes the final iteration, a series of decision epoch and state specific actions ($a_t^*, t = 1, ..., N-1$) will be identified. These sequences will be labeled the optimal policy (δ^*). Figure 2 illustrates this solution for the simple example mentioned above. There are no optimal actions for t_3. Therefore, the optimal utility is simply the state specific reward at time t_3. This is illustrated by the shaded ares in Figure C.2. In step 2, the state specific rewards obtained from step 1 will be weighted by the specific probabilities and become the future rewards for t_2. These future rewards are then discounted by a factor (α). This will recur at the final step (step 3). The system finally stops when there are no more decision nodes to cover. As a result of these iterations state specific policies can be identified. For example for someone who starts at s_2 at time t_1, it is best to choose a_1. Choosing a_1 most likely results in transitioning to s_1 at t_2. If this happens, then the best action to take is to choose a_2, as it result in transitioning to s_2 at t_3. This series of decision rules guarantee the best cumulative reward. In summary, MDP is a powerful tool for Markov problems that involve sequential decisions. However, this tool has been inadequately explored by many modelers in MDM. This set of diagrams provides a visual illustration of MDP that will facilitate the understanding and utilization of this powerful tool in future MDM applications.

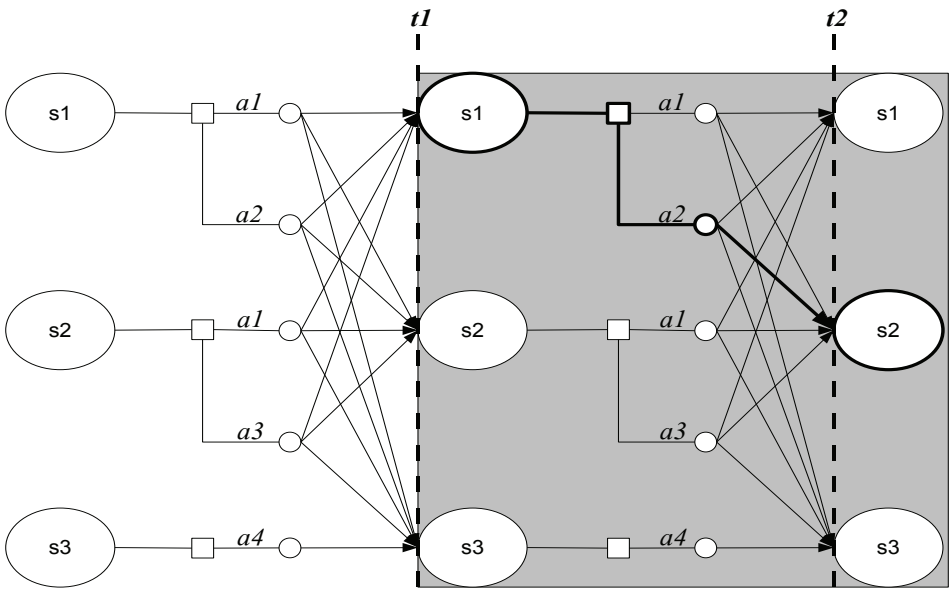
Figure C.2: MDP Example: Step 1



For each $s_i \in S, i = 1, 2, 3$, the optimal state specific utility $u_3^* s_i = r_3(s_i)$

For example, the reward of staying at state s_2 represents the optimal utility for this state.

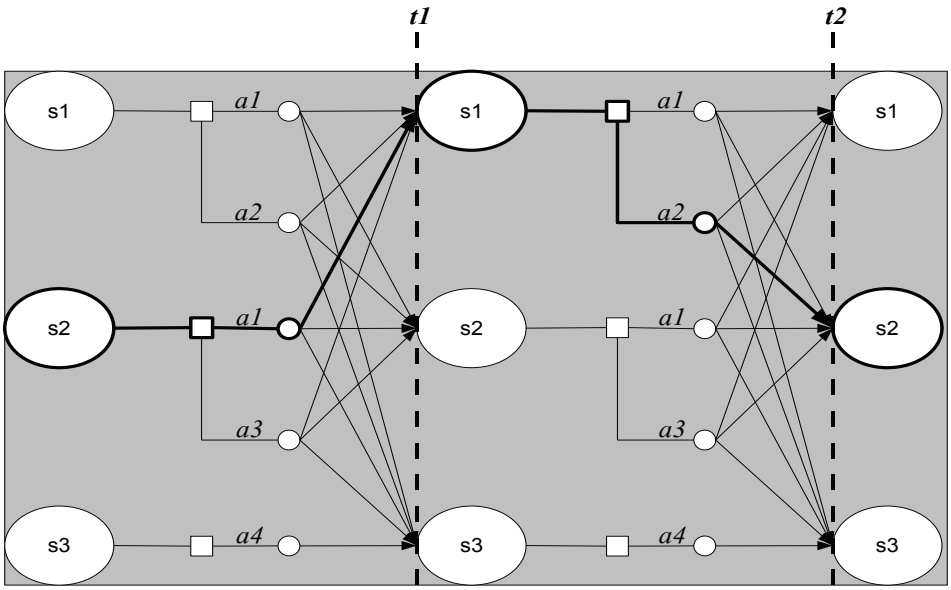
Figure C.3: MDP Example: Step 2



For each $s_i \in S, i = 1, 2, 3$, $u_2^*(s_i) = \max_{a \in A_s} \left\{ (r_2(s_i, a) + (1 - \alpha) \sum_{j \in S} p_2(j|s_i, a) u_3^*(j) \right\}$

For example, action a_2 accumulates the maximum rewards for anyone residing in s_1 at time t_2. Action a_2 will be chosen for state s_1 at time t_2.

Figure C.4: MDP Example: Step 3



For each $s_i \in S, i = 1, 2, 3$, $u_1^*(s_i) = \max_{a \in A_s} \left\{ r_1(s_i, a) + (1 - \alpha) \sum_{j \in S} p_1(j|s_i, a) u_2^*(j) \right\}$

For example, action a_1 will be chosen for s_2 and time t_1. Therefore, the best policy for someone residing in s_2 at time t_1 is $= a_1 \rightarrow a_2$ given the cohort passes through s_1 at time t_2.

Step 4: Stop the algorithm after reaching the first the last iteration (the first decision epoch $t = 1$).

Appendix D

Defining Health States

The health states in Chapter 4 are defined by quintiles of HAQ. In this chapter we present an alternative approach of defining the health states. This approach has two advantages over the simple HAQ quintile classification. First, this approach controls for time varying covariates, such as age, RA disease duration, and comorbidities. HAQ scores are typically higher in older RA patients and those with longer RA duration and higher number of comorbidities. At the same time, we in Chapter 4 we used the period prior to biologics initiation to calculate the transition probabilities for the nonbiologics while the period while on biologics as biologics transition. Thus, those who receive biologics will typically be older, have lengthier disease duration and suffer more comorbidities than those who received nonbiologics.

To control for time varying covariates we estimated a multi-variate regression analysis

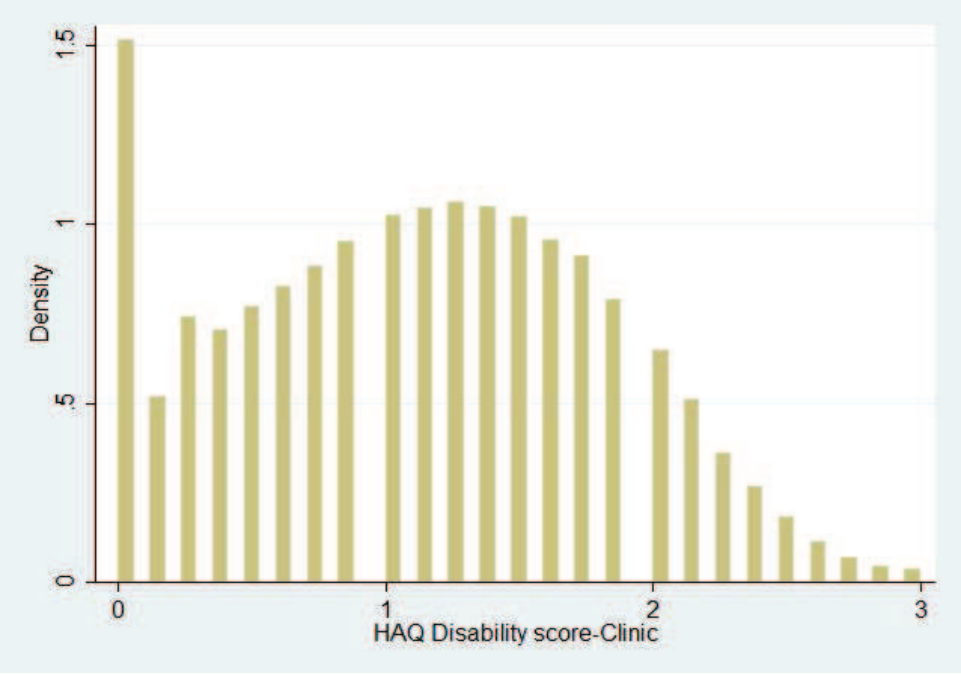
$$\text{HAQ}_{it} = \text{Age}_{it} + \text{Duration}_{it} + \text{Comorbidies}_{it} + e_{it}$$

where i is the individual, t is time, and e is the residual term.

Figure D.1 illustrates the distribution of the unadjusted HAQ scores. This distribution is censored between 0 and 3, with a large peak at 0 indicating a large number of

patient with minimal disability.

Figure D.1: HAQ Distribution



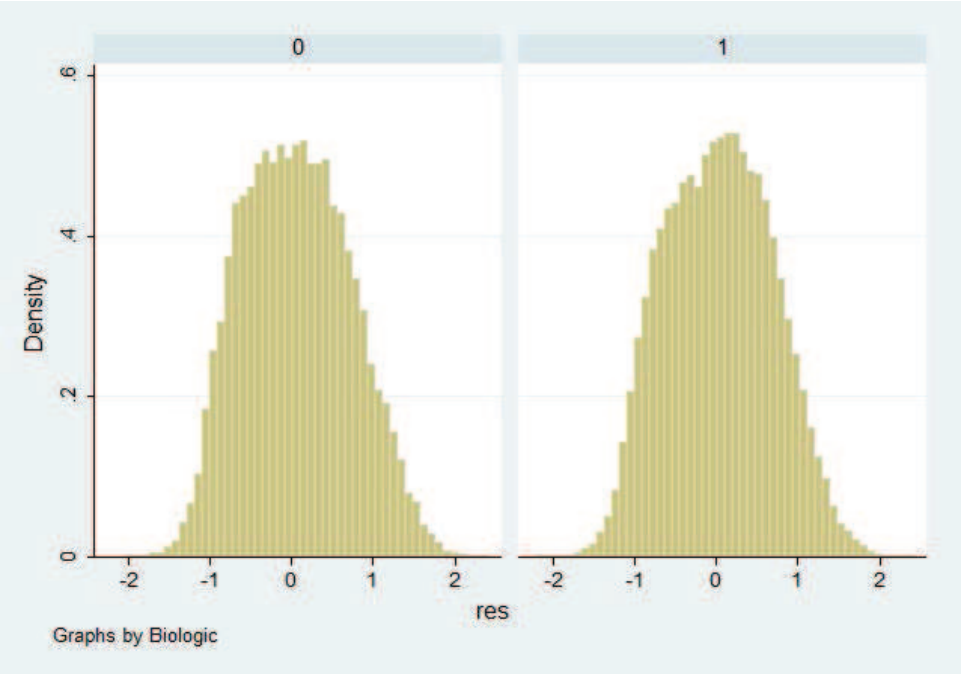
To account for this censoring, we used a Tobit model with upper and lower limits of HAQ, such that

$$y_i^* = \begin{cases} y_i, & \text{if } 0 < y_i < 3 \\ 0, & \text{if } y_i \leq 0 \\ 3, & \text{if } y_i \geq 3 \end{cases}$$

where y_i^* is the latent HAQ score and y_i is the observed HAQ score.

From this model the residual e represents the variation of HAQ unexplained by age, duration or comorbidities, which is the variation we are interested in. Figure D.2 illustrates the distribution of e for biologics and nonbiologics.

Figure D.2: Residuals by Biologics

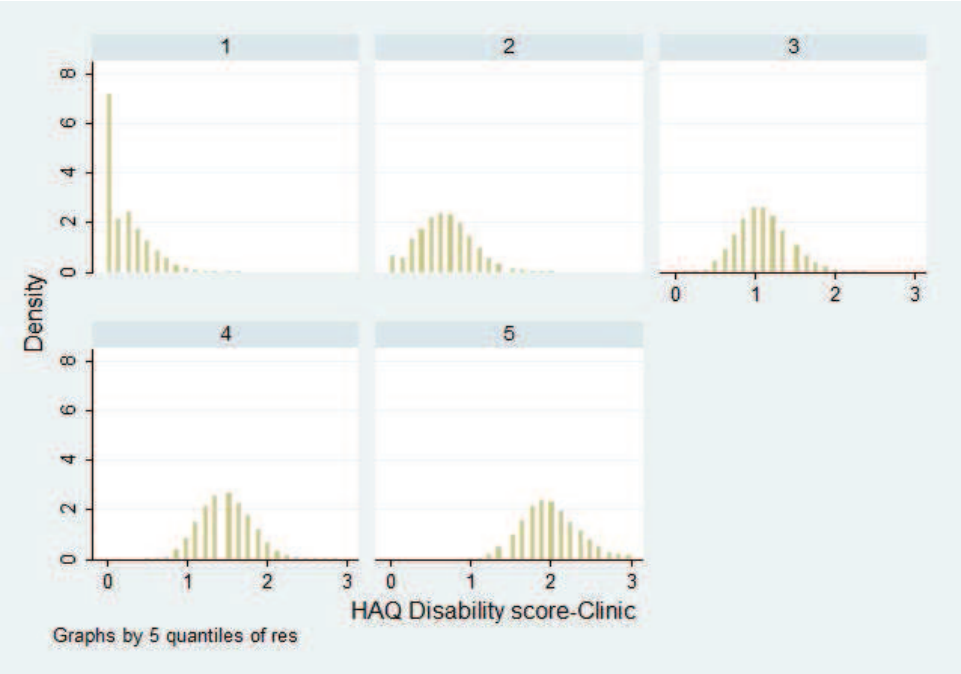


e is normally distributed for both biologics and nonbiologics.

Next, we defined the health states as quintiles of e, and we estimated the mean HAQ score within each quintile and how the RA patients are moving among these quintiles. Figure D.3 illustrates the distribution of the HAQ scores among the residual quintiles.

It is also worth mentioning that the health states defined by quintiles of HAQ vs. quintiles of the residuals were highly correlated (correlation coefficient = 0.93). In addition, defining the health states with quintiles of the residual did not alter the results of the Markov decision processes (MDP) (Chapter 4)significantly. As a result we limited the MDP analysis on the former classification of the health states based on the HAQ quintiles.

Figure D.3: Distribution of HAQ by residual Quintiles



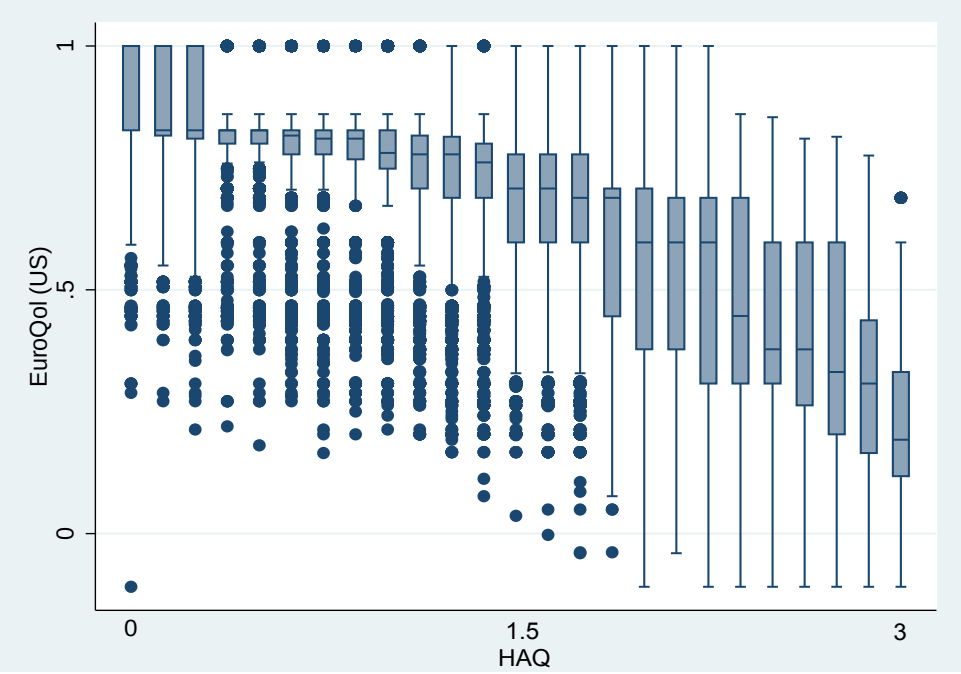
Appendix E

Health-Related Quality of Life

This section presents the relationship between Health-Related Quality of Life (HR-QoL) as measured by the EQ5D preference measurement and the Health Assessment Questionnaire (HAQ) score. Both of these variables are observed in the NDB.

Figure E.1 illustrates the distribution of EQ5D (EuroQoL) by each HAQ category.

Figure E.1: Distribution of EuroQoL preference measures by HAQ



It appears that the relationship between these two variables is more steep in the higher categories of HAQ, i.e., the change in EQ5D corresponding to one unit increase in HAQ is larger in the higher HAQ scores.

To further investigate this non-linearity we first regressed the EuroQoL on the first-order HAQ score.

```
. regress euroqol haq

      Source |       SS       df       MS              Number of obs =  117260
-------------+------------------------------           F(  1,117258) =95365.31
       Model |  1746.11261     1  1746.11261           Prob > F      =  0.0000
    Residual |  2146.96175117258  .018309725           R-squared     =  0.4485
-------------+------------------------------           Adj R-squared =  0.4485
       Total |  3893.07436117259  .033200644           Root MSE      =  .13531

------------------------------------------------------------------------------
     euroqolus |      Coef.   Std. Err.      t    P>|t|     [95% Conf. Interval]
---------------+--------------------------------------------------------------
           HAQ |  -.1679451   .0005438  -308.81   0.000     -.169011   -.1668792
     Intercept |   .9159529   .0006714  1364.18   0.000     .9146369    .9172689
------------------------------------------------------------------------------
```

To examine the presence of non-linearity, we included a second term for HAQ^2.

```
. regress euroqol haq haq2

      Source |       SS       df       MS              Number of obs =  117260
-------------+------------------------------           F(  2,117257) =49396.76
       Model |  1780.18791     2  890.093954           Prob > F      =  0.0000
    Residual |  2112.88645117257  .018019278           R-squared     =  0.4573
-------------+------------------------------           Adj R-squared =  0.4573
       Total |  3893.07436117259  .033200644           Root MSE      =  .13424

------------------------------------------------------------------------------
     euroqolus |      Coef.   Std. Err.      t    P>|t|     [95% Conf. Interval]
---------------+--------------------------------------------------------------
          HAQ  |  -.0977469    .001702   -57.43   0.000    -.1010828   -.0944109
          HAQ2 |  -.0320484    .000737   -43.49   0.000    -.0334928   -.0306039
     Intercept |   .8947341   .0008257  1083.63   0.000     .8931158    .8963525
------------------------------------------------------------------------------
```

Including the second order HAQ score increased the R^2 from 0.449 to 0.457. Because this change was relatively small, we only included the first order HAQ score for calculating the HR-QoL as a function of HAQ in this thesis.