Modelling the Cost-Effectiveness of Early Biologic Disease Modifying Anti-Rheumatic Drugs (bDMARDs) Treatment for Patients with Juvenile Idiopathic Arthritis.

Master Thesis Industrial Engineering & Management,
University of Twente

August 2021

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Management Summary

Juvenile Idiopathic Arthritis (JIA) is a heterogenous group of chronic arthritis related diseases of unknown etiology. It is the most common type of arthritis in children and can often result in persistent joint pain, swelling, and stiffness. Some forms of JIA can also cause growth problems due to permanent joint damage, uveitis, severe fevers, and body wide inflammation. Due to the chronic nature of JIA, the primary goal of treatment is to achieve and maintain inactive disease. With the introduction of biological disease modifying anti-rheumatic drugs (bDMARDs) inactive disease has become more achievable even for severe and refractory JIA. bDMARDs are however expensive with costs ranging between 20 to 500 times more than conventional drugs according to Dutch drug prices.

Current treatment guidelines in the Netherlands and Canada recommend a step-up approach were if a patient fails non-steroidal anti-inflammatory drugs (NSAIDs) and synthetic disease modifying anti-rheumatic drugs (sDMARDs), a bDMARDs can be used. However, as bDMARDs are showing promising results in reducing disease activity and achieving inactive disease the question is whether bDMARDs should be introduced earlier. Clinicians are recommended to evaluate a step-up to the first bDMARD after 3 or 6 months of sDMARD treatment. In this thesis the cost-effectiveness of the earlier treatment of the first bDMARD (3 months after initiation with a sDMARD) compared to the conservative treatment (6 month after initiation) is compared. The following research question is answered:

“What is the cost-effectiveness of the early switching strategy compared to conservative switching strategy for patients with juvenile idiopathic arthritis?”

To answer the research question an individual based state transition model was developed. The model is based on the health states; disease activity, adverse events, response and no response to medication. The medication methotrexate as the sDMARD, and the two bDMARDs adalimumab and etanercept were modelled. A three-year model time horizon was applied, represented by 12 cycles of 3 months. Simulated patients started with methotrexate and progressed to the first and second bDMARD (etanercept or adalimumab) after experiencing no response or adverse event to the medication. Responding patients benefited from improved health outcomes modelled using utility values. Further improvement for responding patients was possible if inactive disease was achieved. Using the prospective data available as of February 2020 individual health state utilities were modelled, supplemented by literature. Indirect and direct costs of JIA were modelled using Dutch data and literature as a part of UCAN CAN-DU. The probability of events per medication and health state were based on literature. The subtypes polyarticular RF-, oligoarticular extended, oligoarticular persistent, and enthesitis related JIA were modelled. The subtype impacted starting utility of a patient and resource costs excluding medication.

Model results showed that the early switching strategy for etanercept as the first bDMARD resulted in minor increase in costs (€45), and health outcomes (0.003 QALYs). The clinical benefit of early switching is very small. The resulting ICER (€17,729) is highly uncertain, due the small difference in time between methotrexate and the first bDMARD. As the NMB and NHB are positive, results suggest that early switching strategy is cost-effective for a WTP of €50,000. Adalimumab as the first bDMARD resulted in a higher ICER (€29,727) and lower, but still positive, NMB and NHB than etanercept. To make the difference between the two strategies more pronounced the probability of no response to methotrexate was increased from the default 0.052. The difference in cost and health outcomes became more pronounced with ICERs ranging between €15,000 and €17,000 for etanercept, suggesting the early switching strategy is indeed cost effective for a WTP of €50,000. The cost-effectiveness of the early switching strategy was compared for the subtype polyarticular RF- and oligoarticular persistent. Both subtypes were cost-effective but polyarticular RF- had a lower ICER highlighting the need for early bDMARD use for severe subtypes of JIA which aligns with current practice. The model estimation showed that the early switching strategy is cost-effective highlighting the need for timely treatment of JIA.

Follow up research should focus on the tapering process after achieving inactive disease as this could greatly benefit the cost-effectiveness of bDMARDs treatment. Additionally, as the model created in this thesis is the first to model individual patients, as opposed to a cohort approach, and the limited available data, the modelling of individual patients should be improved. In particular the synchronization of utility values and total costs between health states and treatment progression. Finally, as the results showed that the clinical impact of the early switching strategy is very limited, we recommend further cost-effectiveness models should investigate bDMARDs as a first line since the potential clinical impact can be far greater.

Preface

Dear reader,

This thesis is the final part of my master studies Industrial Engineering and Management at the University of Twente. As part of my specialization, Healthcare Technology & Management, the thesis project created a cost-effectiveness model for the early treatment of bDMARDs in JIA. The thesis has nine Chapters describing the full process of the model creation from problem identification to results.

The thesis was conducted as a part of the UCAN CAN-DU organization based in the Netherlands and Canada. I want to thank the members of the UCAN CAN-DU health economic group who provided me with their expertise and guidance throughout the master project.

Dr. Ir. H. Koffijberg
Prof. Dr. M. Ijzerman
Dr. M.M.A. Kip
L. Grazziotin
Prof Dr. D.A. Marshall
Dr. G. Currie
Dr. M. Twilt

I worked on my thesis in 2020-2021, a year affected by Covid, which resulted in extra challenges to overcome. I want to extend my gratitude to my supervisors; Hendrik Koffijberg, Maarten Ijzerman, and Michelle Kip for their expertise and guidance.

Finally, I want to thank my family and friends who provided me with guidance and support throughout the entire process.

Enjoy reading this thesis!

Rutger J. Haan
August 2021

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Abbreviations

Abbreviation	Definition
ACR	American College of Rheumatology
ADM	Adalimumab
ANA	Antinuclear Antibody
bDMARD	biologic Disease-Modifying Anti-Rheumatic Drug
CarerQoL	Care-related Quality of Life
CHAQ	Child Health Assessment Questionnaire
CID	Clinically Inactive Disease
cJADAS	clinical Juvenile Arthritis Disease Activity Score
CRF	Case Report Form
DES	Discrete Event Simulation
DMARD	Disease-Modifying Anti-Rheumatic Drug (biologic or synthetic)
EQ-5D-5L	Euro Quality of life - 5 Dimensions - 5 Levels of severity
ETN	Etanercept
HAQ	Health Assessment Questionnaire
ICER	Incremental Cost Effectiveness Ratio
IFX	Infliximab
JAMAR	Juvenile Arthritis Multidimensional Assessment Report
JIA	Juvenile Idiopathic Arthritis
MTX	Methotrexate
NSAID	Non-Steroidal Anti-Inflammatory Drug
NHB	Net Health Benefit
NMB	Net Monetary Benefit
oJIA	oligoarticular Juvenile Idiopathic Arthritis
pcJIA	polyarticular course Juvenile Idiopathic Arthritis
pJIA	polyarticular Juvenile Idiopathic Arthritis
QALY	Quality-Adjusted Life-Year
RA	Rheumatoid Arthritis (adults)
sDMARD	synthetic (or conventional) Disease Modifying Anti-Rheumatic Drug
sJIA	systemic Juvenile Idiopathic Arthritis
STM	State Transition Model
TCZ	Tocilizumab
TNF	Tumour Necrosis Factor
WPAI	Work Productivity and Activity Impairment

1. Introduction

Juvenile Idiopathic Arthritis

Juvenile idiopathic arthritis (JIA) is an umbrella term for all forms of arthritis that develops before the age of 16, has unknown etiology, and persists for at least 6 weeks (Petty et al., 2004). It is the most common form of chronic rheumatic disease in children. Prevalence ranges between 16 and 160 per 100,000 in developed countries (Ravelli & Martini, 2007). It is regarded as an auto-immune disease with the majority of patients diagnosed having inflammation around their joints. Other body parts, such as the eyes, can be affected too. JIA can cause high fever, vision issues, fatigue, reduced mobility due to painful or tender joints. If not treated adequately JIA can cause permanent joint damage resulting in permanent disability. As JIA is chronic and can be debilitating it can have substantial negative effects on the quality of life of patients and create a high economic burden on parents and society (Bernatsky et al., 2007). The economic and health burden depends on the individual patient and disease subtype. JIA is commonly subdivided in the following 7 subtypes by Petty et al, (2004):

1. Oligoarticular JIA
2. Polyarticular rheumatoid factor negative JIA
3. Polyarticular rheumatoid factor positive JIA
4. Systemic JIA
5. Enthesitis related JIA
6. Psoriatic arthritis
7. Undifferentiated JIA.

Oligoarticular JIA is defined as arthritis of 4 joints or less during the onset of disease. If after 6 months of disease onset more than 4 joints are affected, patients are categorized as oligoarticular extended else patients are classified as oligoarticular persistent. Polyarticular indicates five or more joints are affected at disease onset and is further subdivided based on a positive or negative rheumatoid factor (RF). Systemic JIA is a rare subtype which is defined by severe body wide inflammation instead of just affecting the joints often resulting in body wide rashes and long-lasting fevers. Psoriatic JIA is also a rare subtype and indicates the presence of psoriasis or arthritis with dactylitis and or nail pitting. Enthesitis related JIA is characterized by inflammation of the entheses and/or with acute anterior uveitis.

Historically, therapeutic advances for JIA have been slow due to its unknown etiology and the difficulty of working with children, whose treatment is more complex and dynamic than adults with rheumatoid arthritis (RA) (Becker, 2013). More is known about adult RA therefore, advances in JIA follow those made in adults. Nonetheless, there are now multiple treatment options available specifically for JIA: pharmaceutical, surgical, physical, psychological, and occupational treatment. Pharmaceutical options are the primary treatment option for JIA with steroids, non-steroidal anti-inflammatory drugs (NSAIDs), synthetic disease modifying anti-rheumatic drugs (sDMARDs), small molecules, and biological disease modifying anti-rheumatic drugs (bDMARDs),

encompassing the five main medication types. As JIA is chronic, the goal of the pharmaceutical treatment is to reduce symptoms to a degree where JIA becomes and remains inactive over the long term. Physical, psychological, and occupational therapy are supportive treatment options. If all else fails surgical intervention can be used, although this is very rare thanks to the strength of pharmaceutical options in halting disease progression and achieving inactive disease.

Most JIA patients are treated using a step-up program where standard treatment is to start with a NSAIDs and/or steroids. Both options are rarely used long term due to the toxicity of steroids and most patients not responding to NSAIDs for longer periods of time. If necessary, patients can receive a sDMARD next, which are less toxic than steroids and can be effective for longer periods of time. sDMARDs, especially methotrexate (MTX), is considered as the conventional medication for the treatment of JIA. If sDMARDs fail, a bDMARD is often introduced. bDMARDs commonly referred as biologic therapy are newer and far more expensive compared to NSAIDs or sDMARDs, contributing 84.7% of total JIA drug costs for one hospital in the Netherlands (Schreijer et al., 2019).

UCAN CAN-DU

UCAN CAN-DU is a research network program based in the Netherlands and Canada that tackles multiple research subjects related to JIA. UCAN CAN-DU focusses on improving the individual treatment approaches and outcomes for patients with JIA, with special attention paid to the role of bDMARDs. One of the three main study activities is the health-economics of JIA, which this thesis is a part of. The health economic arm of UCAN CAN-DU looks at how the different treatment pathways of JIA patients impact their respective subsequent health outcomes and the general healthcare resource utilization. UCAN CAN-DU has partnered with all child rheumatologists in Canada and the Netherlands in order to prospectively collect a large variety of data on patients with JIA. Extensive economic and clinical data are collected for each patient enrolled in the prospective study. The collection of the data is expected to be completed in 2022. The data collected and processed as of February 2021 was available for this thesis. An overview of the prospective data and the February 2021 data are given in Section 2.1. The prospective study is expected to yield critical data related to economic and clinical outcomes which are currently unavailable in literature. When the study is completed, better insight can be gained into the health and economic impact of JIA treatment.

1.1 Problem Statement

In the Netherlands bDMARDs are only recommended as a first line for systemic JIA. For the other subtypes bDMARDs are recommended to be used after the first sDMARD is inadequate in reducing disease activity which is known as the step-up treatment approach. The Dutch association of pediatrics recommends the use of the first bDMARD no earlier than 3 to 6 months after starting the first sDMARD if the clinician deems the response to the first sDMARD to be inadequate (NVK, 2017). The American College of Rheumatolostists (ACR) also recommends a

step-up treatment plan to the first bDMARD no earlier than 3 to 6 months after the first sDMARD is initiated and if disease activity remains medium or high (Ringgold, 2019). Often clinicians wait until the 6-month period before initiating the first bDMARD due to the time it takes for the first sDMARD to become effective as well as national or provincial guidelines common in Canada. For the patients that fail sDMARD treatment it might be beneficial to start a bDMARD earlier or even at the same time as a sDMARD. This is especially important when considering that inadequate treatment at the start of disease onset can result in irreversible joint damage and lifelong health issues.

Both timely and adequate treatment of JIA is important within the so called "treatment window" of JIA. bDMARDs treatment are showing promising results for achieving inactive disease and overall disease reduction compared to the conventional treatment of methotrexate, including as a first line treatment (Murray, 2021). However, clinical studies investigating the effectiveness of early bDMARD use for patients are lacking. Furthermore, as stated previously, the downside of early bDMARD treatment is that bDMARDs are far more expensive, with costs ranging between 20 to 500 times more than sDMARDs such as methotrexate (Kip, 2020). Due to a limited insight in the effectiveness of bDMARDs, difficulty in identifying patients that would benefit from early bDMARD use, and the very high medication costs, decision makers are hesitant to use a bDMARD earlier. The high costs of bDMARDs and limited evidence of effectiveness over sDMARDs raises the question what the cost effectiveness is of early bDMARD treatment. With limited resources it is important for decision makers to make informed decisions on how to utilize these resources as effectively as possible. Knowing the cost-effectiveness of different treatment strategies allows decisions makers to make informed decisions on which strategy should be chosen.

UCAN CAN-DU wants to investigate whether using biologicals earlier in JIA is cost-effective. Cost-effectiveness trials provide ideal evidence for determining the cost-effectiveness of early bDMARD treatment, but these trials are expensive, take a long period to conduct, and need to be safe for patients. As a result, these trials are currently not an option for UCAN CAN-DU. Alternatively, a model can be used to estimate the cost-effectiveness of early bDMARD treatment. A cost-effectiveness model synthesizes information based on a range of variables (such as disease progression, disease characteristics, health effects, and resource cost) in order to estimate total quality of life and total cost over a predefined period of time of a patient. Both standard treatment and an intervention treatment can be modelled, and the cost-effectiveness compared in order to aid decision makers in determining if it is worth using the intervention. The advantage of a model approach is that it is possible to estimate cost-effectiveness output of an intervention strategy that has not, or cannot be, investigated by cost-effectiveness trials.

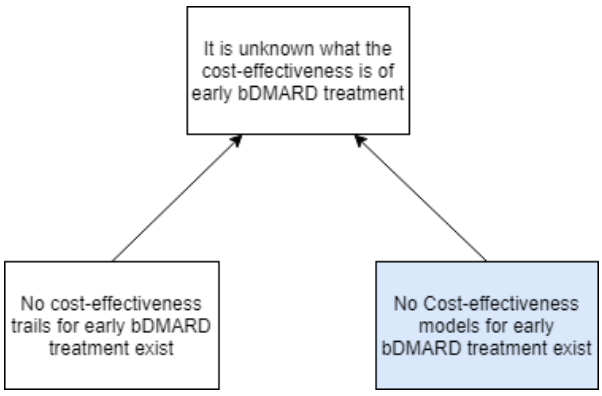

Figure 1: Problem cluster. Blue = core problem

The problem cluster is shown in Figure 1. As UCAN CAN-DU wants to investigate the cost-effectiveness of early bDMARD treatment, and only a cost-effectiveness model can be developed, the core problem is defined as:

There is no model available for which could be used to investigate the cost-effectiveness of early bDMARDs treatment for patients with JIA.

1.2 Research Objective

There are existing cost-effectiveness models for JIA that look at the impact of first line bDMARD instead of a sDMARD. There are other forms of early bDMARD treatment that have not yet been investigated and may prove worthwhile. One of these is switching to bDMARDs earlier when sDMARDs are yielding an inadequate response in the patient. As noted in the problem statement the first bDMARD can be used after month 3 or month 6 of sDMARD treatment according to Dutch and American guidelines if response is inadequate, however, it is not clear if clinicians should wait 3 months or 6 months after sDMARD initiation to switch to the first bDMARD. Therefore, in terms of early bDMARD treatment, we investigate the impact of switching immediately if the patient has no response after 3 months of initiating the sDMARD or waiting an extra 3 months. We define two treatment strategies for early bDMARD treatment, the early switching strategy and the conservative switching strategy:

- Early switching strategy is defined as immediately switching to the first bDMARD if no response to sDMARD after 3 months.
- Conservative switching strategy (standard care) is defined as waiting an extra 3 months before switching to the first bDMARD if no response to sDMARD after 3 months.

As clinicians often wait until the 6 months period the conservative switching strategy is considered to be the standard care in this thesis, while the early switching strategy is defined as the treatment intervention. The model we create should be able to estimate the cost-effectiveness of the early switching strategy. Furthermore, the model should be able to capture the complexity of treatment and the heterogeneity of JIA. In terms of patient heterogeneity, the model should at least include the patient's JIA subtype. A clinical and societal perspective is taken for the model, meaning that both direct and indirect costs and effects should be included. As the treatment switch from the first

sDMARD to the first bDMARD is investigated, at least two lines of treatment are investigated. In order to properly understand the long-term effects of the two lines of treatment, a time horizon of multiple years should be modelled. The input parameters of the model should be primarily based on the outcomes of the prospective study, and as the prospective study only enrolls children; adults with JIA are not included in the model.

1.3 Research Questions

Following from the problem statement and research objective we define the main research question as:

"What is the cost-effectiveness of the early switching strategy compared to conservative switching strategy for patients with juvenile idiopathic arthritis?"

The main research question is too comprehensive to answer all at once, therefore we define the following sub-questions:

1. *"What does early bDMARD treatment entail and what are the impacts on health and cost outcomes?"*

Before a model can be developed, early bDMARD treatment needs to be defined and more importantly the effects on health outcomes of early bDMARD treatment need to be known. This research sub-question will be answered using a literature review. Results from the literature review are expected to help with defining bDMARD progression and the health impact of early bDMARD treatment. Additionally, results from the literature review might yield insight in the clinical decision regarding when or why the first bDMARD is prescribed. Finally, the literature review is expected to identify critical components the model should include in terms of health states, bDMARDs medication, and an appropriate time horizon.

2. *"What current cost-effectiveness models exist for JIA and what insights do they provide?"*
    a. *"How do the cost-effectiveness models differ for adult RA?"*

There are existing cost-effectiveness models for JIA. These should be identified using a systematic literature review and analyzed. The goal is to identify and gain insight into different health states, time horizons, medication, and sources used by the model creators to populate their model. Any model assumptions and limitations will be investigated. As in adult RA DMARDs are also used and there is far more known on impact on costs and health outcomes compared to JIA, we are also interested in what models are developed for adults. Insights gained from the literature review will help to define and create the model, as well to avoid common pitfalls.

3. *"Which data will be collected in the prospective study?"*
    b. *"What can be used from the February 2021 data?"*

The prospective data should be relied on to populate the model after the completion of the study. Therefore, it is key to understand what data the prospective study will collect and what can be used to populate the model. The February 2021 data from the prospective study will also be analyzed using the programming software R and results will be used in the population of the model.

4. *"What will a cost-effectiveness model investigating early bDMARD use look like?"*
    a. *"What type of cost-effectiveness model should be used?"*

After the first three research questions are answered, the model framework used to investigate the cost-effectiveness of early bDMARDs will be developed. Multiple types of models exist for cost-effectiveness analysis in healthcare, and it needs to be determined which type of model is most suitable for the research question and available data.

5. *"What data will be used to populate the model?"*

After the model framework is defined, the model will be populated using literature and the prospective data. Sources found from answering research question 1 and 2 will be used. Any gaps will be filled by additional literature.

The model will be coded in the programming language R. Finally, simulations and scenarios are defined, and simulations will be run with the model to answer the following research questions:

6. *"What is the cost-effectiveness of early bDMARD treatment compared with conservative treatment as estimated by the model?"*
    a. *"What is the impact of using different bDMARDs?"*
    b. "*What is the impact of subtypes on the cost-effectiveness?"*

Answering the five research questions leads to an answer to the main research question and research problem.

1.4 Chapter Outline

The chapters of the thesis follow the order of research questions. Starting in Chapter 2 the literature review and results on early bDMARD treatment are described. In Chapter 3 the literature review and results of the existing JIA cost-effectiveness models are presented. Next, Chapter 4 will discuss the prospective data and February 2021 data. In Chapter 5 the chosen model and assumptions are described. The chosen model is then populated using literature and prospective data in Chapter 6. With the model complete, simulations are defined, and results presented in Chapter 7. In the final two chapters results of the thesis are elaborated on in the conclusion and discussion.

2. Early bDMARD Treatment

In this chapter the literature review on the early bDMARD treatment we conducted is described. The aim of the literature review was to gain knowledge on what early bDMARD treatment entails and the impact early treatment strategies have. Using this information, key decisions regarding important factors of a cost-effectiveness model including time horizon, health states and health outcomes can be made.

2.1 Search Terms & Selection Criteria

Titles and abstracts were searched using a combination of "juvenile idiopathic arthritis", "biologic", and synonyms for early treatment in Pubmed. Articles which provided evidence on or discussed early bDMARD treatment, including bDMARD as a first line, were selected. The search terms used and the PRISMA flow diagram can be found in Appendix A.

2.2 Findings

The literature review yielded 12 articles, summed up in Table 1, with different relevance for early bDMARD treatment. The articles are sorted by the strength of the study conducted and evidence provided.

Reference	**Article Relevance**	**Title**
Tynjala et al. (2011)	Clinical trial of first line bDMARD use for pJIA	Aggressive combination drug therapy in very early polyarticular juvenile idiopathic arthritis (ACUTE-JIA): a multicentre randomized open-label clinical trial.
Wallace et al. (2012)	Clinical trial of first line bDMARD use for pJIA	Trial of early aggressive therapy in polyarticular juvenile idiopathic arthritis.
Huang et al. (2020)	Statistical analysis of early use of bDMARDs pcJIA for adalimumab and etanercept	Timing matters: real world effectiveness of early combination of biologic and conventional synthetic disease modified anti rheumatic drugs for treating newly diagnosed polyarticular course juvenile idiopathic arthritis.
Minden et al. (2019)	Retrospective study & overall trends/correlation	Time of Disease-Modifying Antirheumatic Drug Start in Juvenile Idiopathic Arthritis and the Likelihood of a Drug-Free Remission in Young Adulthood.
Otten et al. (2015)	Treatment pattern observation of	Trends in prescription of biological agents and outcomes of juvenile idiopathic arthritis:

Reference	Article Relevance	Title
	bDMARDs and sDMARDs	results of the Dutch national arthritis and biologics in children register.
Yue et al. (2021)	Treatment pattern observation of bDMARDs and sDMARDs	Prescribing Patterns and Impact of Factors Associated with Time to Initial Biologic Therapy among Children with Non-systemic Juvenile Idiopathic Arthritis.
Swart, van Dijkhuizen, Wulffraat, & de Roock (2018)	Identification of early bDMARD use for pJIA and oJIA using JADAS71 score	Clinical Juvenile Arthritis Disease Activity Score proves to be a useful tool in treat-to-target therapy in juvenile idiopathic arthritis.
Nalbanti et al. (2018)	Identification of early bDMARD use for pJIA using JADAS71 score	Juvenile idiopathic arthritis in the biologic era: predictors of the disease progression and need for early introduction of biologic treatment.
Prince & van Suijlekom-Smit (2013)	Retrospective study & overall trends/correlation on medication costs	Cost of biologics in the treatment of juvenile idiopathic arthritis: a factor not to be overlooked.
Southwood (2014)	Review/commentary on bDMARDs	Treatment of JIA in the biologic era: what are we waiting for?
Marzan & Reiff, (2008)	Review/commentary on bDMARDs	Adalimumab in juvenile rheumatoid arthritis/juvenile idiopathic arthritis.
Murray, Sen, & Ramanan (2021)	Review/commentary on bDMARDs	Advancing treatment of juvenile idiopathic arthritis.

Table 1: Overview of the 12 articles found and their relevance to early bDMARD use. JIA = Juvenile Idiopathic Arthritis, pJIA = Polyarticular JIA, pcJIA = Polyarticular Course JIA, oJIA = Oligoarticular JIA, bDMARDs = Biologic Disease Modifying Anti Rheumatic Drugs, JADAS71 = Juvenile Arthritis Disease Activity Score.

In all articles selected there is a consensus that early bDMARD treatment is more expensive, but also beneficial for at least polyarticular and systemic JIA. The definition of early bDMARD treatment or what parameters indicate the need for a bDMARD are poorly described in the articles found. The two articles by Tynjala et al (2011) and Wallace et al (2012) investigated bDMARD as a first line, while the article Huang et al (2020) and Minden et al (2019) investigated the difference in time to the first bDMARD after starting with a sDMARD. The remaining 8 articles did not have precise definitions of early bDMARD treatment. Evidence for the conclusion that early bDMARD is more beneficial differed widely per article. Of the 12 articles selected, 6 studied the effects of early bDMARD treatment in an independent study, see Table 2.

Reference	Study type	Country	DMARDs naïve	Subtype	Medication	Time horizon
Tynjala (2011)	Head-tot-head clinical trial	Finland	Yes	pJIA	INX	1 year
Wallace (2012)	Head-to-head clinical trial	US	No	pJIA	ETN	1 year
Huang (2020)	Retrospective Statistical analysis	US	Yes	pcJIA	MTX, ADM, ETN	1 year
Minden (2019)	Prospective statistical analysis	Germany	Yes	All	All bDMARDs	10 years
Otten (2015)	Treatment pattern observations	Netherlands	Unknown	All	All bDMARDs	12 years
Yue (2021)	Treatment pattern observations	US	Unknown	All	All bDMARDs	10 years

Table 2: Summary of the 6 studies examining the effects of early bDMARD use. JIA = Juvenile Idiopathic Arthritis, pJIA = Polyarticular JIA, pcJIA = polyarticular course JIA, MTX = Methotrexate, ADM = Adalimumab, ETN = Etanercept, INX = Infliximab, DMARDs = Disease Modifying Anti Rheumatic Drugs.

All 6 studies affirmed the effectiveness of aggressive biologic use for subtypes with worse disease outcomes. Wallace et al. (2012) and Tynjala et al. (2011) were the only clinical studies testing aggressive bDMARDs strategies for polyarticular JIA. In both cases using a bDMARD combination therapy instead of a non-biologic as a first line treatment were compared.

Tynjala et al. (2011) conducted a multicentered randomized open-label clinical trial in Finland to investigate the effects of bDMARDs as a first line DMARD instead of only methotrexate, also known as the ACUTE trial. DMARDs naïve patients were split in three treatment arms: methotrexate plus the bDMARD infliximab (INX), methotrexate alone, and methotrexate plus sulfasalazine and hydroxychloroquine (COMBO). All patients had the subtype polyarticular JIA and were followed for one year. ACR Pedi 75 response was the primary endpoint while inactive disease, drug survival, number of adverse events, and ACR Pedi 30, 50, 70, 90, and 100 response were secondary outcomes. ACR Pedi are criteria set by the American college of rheumatologists indicating a percentage improvement from baseline on 6 variables. The treatment arm with INX had a significantly higher probability of reaching ACR Pedi 75 after one year compared to methotrexate alone or COMBO. The probability of response for ACR Pedi 30, 50, 70, 90, and 100 was also higher for INX compared to methotrexate or COMBO. The frequency of adverse events was not found to be higher for the INX treatment arm. Finally, more patients in the INX group achieve inactive disease at the one-year mark and patients spent on average a longer time in inactive disease.

Wallace et al. (2012) conducted a multicenter randomized double-blind placebo-controlled trial to investigate the effects of two aggressive treatments for JIA known as the TREAT trial. Patients were bDMARDs naïve, but could receive methotrexate no earlier than 6 weeks prior to enrollment. Two treatment arms were investigated: prednisolone plus methotrexate plus the bDMARD etanercept (ETN) and methotrexate alone. Both arms were considered aggressive due to the high dosage of methotrexate while the ETN arm was considered as the more aggressive of the two. The primary end point was inactive disease for 6 months with secondary outcomes being ACR Pedi 70 response, adverse events, and inactive disease. The inactive disease and ACR Pedi 70 were measured at 6 and 12 months follow up. Independent of treatment arm inactive disease was achieved for 32% and 66% of patients at 6 and 12 months follow up. In the ETN arm 38% of patients achieved inactive disease compared to 22% in the methotrexate only arm. The ACR-Pedi 70 response was significantly higher for the ETN arm. No statistically significant difference was noted for the probability and severity of adverse events between both arms. For the primary end point, inactive disease for the duration of 6 months, no statistical difference was found between both arms.

Huang et al. (2020) completed a statistical study (retrospective) on the effects of early bDMARDs switching by comparing the health outcomes of an aggressive treatment strategy group with the conservative group at 6 and 12 months follow up for DMARDs naïve patients. The aggressive strategy was defined as patients initiated on a bDMARD within 2 months of starting the first sDMARD while the conservative group did not receive a bDMARD within 3 months of initiating a sDMARD. Patients with polyarticular course JIA were selected which is an uncommon grouping of JIA subtypes with four or more joints hence encompassing systemic, polyarticular, and oligoarticular extended subtypes. The sDMARD used was methotrexate. bDMARDs were the anti-TNFs adalimumab and etanercept. The primary health outcomes were clinical juvenile arthritis disease activity score (cJADAS) and pediatric quality of life inventory (PedsQL). cJADAS, ranging between 0-30 with higher scores indicating the high disease activity, was measured at 0, 6, and 12 months. PedsQL, ranging between 0 to 100 with higher score indicating better health, was measured at 0, 6 and 12 months follow up. The aggressive group had higher cJADAS and lower PedsQL at 0 months indicating that sicker patients are more likely to receive aggressive treatment. Bayesian causal inference with gaussian process was used to balance out the confounding-by-indication bias and to predict the cJADAS score for all patients if they had gone through the aggressive and conservative treatment strategy. After 6 and 12 months both the cJADAS and PedsQL improved after 6 and 12 months. The early aggressive group had a statistically better improvement in the predicted cJADAS after 6 months of treatment with on average an expected -2.17 reduction at 6 months. At 12 months the average treatment benefit for cJADAS was less pronounced at -0.36. The effectiveness of the aggressive group for quality of life (PedsQL) was not statically significantly for 6 and 12 months.

Minden et al. (2019) prospectively followed three groups based on time from symptom onset to first bDMARDs (Group 1: less than 2 years, Group 2 between 2 and 5 years, group 3 more than 5 years) for a 10-year period in Germany. They concluded that early bDMARDs use is beneficial for long term outcomes. Patients switched to a bDMARD in case of refractory disease or intolerance to conventional treatment. All subtypes were included, but most patients had the pJIA subtype. Group 1 had the highest fraction of pJIA patients (19% vs 10% and 3%) which reflects clinician's choice to treat patients with the worst disease onset more aggressively. The outcomes measured at the 10-years follow up period were disease activity, inactive disease, drug free inactive disease, disability, and patient wellbeing. 19% of patients in group 1 was in drug free inactive disease at 10-years follow up, while group 2 and group 3 had a rate of 10% and 5% respectively. Furthermore, group 1 patients had a significantly lower disease activity and less disability than those in group 2 and 3. The authors concluded that these observations support the window of opportunity concept and that early bDMARDs use is beneficial for long term outcomes. It should be noted that the 10-year follow-up period starts at disease onset instead of start of the first bDMARD. This distinction is important as patients in group 2 and 3 had far lower treatment duration on bDMARDs than group 1. It is questionable if this comparison is fair and if the findings can support the conclusion made by the authors. Another issue with the study is that a higher percentage of patients in group 3 compared to group 1 had oligoarticular extended JIA (30% and 3% respectively). Oligoarticular extended JIA is diagnosed at its earliest 6 months after disease onset if initial diagnosis is oligoarticular (4 or less joints affected) and after 6 months more than 4 joints are affected. The authors noted that the oligoarticular extended group was less aggressively treated while their outcomes are comparable to polyarticular JIA. The issue is that it is not clear at what time point the patient's diagnosis was updated to oligoarticular extended, which can range between 25 and 112 months (Nalbanti, 2018).

Otten et al. (2015) and Yue et al. (2021) noted overall trends related to increasing and aggressive bDMARDs use and an improvement in health outcomes. Otten (2015) observed that in a 12-year retrospective study (1999-2011) in the Netherlands bDMARDs are prescribed at a higher rate, earlier, as well as for patients with lower disease activity. These patterns are most pronounced for systemic JIA, but are also present for non-systemic JIA (mainly polyarticular and oligoarticular extended). The more aggressive treatment approach resulted in more patients achieving inactive disease after 3 and 15 months follow up plus overall better short term (2 years or less) disease outcome for both groups.

Yue (2021) investigated the treatment patterns over a 10-year period (2009-2018) in the US of patients not diagnosed with systemic JIA and noted that early bDMARD use was correlated with better disease outcomes for polyarticular JIA patients. This conclusion is poorly substantiated as no numbers are provided which show that early bDMARD use results in better disease outcome.

The 6 articles described above all showed that early bDMARDs treatment are beneficial for short term health outcomes using independent studies. The other 6 articles added no new evidence on the impact of early bDMARDs use for JIA. Four articles were overviews of aggressive treatment with bDMARDs referencing the ACUTE and TREAT trials as primary evidence sources and agreed that early bDMARD use is beneficial. All articles also noted that early bDMARDs treatment results in greater medication costs and only Prince (2013) noted that if bDMARDs are more effective at achieving inactive disease or reducing disease activity non-medication costs could be lower due to bDMARDs treatment.

Swart et al. (2018) investigated if the JADAS71 score could be used to predict patients in need of anti-TNF bDMARDs at 3 and 6 months after starting methotrexate based on a retrospective study in the Netherlands. For patients with oligoarticular the JADAS cut of point was greater than 5 and greater than 3 for 3 and 6 months respectively. Similarly, Nalbanti, (2018) investigated JADAS71 as a predictor for disease progression to oligoarticular extended JIA for patients diagnosed with oligoarticular in Greece. A JADAS71 score of greater than 9 at disease onset was found to be predictor of oligoarticular extended and the need for bDMARD treatment. Both articles noted the importance of the correct timing of bDMARDs and the need for additional clinical guidelines or predictors for patients requiring bDMARDs. However, when the optimal time is to introduce a bDMARD and what the effects are was not further explored by both articles.

Subtype Classification

Huang (2019) and Nalbanti (2018) use polyarticular course JIA (pcJIA) as a grouped subtype for their investigation. pcJIA is not commonly used and there is no consensus on the definition of pcJIA. Webb & Wedderburn (2015) categorize pcJIA as any subtype of JIA with more than 5 active joints which thus includes polyarticular and oligoarticular extended JIA. It may also include enthesitis-related arthritis, systemic and psoriatic JIA as these subtypes are not categorized by the active joint counts. Huang (2019) includes all mentioned subtypes under pcJIA while Nalbanti (2018) only includes polyarticular and oligoarticular extended JIA. Grouping the subtypes in this manner could solve data issues related to the prospective data. However, the clinical validity of grouping this subtype is unknown and is probably undesirable as systemic JIA is included while in literature it is noted that the difference between systemic and non-systemic JIA subtypes is substantial, even resulting in calls for systemic JIA to be a characterized as a disease separate of JIA (Ombrello, 2017). Combining polyarticular and oligoarticular extended as done by Nalbanti (2018) might be more desirable. Interestingly, Minden (2019) noted that oligoarticular extended has the same disease outcome as polyarticular while it is treated less aggressively than polyarticular in Germany. Swart (2018) and Nalbanti (2018) predicted the need for bDMARDs for oligoarticular patients at diagnosis. The findings on polyarticular and oligoarticular extended JIA highlight an interesting subgroup of patients which could be used to compare the impact of early aggressive bDMARD use. Oligoarticular disease progression and need for early bDMARDs should be further investigated.

2.3 Conclusion

In this chapter a literature review was conducted to answer the following research question: *"What does early bDMARD treatment entail and what are the impacts on health and cost outcomes?"*

There is consensus in literature on the treatment window and need for early bDMARD use for patients with higher disease activity than the average JIA patient. Severe JIA patients can suffer irreversible joint damage if not treated adequately from the start of disease onset. The evidence for the health impact of early bDMARDs is, however, limited. Short-term effects of early switching for polyarticular or polyarticular course JIA is strong and suggest statistical improvement over conservative strategies. Long-term effects are noted by two articles but are poorly substantiated. Greater reduction in disability, greater improvement in utility, and a greater probability of achieving inactive disease is reported for patients who use early bDMARD treatment strategies compared to conservative strategies. Anti-TNF bDMARDs are the primary medication investigated in the articles. The subtypes polyarticular and oligoarticular JIA are the most relevant patient groups for investigating the impact of early bDMARD use. All articles noted that early bDMARD treatment results in far greater medication costs while non-medication costs could be reduced if early bDMARD treatment reduces disease activity. Only three articles defined precily what early bDMARD treatment means. Two defined it as first line, while only one article looked at the difference between a 3- and 6-month switch after initiation of methotrexate. The remaining articles had no precise definition of early bDMARD treatment. None of the articles precisely indicated when or why a first bDMARD should be used.

Model Implications

A model investigating the cost-effectiveness of aggressive bDMARD use must be able to model the short term (2 years) impact on utility and on reaching inactive disease. Evidence for long term impact of aggressive bDMARD is poor, but the model should be flexible enough to include long term effects. Long term impact of early bDMARD use, taking advantage of the "treatment window", could result in positive health outcomes such as a better prospect for achieving inactive disease or lower disease activity. At least the subtypes polyarticular JIA and oligoarticular JIA should be included in the model as these subtypes are investigated the most in terms of early bDMARD use and thus the most evidence is available for these subtypes, in particular for polyarticular JIA. Oligoarticular could be of particular interest due to the uncertainty of disease progression and lack of aggressive bDMARD treatment while it might be necessary for a large group of patients. Finally, the anti-TNF bDMARDs, adalimumab and etanercept, are the most common medications investigated due to frequent usage and should thus be included in the model.

3. Existing JIA Cost-Effectiveness Models

In this chapter the literature review we conducted on the existing JIA cost-effectiveness models is described. The goal is to identify and analyze currently existing models in order to make informed decisions on model type, structure, health states, and key parameters for our model. A secondary goal is to identify the sources used for the population of the models to later use in our own model.

3.1 Search Terms & Selection Criteria

Titles and abstracts were searched using a combination of juvenile idiopathic arthritis, modelling terminology, and synonyms of cost-effectiveness. Papers only reporting on cost-effectiveness without the use of a model were excluded. Systematic reviews including models for JIA were selected even if no model was created. Only models related to JIA were included even if a life-time horizon was applied. During the PubMed searches it was noted that there were references to models created for national health care institutes for which no full papers existed. Hence, searches were conducted in Google Scholar as well to find models not published in scientific literature. The PRISMA flow diagram and search terms can be found in Appendix B.

3.2 Findings

Reference	Model type	Health states	Time Horizon	Cycles	Analysis type	Discount
Cummins, Connock, Fry-Smith, & Burls (2002)	Unknown	Unknown	Lifetime	Unknown	Cost utility	6% cost 1% utility
Hughes et al. (2019)	Markov	(3) Visual impairment, no visual impairment, death	10 years	1 year	Cost utility	3.5%
Kittiratchakool et al. (2020)	Markov	(4) Active disease, inactive disease, 6 months inactive disease, death	Lifetime	3 months	Cost utility	3%
Luca et al. (2016)	Markov	(8) Active disease (+-AE*), ACR70 (+-AE), inactive disease (+-AE), refractory disease, inactive disease (off treatment)	5 years	1 month	Cost utility	3%
NICE (2011)	Markov	(6) no response, ACR response 30, 50, 70, 90, death. (22) ACR for five medications	30 years	12 months	Cost Utility	3.5%

Reference	Model type	Health states	Time Horizon	Cycles	Analysis type	Discount
Shepherd, Cooper, Harris, Picot, & Rose (2016)	Markov	(5) Death, on treatment, off treatment, inactive disease off treatment, switch treatment	30 years starting at age 11	3 months	Cost utility	3.5%
Ungar, Costa, Hancock-Howard,Feldman, & Laxer (2011)	Decision tree	(2) on or off treatment	1 year	6 months	Cost effectiveness	0%
Vicente, Sabapathy, Formica, Maturi, & Piwko (2013)	Markov	(6) no response, ACR response 30, 50, 70, 90, death	16 years	12 months	Cost Utility	5%

Table 3: Summary of the models found from pub med. AE = Adverse Events, ACR response = American College of Rheumatologists response, stands for adverse events.

There were 8 models found from database searches, see Table 3, ordered alphabetically. Shepherd (2016) investigated the cost-effectiveness of adalimumab, etanercept, tocilizumab and abatacept for the NHS. An extensive systematic literature review was performed and manufactures of four biologics were approached for their cost-effectiveness analyses. Two more models were found which could not be accessed, but were described by Shepherd (2016), see Table 4. A Markov model was submitted by the pharmaceutical company Roche. The second model found is from Simpson (2012) which is an article written in Russian. DeepL Translate was used to translate the article and in addition the description in Shepherd's study (2016) was used to analyze the model.

Reference	Model type	Health states	Time horizon	Cycles	Analysis type	Discount
Roche model*	Markov	(4) Active disease, active disease off treatment, on treatment, and death	25 years	6 months	Cost utility	3.5%
Simpson, Marlow, Shaw, & Rudakova (2012)	Markov	(8) Inactive (no disease), inactive, inactive (with disease), active mild, active moderate, active severe, death	7 years & lifetime	4 months	Cost utility	3-5% cost only

*Table 4: Summary of the secondary models found. *Roche model is described in (Shepherd, 2016).*

A total of 10 models were selected, see Table 3 and Table 4. All models investigated the cost-effectiveness of bDMARD for JIA while the search terms for the review did not specify medication type. Most models were cohort Markov models (8). One decision tree was found. The model type created by Cummins (2002) is unknown as it was not described adequately. No discrete event simulation (DES) models or any other form of individual sampling model was found. All models compared the cost-effectiveness of bDMARDs with at least the standard treatment of methotrexate except for the model submitted by Bristol Myers Squibb which only looked at costs. For the 10

models investigating cost-effectiveness of bDMARDs, 9 models reported ICER values while Ungar (2011) used costs per additional ACR Pedi 30 response. All models except the last one (Ungar, 2011) applied discounting after one year. Preference was for 3.5% for utility and costs as recommended by NICE (O'Mahony & Paulden, 2014) for 4 models. Cummins (2002) used a higher discount factor for costs than utility (6% and 1% respectively). The Markov models are of particular interest for this project as they can better capture the cost and effects of different health states a patient might experience for the treatment of JIA with bDMARDs or sDMARDs than a decision tree model. A detailed overview of the 8 Markov models are summarized in Table 5:

Reference	Time horizon / cycle	Strategy	Subtype	Range Utility	Original Costs	ICER*
Luca (2016)	5 years/ 1 month	ETN first vs ETN second	pJIA	0.53-1.00 Adult version	Direct & Indirect Canada 2008	€62,489
Shepherd (2016)	30 years/ 3 months	ADM, TCZ, ETN vs MTX	pJIA	0.53-0.78***	Direct (NHS), UK 2013	ADM: €49,976 ETN: €42,634 TCZ: €50,670
Hughes (2019)	10 years/ 1 year	ADM vs MTX	Uveitis	0.83-0.87	Direct (NHS), UK 2015	€177,828
Kittiratchakool (2020)	Lifetime/ 3 months	TCZ vs MTX	sJIA	0-1 Gamma distributions**	Direct & Indirect, Thailand	€29,391
NICE (2011)	30 years/ 1 year	INX TCZ vs INX ANA TCZ vs ANA	sJIA	0.19-0.77	Direct & Indirect (NHS) UK 2011	€41,041 €22,675
Vicente (2013)	16 years/ 1 year	TCZ vs MTX	sJIA	0.19-0.77	Direct & Indirect Canada 2011	€56,310
Roche Model	25 years/ 6 months	ADM vs TCZ	pJIA	0.53-0.73***	Direct, Netherlands ***	Combo: €481,779 Mono: TOC dominant
Simpson (2012)	7 years & lifetime/ 4 months	ADM vs MTX	All	0.18-1.00	Direct & Indirect Russia	7 years: €22,249 Lifetime: €1,850

*Table 5: The 8 Markov models summary of key input and output variables for the cost-effectiveness analysis. *ICERs are reported with the first strategy investigated as intervention and set in the north-east quadrant of the cost-effectiveness plane unless specified otherwise. **Gamma distribution used for PSA. *** cost or utility taken from (F. H. M. Prince et al., 2011). JIA = Juvenile Idiopathic Arthritis, pJIA = Polyarticular JIA, sJIA = Systemic JIA, ETN = Etanercept, ADM = Adalimumab, TCZ = Tocilizumab, MTX = Methotrexate, ANA = Anakinra, ICER = Incremental Cost-Effectiveness Ratio, INX = Infliximab.*

All Markov models had a time horizon of 5 years or more. Luca (2016) and Simpson (2012) modelled the shortest time horizon with 5 years and 7 years respectively. Both models did not include death as a health state although Simpson (2012) used it for the lifetime horizon model iteration. The 6 other models all modelled death as an absorbing health state with the time horizon ranging between 10 years and lifetime. For the models that explicitly stated how death was modelled the probability of death was equal to the general population and was thus independent of age, gender, health state, and medication. Models which included a long enough time horizon where a juvenile patient would turn into an adult in the model did not account for this change. As no individual sampling is used and all models adhered to the Markovian property the duration of the patient in the model did not alter transition probabilities. This is a limitation of lifetime JIA models as old age impacts utility and the probability of death. The cycle length used ranged between 1 month and 1 year. Only Shepherd (2016) motivated the use of a 3-month cycle, noting that a 3-month cycle was in line with the timing of outpatient appointments in clinical practice. All Markov models investigated the cost-effectiveness of bDMARD use. Luca (2016) investigated the first line cost-effectiveness of etanercept versus first line methotrexate and second line etanercept. The model variables for etanercept treatment are dependent on whether etanercept is applied as a first- or second-line treatment. The 7 remaining models investigated the cost-effectiveness of bDMARDs without specifically looking at the order of treatment. The primary subtypes investigated were systemic and polyarticular JIA. Simpson (2012) did not specify subtypes and Hughes (2019) looked at all JIA patients with uveitis. The health states varied between the 8 Markov models: 6 models used forms of inactive and active disease as their primary health states. Inactive and active disease were further subdivided by most models. Active disease was subdivided further as refractory disease and active disease by Luca (2016) and in mild, moderate, and severe active disease by Simpson (2012). Inactive disease was subdivided as inactive disease off or on treatment, inactive disease for 6 months on treatment, and inactive disease with or without residual limitation of joint mobility. NICE (2011) technology appraisal model and Vicente (2013) were the only two models utilizing medication response with active disease as primary health states. Both used 6 health states per medication: no response, ACR-pedi (30, 50, 70, 90), and death. Luca (2016) used ACR-pedi response with inactive or active disease to model patient progression. Adverse events were only explicitly modelled as a separate health state by Luca (2016), but Shepherd (2016) included a chance for adverse events at every cycle. More than two DMARD treatment sequences were included in three models, Luca (2016), Shepherd (2016), and NICE (2011) included five maximum treatment sequences. The treatment sequences are predetermined for all three models. All Markov models conducted cost-utility analyses and reported ICERs for the treatment investigated. Direct costs were used in all models and indirect costs were used in 5 of the 8 models. The indirect costs were generally poorly defined and did not include productivity losses. Utility values ranged between 0-1 depending on the medication and health state. Shepherd (2016) did apply a different utility based on model duration with utility increasing slightly every few cycles in the active disease health state for the first year. All models included sensitivity

analysis. Variables investigated with sensitivity analysis were costs, utility, discount factor, time horizon, and probability of event.

3.3 Other Findings

Shepherd (2016) found no DES model and did not create a DES model even though this was one of the goals. No motivation was given as to why they did not create a DES model. Shepherd (2016) noted that the manufacturers of anti-TNFs bDMARDs assumed that all anti-TNFs have the same effectiveness. As such, in their model as well as in the Roche model, utility for different anti-TNFs were set the same based on the etanercept efficacy as reported by Prince (2011). However, both the probability of remission and probability of flaring per cycle was different per anti-TNF bDMARD used.

3.4 DES Models in Adult RA

The literature review found no DES models for JIA. Only adult rheumatoid arthritis (RA) papers were found using DES models. A systematic literature review for adult RA modelling by Scholz & Mittendorf (2014) found 7 DES models out of the 58 publications identified between 1996 and 2012. The majority of DES models were developed for the UK using or building upon the Birmingham Preliminary Model (BPM) or the Birmingham Rheumatoid Arthritis Model (BRAM) to evaluate the cost-effectiveness of bDMARDs. DES models were noted as more flexible in modelling disease course of RA, especially with competing events and time to events. However, the need for reliable and plentiful data was also noted as prerequisite. Finally, the DES models compared to the other models evaluated far more treatment strategies as entire treatment pathways and patterns are modelled more often. No reasons were found in literature as to why DES models were only found in adult RA. Theorized reasons for this discrepancy are the overall lack of research into JIA compared to RA. This manifests itself in two ways. First, less data are available for JIA which is necessary to leverage the advantages of a DES model. Second, as DES models are often seen as more complex it might require a "first mover" for JIA modelling. As noted by Scholtz (2014) DES models in adult RA are developed and improved over time by different studies from the UK while Markov models and decision models are more often reported as independently developed. Furthermore, as JIA only includes children it is limited in time horizon. Therefore, long term data, which a DES model can utilize more effectively than other models, is very limited. This is especially true for the modelling of death which is only relevant for JIA if the patient lifetime is modelled. Due to a lack of motivation for model choices for JIA this trend could not be confirmed for the found models. The 7 DES models as found by Scholtz (2014) are in fact only two models, the BRAM model (basis of 5 models) and a Swedish model (basis of 2 models). Both were read with the goal of finding addition information which could be relevant for the creation of a JIA DES model. Since the (Scholtz 2014) systematic literature review is out of date, a 2020 systematic literature review of economic evaluation of biological treatment in RA (Ghabri, Lam, Bocquet, & Spath, 2020) was consulted to find any additional DES models. Six DES models were identified out of a total of 51 models, 5 of which are the BRAM model and one incomplete conceptual model

(Alemao et al., 2018). Hence, only the two models BRAM and the Swedish model are further described based on their DES properties and any additional information that might aid in model decision making. The structure of both models can be found in Appendix C. As secondary finding is that Ghabri (2020) found 17 (Markovian) micro simulation models out of 51 and Scholtz (2014) found 13 out of 58 for adult rheumatoid arthritis while none could be found for JIA.

The first BRAM was developed in 2004 based on the 2002 BPM for the use of health technology assessment of bDMARDs in the UK for rheumatoid arthritis (Barton, Jobanputra, Wilson, Bryan, & Burls, 2004). All BRAM models evaluate the full cost-effectiveness of patient pathway on bDMARDs with a primary focus on anti-TNF bDMARDs. As such, a patient always starts on treatment for a specific bDMARD and events occur which can move a patient off the first treatment (death and quit bDMARD) or keep the patient on the first treatment with a chance of a negative event occurring (joint replacement or an increase in the health assessment questionnaire score (HAQ) which signifies an increase in disability). As each BRAM differs based on the version for the sake of consistency the third version is used (Barton, 2011). Relevant DES modelling techniques included in BRAM are patient level simulation, continuous time to events, competing events (death, joint replacement, HAQ increase, and quitting DMARD treatment) and dynamically changing rewards and costs based on changing patient characteristics, time to events and previous health states. Individual patients are simulated with a starting age, gender, and starting utility. Starting utility depends on age and gender. Current age, gender, and utility impacts mortality risk. Survival probability on a DMARD depends on the time on treatment and on the specific DMARD. BRAM either models competing risks using two strategies: 1) sample time to event first from a unimodal survival curve and then draw the event from the conditional probability of each event and 2) sample time for each event separately and select the minimum time as event (Barton et al., 2004). The survival distribution for death was based on life tables adjusted for utility, while Weibull distributions were used to model joint replacement and time on DMARDs. HAQ increase was not modelled as a competing event. Instead HAQ are assumed to always occur as the patient ages no matter the event.
The Swedish model (Kobelt, Lindgren, & Geborek, 2009) is the second independently developed DES model found in adult RA. Just as with the BRAM model treatment sequences of bDMARDs were investigated and as such the starting health state is on treatment with a bDMARD. The other states are off treatment and death. On treatment is further subdivided in high or low disease activity with patients off treatment assumed to be in high disease activity. The DES relevant modelling techniques used are patient level simulation and continuous time to events. Gender, age, starting disease activity and functional scores were modelled individually. These attributes are dynamically updated based on events and can drive cost, health reward, and time to next event. The time to events for treatment discontinuation and treatment resumption are modelled using a Weibull distribution. Death is modelled using disease adjusted general population lifetime tables from Sweden.

3.5 Conclusion:

In this chapter we conducted a literature review to answer the second research question:
"What current cost-effectiveness models exist for JIA and what insights do they provide?"
Furthermore, we also wanted to answer how JIA models differed from adult RA models.
As a result of the literature review 10 cost-effectiveness models were found. Most models were Markov cohort models (8) while no DES or micro simulations models were found for JIA. Therefore, time to events were cyclical, no individual patients were simulated, and the Markovian property was applied. No consensus could be established on the use of health states, time horizon, cycle length, and discount factor for the Markov models. The Markov models did not limit the time horizon to the short term. Instead, lifetime models were common and most included death as an absorbing health state. There are doubts over the validity of modelling JIA into adulthood regarding death and disease progression for lifetime models. The model variables (cost, utility, transition probability) were only dependent on treatment and health state except in two models. All Markov models investigated the cost-utility of bDMARDs compared to methotrexate or another bDMARD. The motivation for utilizing Markov cohort model for JIA instead of a DES or micro simulation could not be established. In adult RA DES models and micro simulations are as common as Markov models. Proposed causes for this discrepancy are the lack of data and the immaturity of JIA modelling compared to adult RA. This is particularly true for DES, as the 8 DES models found in adult RA are all based on just two models: the BRAM and a Swedish model.

Model Implications

The major advantage of a DES model over other models is the ability to better model time to events and competing events. Leveraging this advantage for JIA is challenging due to the lack of data, issues with modelling long time horizons, and no example models for JIA. Utilizing an individual sampling method instead of a cohort approach is difficult for JIA due to a lack of data. The prospected data for the UCAN CAN-DU-project will provide poor long-term data with sufficient follow up periods as well as synchronizations issues with the different cohorts. In adult RA age and gender is the primary variable for individual sampling as it impacts utility, cost, probability of events, and time to events. The impact of age of a child on utility, cost, probability of events, and time to events is unknown for JIA. As Markov cohort models are the primary cost-effectiveness models for JIA there are numerous sources and examples that can be used to build a Markov cohort model. For JIA models time horizon beyond childhood needs to be carefully modelled and motivated. A model cycle of 3-4 months should be used if modelling a state transition model (Markov cohort model or micro simulation model) as most models use a similar cycle length due to a 3–4-month cycle being in line with the periodic follow up visits for JIA patients at clinicians or in studies. Furthermore, a 3–4-month cycle aligns with the time taken for most DMARDs to start working. As we investigate the difference in switching strategy of 3 months, we chose 3 months cycle instead of 4 months.

4. Prospective Data

The prospective data from the UCAN CAN-DU study is key in developing the model. One of the research objectives is that the prospective data should inform the model once it becomes available. Relying on one data source for model parameter estimation of the model is recommended as a best practice according to ISPOR (Briggs, 2012). It helps mitigate uncertainty and increases the validity of the model. It furthermore drastically reduces the complexity of synthesizing data from different study populations. The prospective data collection within the UCAN CAN-DU study will not be fully completed before 2022. As of February 2021, a small part of the prospective data of 410 patients was available. In this chapter the prospective data is investigated, and the February 2021 data is analyzed for use in the model developed in this thesis.

4.1 Description of Prospective Data

The prospective data are collected from partner hospitals and clinics in Canada and the Netherlands. All child rheumatologists in Canada and the Netherlands participate in this study. Patients included are children up to 18 years with active arthritis which is suspected to be JIA. When a patient is enrolled in the study, they are enrolled into one or multiple cohorts depending on their treatment or JIA characteristics. Three cohorts are defined, see Table 6, according to the patient's treatment. A patient is followed for 12 months in all cohorts (except cohort 3) although what data are collected at which time points differs per cohort. A patient is enrolled in cohort 1 if they are treatment naïve, which means a patient is only allowed to have received NSAIDs within the first 6 months of JIA diagnosis. A patient enrolls in cohort 2 if a bDMARD is started. The patient does not have to be bDMARD naïve and may thus start their second, third or even fourth bDMARD in cohort 2. A patient can be enrolled in cohort 1 first and later in cohort 2. If the first bDMARD is used within the 12 months follow up of cohort 1, then a patient can be enrolled in cohort 1 and 2 at the same time. A patient discontinuing a bDMARD due to achieving inactive disease is enrolled in cohort 3.

	Cohort 1 Biologic Basis of JIA	Cohort 2 Start Biologics	Cohort 3 Stop Biologics
Inclusion Criteria	▪ ≤18 years* ▪ Active objective arthritis suspected to be JIA ▪ *Treatment naïve* except for NSAIDs - allowed to have received NSAIDS within 6 months of diagnosis	▪ JIA diagnosis as per ILAR criteria (all subtypes) ▪ ≤18 years* ▪ Active arthritis - For sJIA, active disease not necessarily with arthritis. ▪ Time of start, restart or switch biologic therapy.	▪ JIA diagnosis as per ILAR criteria (all subtypes) ▪ ≤18 years* ▪ Inactive disease ▪ Discontinuing/tapering biologics for inactive disease
Exclusion Criteria	▪ Arthritis explained by another diagnosis ▪ Joint injections as previous treatment	▪ Arthritis explained by any other cause ▪ Start on biologics as an indication for uveitis only	▪ Tapering scheme > 12 months to complete biologics stop ▪ Continuing conventional DMARDs beyond the stop of biologics
*At time of inclusion			

Table 6: The inclusion and exclusion criteria for cohorts 1, 2, and 3. (Copied from UCAN CAN-DU Protocols, 03.06.2020). JIA = Juvenile Idiopathic Arthritis, NSAIDs = Non-Steroidal Anti-Inflammatory Drugs, sJIA = Systemic JIA, ILAR = International League of Associations of Rheumatology, DMARDs = Disease Modifying Anti-Rheumatic Drugs.

For each cohort the patient data are collected at set follow up points. Case report forms (CRF), biomarker testing outcomes, patient and caregiver reported outcomes, and administrative data are collected. The CRF includes a wide variety of clinical reported health outcomes such as JIA subtype, number of active joints, location of active joints, co-morbidities, physician global assessment score, and disease status. It also includes the full patient medication history, current medication, country of origin, and patient characteristics such as age and sex. The CRF medication history and current medication includes dosage, frequency of medication intake, and reason for switching medication. The goal of biomarker testing is to create tools for predicting response to treatment to enhance personalized treatment resulting in lower costs and improved health outcomes. Biomarker testing will not be used in the model developed for this thesis, but could be included after the results of the biomarker analysis becomes available. Patient and caregiver outcomes are collected through questionnaires. The childhood health assessment questionnaire (CHAQ), juvenile arthritis multidimensional assessment report (JAMAR), and the health economics PROs package are all collected through questionnaires. The health economics PROs package consists of the EQ-5D-5L child and caregiver questionnaire, care-related quality of life questionnaire (CarerQoL), work productivity and activity impairment questionnaire (WPAI), and health economics burden patient reported survey also known as the CALC. The CALC questionnaire collects extensive data related to indirect costs such as traveling, house or car changes, additional help from non-medical personnel, and additional equipment or tools as a result of JIA. It furthermore collects data on the impact of JIA on the work and personal life of the parent as well as the impact of the schooling of the child. With the health economics PROs, patient and

parent utility can be determined. The direct economic costs can be determined using administrative data and medication data from the CRF while other direct and indirect economic costs of JIA can be determined with the health economics PROs questionnaire. The CRF, CHAQ, and JAMAR can be used to determine patient health states such as inactive disease, active disease, treatment or no treatment, and response or no response to treatment.

A patient is followed for 12 months per cohort with different data collection points per cohort. For cohort 1 & 2 the clinical outcomes (CRF, JAMAR, and CHAQ), health economics, and biomarkers are collected at the start and at six months follow up, see

Figure 2. The health economics are also collected at three, nine, and 12 months. Crucially, disease status and other clinical outcomes are not known at 9 or 12 months of follow up which severely limits the time horizon the prospective study can provide data on.

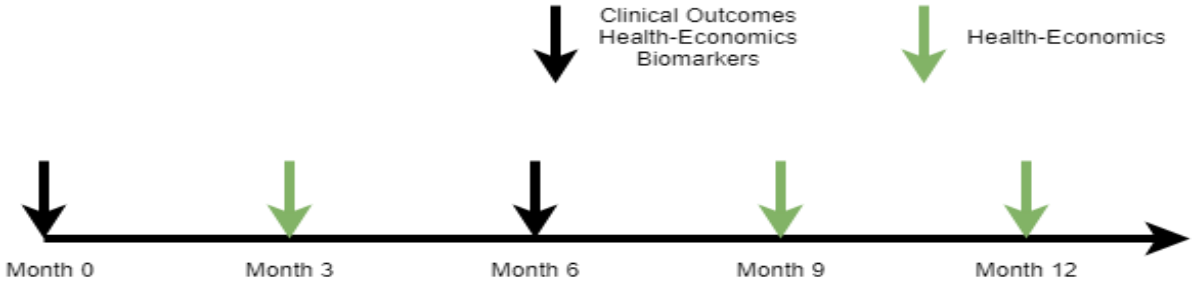

Figure 2: Patient Timeline for Cohort 1 & 2.

The timeline of cohort 3 is more complicated as it depends on when the decision is made to taper or stop the bDMARD and when the actual stop visit takes place. A stop visit is planned for the date when the medication is stopped or tapered. A maximum of 12 months is allowed between the decision to stop and the stop visit. The timeline starts at the decision to stop bDMARD and ends after 12 months of the visit when the medication is stopped. The health economics are collected every 3 months for a maximum of 24 months. Clinical outcomes and biomarkers are measured at the start, stop visit, and follow up visit at 12 months. If any flares occur, clinical outcomes, biomarkers, and health economics are collected at that point in time. Cohort 3 data are key for any model that models the health states after inactive disease occurs. Clinicians taper or remove medication after a patient achieves inactive disease with a risk of the patient flaring. The literature and data related to discontinuation of bDMARDs in inactive disease is very sparse. The effects of different discontinuation strategies in terms of risks and benefits are poorly understood.

4.2 Description of Prospective Data of February 2021

For the February 2021 data of the prospective data the CRF, medication history, patient and caregiver reported EQ-5D-5L were available. Not all economic data was available. Cost components of resources used were not available. If the final model should rely on the prospective data, it is key to understand what the data will look like. Therefore, the February 2021 data are analyzed, with in particular subtypes, medication patterns, and enrolment in different cohorts as well as the extent of missing data.

Six databases were analyzed with each a different number of patients, see Figure 3. Databases were linked by patient ID. Logically, patient information containing demographic data, included the most patients (410). The CRF database contained key clinical data such as subtype, joint count, and disease status per visit per cohort enrolled. Multiple visits per cohort were collected in the CRF however, a large number was missing as with 396 patients at least 792 follow up visits are expected whereas CRF only had 649 observations. For both, the CRF and the patient information, 358 patients had a full medication overview (history & current medication) while the remaining patients had no medication data. For 215 patients the proxy EQ-5D-5L was reported whereas only 87 patients self-reported. The expected number of observations for the EQ-5D-5L is at least five per patient (0, 3 ,6, 9, 12 months) per cohort 1 or 2. At least 1075 observations are expected while only 381 observations are recorded.

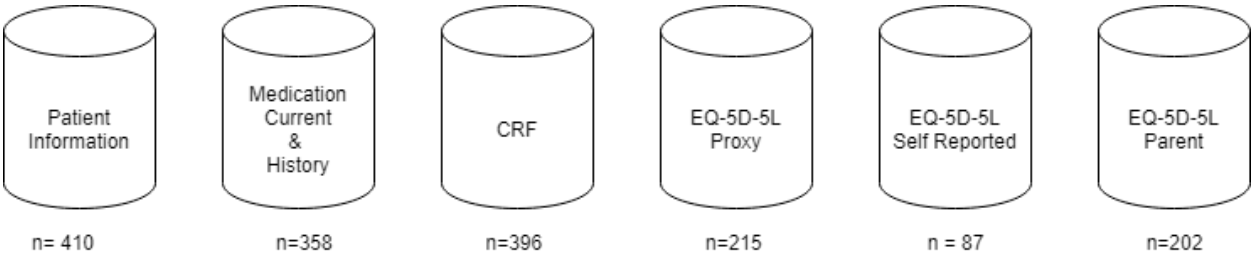

Figure 3: Number of patients per data base in the February 2021 prospective data.

For the February 2021 data a large percentage of data are missing per patient. Causes for data missing are unknown and still being investigated. For the population of the model, it is key that data are as complete as possible, especially with regards to follow up visits for the CRF, EQ-5D-5L data, expected economic data, and medication.

Of the 358 patients with full medication history and CRF entries available, the majority was enrolled in cohort 1 and 2, while cohort 3 and 4 had far less patients enrolled, as shown in Table 7. It is concerning that the expected enrolment for cohort 3 is lagging behind cohort 1 and cohort 2 as at least double the cohort 3 patients are expected. As stated previously, cohort 3 is key for the long-term picture of bDMARD use. Furthermore, only 4.4% of patients transition from one cohort

to another. As there are only two clinical data collection points per cohort 1 and 2, at the start and 6 months follow up, the clinical follow up period per patient is severely limited.

Prospective data	Cohort 1	Cohort 2	Cohort 3	Total
Expected end study	1600	900	1000	3500
February 2021	169	122	53	332*

***Table** 7: Expected number of patients enrolled at the end of the study & in the data of February 2021. *Unique patients, 16 patients are enrolled in multiple cohorts at the same time.*

The lack of patients enrolled in cohort 3 and the missing data for EQ-5D-5L is not the only issue with the February 2021 data. The synchronization of visits across the different databases is problematical. Especially CRF visits, medication start and stop data, as well as EQ-5D-5L visits are hard to synchronize. This issue is compounded by the missing data for follow up visits and the incorrect entry of data. Synchronization issues limit the analysis that can be conducted with the February 2021 data and more importantly limits the validity of the results of the analysis.

Subtype and Medication

In order to investigate what medication and subtypes are found in the prospective data the CRF and medication database needs to be synchronized and patients with missing data removed. All 358 patients in the medication file are found in the CRF file. There are 36 patients who have undefined subtype, and four patients are missing baseline visits. 318 patients remain with a defined subtype, cohort number, and updated medication. 235 patients use a sDMARD at least once with 221 patients using methotrexate (94%). 185 patients received a bDMARD at some point of their disease course, and all subtypes were bDMARD users, see Table 8. A low number of patients are diagnosed with the subtypes systemic, psoriatic, and polyarticular RF+ JIA which is expected as these are the least common subtypes. The subtypes systemic, psoriatic, and oligoarticular have the lowest percentage of bDMARD users.

	All patients	bDMARD users
Number of patients	318 (100%)	185 (58%)
JIA Subtype:	n (% of patients)	n (% of subtype)
Oligoarticular	65 (20%)	21 (32%)
Oligoarticular persistent	52 (16%)	34 (65%)
Oligoarticular Extended	33 (10%)	29 (88%)
Polyarticular RF-	78 (25%)	57 (73%)
Polyarticular Rf+	21 (7%)	15 (71%)
Systemic	22 (7%)	5 (22%)
Psoriatic	5 (2%)	1 (20%)
Enthesitis	42 (13%)	23 (55%)

Table 8: *Patient subtype at first entry and bDMARD use in the February 2021 prospective data.*

Of the 185 patients receiving a bDMARD at some point during their disease course, 25 receive the bDMARD as first line DMARD (less than 2 months of start with the first sDMARD). 160 patients start the first bDMARD after starting with sDMARD. 85 patients use adalimumab (53%) and 57 etanercept (36%) as the first bDMARD, see Table 9 . Both are anti-TNF bDMARDs which are frequently used in the cost-effectiveness JIA models identified in the literature review. Etanercept was the most frequently prescribed bDMARD, but there is an overall trend of more clinicians prescribing adalimumab. There were 18 patients and 23 patients starting adalimumab and etanercept as their first bDMARD switch to a secondary bDMARD (the remaining patients do not switch within the follow up period). Etanercept patients switch to adalimumab 57% of the time and adalimumab patients switch to etanercept 28% of the time.

bDMARD	First bDMARD (start with sDMARD) Total = 160 N (%)	Second bDMARD (first adalimumab) Total = 18 N (%)	Second bDMARD (first etanercept) Total = 23 N (%)
Abatacept	2 (1%)	0 (0%)	1 (4%)
Anakinra*	0 (0%)	0 (0%)	1 (4%)
Adalimumab*	85 (53%)	-	13 (57%)
Etanercept*	57 (36%)	5 (28%)	-
Golimumab*	6 (4%)	4 (22%)	2 (9%)
Infliximab*	5 (3%)	2 (11%)	4 (17%)
Tocilizumab	3 (2%)	7 (39%)	2 (9%)
Tofactinib	1 (1%)	0 (0%)	0 (0%)
Certolizumab*	1 (1%)	0 (0%)	0 (0%)

Table 9*: bDMARD treatment line after starting with sDMARD in the February 2021 prospective data.*
* anti-TNF bDMARDs.

The majority of first and second line bDMARD medication used are anti-TNF bDMARDs except for tocilizumab which is used 39% of the time after adalimumab first. Methotrexate and anti-TNF bDMARDs, particularly adalimumab and etanercept are therefore recommended to be the focus of the model.

Inactive and Active Disease

The disease status is filled out by the clinician during each clinical visit. The definition used by clinicians for inactive and active disease is not recorded. The Wallace criteria (Wallace, Giannini, Huang, Itert, & Ruperto, 2011) of inactive disease is a widely recognized standard tool for defining inactive disease for JIA. Inactive disease according to the Wallace criteria is defined as:

- Zero joints with active arthritis.
- No fever, rash, serositis, splenomegaly, lymphadenopathy due to JIA.
- No active uveitis.
- Erythrocyte sedimentation rate (ESR) or C-reactive protein (CRP) levels within normal limits.

- Lowest score on the physician's global assessment of disease activity (score of 0).
- Duration morning stiffness no longer than 15 minutes.

CRP and ESR are measurements of inflammation. The limit for CRP is10 mg/L. ESR has to be less than 20 mm/hour. In the CRF the number of joints with active arthritis, ESR, CRP, and the physician's global assessment is collected. 396 patients were recorded in the CRF of the February 2021 data with 649 observations. Inactive disease was recorded 181 (28%), active disease 411 (63%), and undefined 57 (9%) times, see Table 10. The four Wallace variables collected in the CRF were not collected with the same frequency. Morning stiffness was missing 82% of the time while PGA and active joints were missing 4% and 6% of the time. Active joints and PGA were strong indicators if a clinician recorded the patient as inactive or active. There are however discrepancies with 29% of patients in inactive disease having an active joint count while 15% of patients in inactive disease had a PGA of greater than 0.

		Indicates Inactive disease *	Indicates Active disease **	
Morning stiffness	**NA**	**15 or less**	**>15**	**Total**
All patients	531 (82%)	28 (4%)	90 (14%)	649
Inactive disease	175 (97%)	4 (2%)	2 (1%)	181
Active disease	301 (73%)	24 (6%)	86 (21%)	411
Undefined	55 (96%)	0 (0%)	2 (4%)	57
Active joints	**NA**	**Inactive**	**Active**	**Total**
All patients	28 (4%)	156 (24%)	465 (72%)	649
Inactive disease	2 (1%)	127 (70%)	52 (29%)	181
Active disease	0 (0%)	18 (4%)	393 (96%)	411
Undefined	26 (46%)	11 (19%)	20 (35%)	57
PGA	**NA**	**0**	**> 0**	**Total**
All patients	37 (6%)	165 (25%)	447 (69%)	649
Inactive disease	8 (4%)	146 (81%)	27 (15%)	181
Active disease	2 (0%)	10 (2%)	399 (97%)	411
Undefined	27 (47%)	9 (16%)	21 (37%)	57
ESR	**NA**	**20 mm or less**	**> 20mm/hour**	**Total**
All patients	126 (19%)	395 (61%)	128 (20%)	649
Inactive disease	36 (20%)	139 (77%)	6 (3%)	181
Active disease	69 (17%)	230 (56%)	112 (27%)	411
Undefined	21 (37%)	26 (46%)	10 (18%)	57

*Table 10: Observations of disease Status (Inactive, active, and undefined) as defined by the clinician in the prospective data compared to four Wallace criteria. * All four variables need to indicate inactive disease. ** If any of the four variables indicate active disease the Wallace criteria defines disease status as active.*

The discrepancies highlight that the clinicians differ in their definition of disease status and do not always utilize the same definition of inactive disease as the Wallace criteria. In a model including health states inactive or active disease it is key to have consistent definition of disease status. Furthermore, 9% of the entries of disease status are missing and an accepted criterion for disease status would allow some of these entries to still be defined post-hoc. A lack of observation of disease status, difficulty with synchronizing disease status observation with active medication, as well as an inconsistent definition of active or inactive disease means the February 2021 data were not used for determining changes in disease status due to medication use. Instead, literature was used to determine the changes in disease status due to medication use, as further reviewed/explained in Section 5.4, until the full prospective data are collected and analyzed.

4.3. Conclusion

We investigated the prospective data to answer the third research question:
"Which data will be collected in the prospective study?"
In order to know what data after the prospective study is completed can be used to populate the model. Furthermore, the February 2021 data from the prospective study was also analyzed for use in the model.

The prospective data can provide a large quantity of unique data for the population of a cost-effectiveness model of early bDMARD use. Cohort 1 and 2 are of particular interest for the model especially if a large number of patients are enrolled in both cohorts within a timeframe of a year which would capture the treatment pathway of first sDMARD use to first bDMARD use. However, in the February 2021 data only 14 patients (4%) were enrolled in both cohorts. The February 2021 data also suggests that the expected number of patients enrolled in cohort 3 will be far lower than expected. Limited data are expected to be available for modelling the effects of medication discontinuation. Furthermore, a potential lack of patients in cohort 3 and the lack of patients enrolled in both cohort 1 and 2 means the frequency of clinical data collected and the time horizon of a patient followed in the prospective data are severely limited. The prospective data provides multiple sources for health outcomes with the child and proxy reported EQ-5D-5L being of key importance for utility calculations. A large amount of data are incomplete in the February 21 data for the EQ-5D-5L, especially a lack of follow up data. Utility data will thus need to be supplemented with literature. Data for prices are not collected prospectively therefore literature and retrospective data will have to be used. Changes in disease status related to medication use or length of follow up could not be determined and will also require literature estimation. As methotrexate, etanercept, and adalimumab are the most frequently prescribed DMARD, these are recommended to be used in the model. All subtypes except for systemic, undefined, and psoriatic can be included as these subtypes are either underrepresented or do not use bDMARDs often.

5. The Simulation Model

The Chapters "Literature Study" and "Prospective Data" gave an overview on the available evidence and expected evidence for a cost-effectiveness model of early bDMARD use. In this chapter the motivation and assumptions behind the developed individual-based state transition model is described.

5.1 Motivation Model Type

For cost-effectiveness models in health care three models are commonly used: decision trees, state transition models (STMs), and discrete event simulations (DES). Decision trees are the simplest models, but have a limited ability to reflect time and repeated events (Siebert et al., 2012). Modelling time and repeated events (inactive disease, flares, or response) are key parts of a chronic disease such as JIA. In the literature study on existing JIA cost-effectiveness models only one of the 10 identified models was a decision tree. STM and DES models can reflect time and repeated events in a better manner than a decision tree.

The advantages of a DES model over a STM is the ability to manage time in a flexible manner (Karnon et al., 2012). Events can occur at any point in time wherein events and probability of events are often modelled as a survival curve, while in a STM events can only occur after discrete cycles with a fixed duration. In a STM, time to event and probability of events are not linked while this is key in chronic or long-term diseases such as JIA. Furthermore, DES models are more flexible in modelling competing events with multiple strategies available as described by Degeling, Koffijberg, Franken, Koopman, & IJzerman (2019). Modelling competing events in a STM can be approximated by using short cycle lengths with the downside of increasing the computational burden of the simulation. Modelling individual patients as entities is a core concept of DES models. Individual patients contain attributes which can impact time to events, probability of event, as well as costs and rewards per health state. Furthermore, individual patients can consume resources and enter queues. Consumption of resources and entering queues is relevant when limited resources (e.g. hospital beds) in health settings need to be reflected, which is not commonly included in disease progression and treatment models used for health economic analyses. Patient attributes are dynamic and can be updated during treatment events in the model which allows for the personalized treatment of an individual patient to be better represented (Karnon & Haji Ali Afzali, 2014). JIA is a disease with high heterogeneity and could thus benefit greatly from modelling individual patients. The ability to include memory when modelling patients as individual entities is key for creating a more dynamic model were time to events or probability of events, costs and rewards can depend on the previous health states as well as events the patient experienced. Modelling individual patients is not exclusive to DES as STM can also model individual patients known as individual based (i.e. patient-level) STMs, microsimulations, or first-order Monte Carlo models (Siebert et al., 2012).

As described in Chapter 3 “Existing JIA Cost-Effectiveness Models”, although there are considerable advantages to modelling JIA disease progression as a DES model, no DES models were found in the literature study. Instead, nine of the 10 models found were cohort based STMs. No explicit motivation for utilizing a STM was found. Reasons are the lack of long-term data for events, limited follow up periods, lack of individual patient data, and lack of previously developed DES JIA models. The literature review of cost-effectiveness models for adult RA by Scholz & Mittendorf (2014) revealed DES models for the adult RA population and noted that there is a need for more data to leverage the advantages of a DES model over a STM. As concluded in the previous Chapter “Prospective Data”, it is expected that the average follow-up period of patients will not be more than 12 months with two visits to determine clinical status at the start and at 6 months. This severely limits the ability to estimate survival curves for (long-term) events. The JIA STM cost-effectiveness models found in literature did use a long-term time horizon in their models, but this was based on 12- or 24-month clinical data with limited follow up visits. Therefore, the STM models defined the probability of events per cycle for a specific DMARD treatment independent of DMARD treatment duration. Although an advantage of a DES model over a STM is the ability to better model time to events, the cost-effectiveness outcomes do not have to be substantially different between both models if the same evidence is used (Degeling et al., 2018). Furthermore, even though a set cycle length hinders the representation of time to events in a STM, it can allow for better representation of when clinical decisions are made. Both in literature and the prospective data, follow up periods of 3 months are used after starting treatment on a DMARD as clinicians often use a 3-month period to reflect on treatment results and make treatment decisions. Therefore, due to a lack of long-term data and follow up periods in both literature and the prospective data, plus the ability to model individual patients in STM, it was felt that a DES model could not leverage its advantages and would not result in more efficient use of available data, or more accurate results, the choice was made to not create a DES model.

This still leaves the choice of creating a Markov cohort STM or an individual based STM. The greatest advantage of an individual based STM is the ability to model patients individually and thus include memory which can then impact transition probabilities, costs, and health effects. This allows for more dynamic and precise modelling which increases the validity of the model. A Markov cohort STM simulates patients as a cohort and assumes that transition probabilities, but also costs and rewards, do not depend on previous health states nor on the time spent in the current health state. This lack of memory of past events is known as the Markovian property. The only way Markov cohort STMs can include memory is by adding additional states representing disease progression with the downside of risking a state explosion if a large number of states have to be added (Siebert et al., 2012). An individual based STM requires more data to leverage its advantages over a Markov cohort STM. The literature review only found Markov cohort state transition models. The majority of models were old and did not have the ability to populate a model based on the comprehensive prospective data which will be available for this model. However, as noted in Chapter 4 “Prospective Data”, not all data are currently available. This limits the heterogeneity

modelled in the preliminary model. Nonetheless the choice was made to create an individual based STM as the goal is to create a model which can be expanded when the full prospective data become available. Especially biomarkers predictors of response to treatment are a key area UCAN CAN-DU is still investigating and could be included in the model at a later stage. Furthermore, if in the future a DES model should be developed, an individual based STM can serve as a steppingstone.

5.2 Individual Based State Transition Model

A state transition model, see Figure 4, was developed modelling a patient's treatment pathway starting with methotrexate as the first medication. A patient can also be treated with a first bDMARD and a second bDMARD if necessary. A patient switches medication if an adverse event or intolerance as a result of the medication occurs which warrants a discontinuation of the treatment. A patient can also switch to the next medication if the clinician determines that the patient's response to the treatment is not adequate and a new or additional medication is necessary. The patient's progresses through the model in 3-month cycles. A 3-month cycles is used as this corresponds to the follow up period used clinically and in the prospective data.

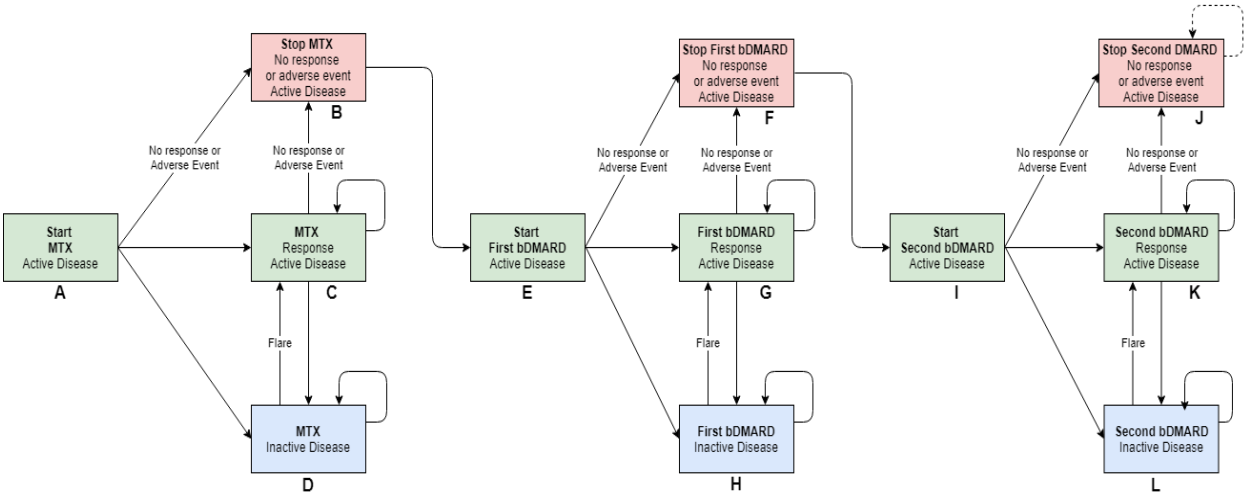

Figure 4: State transition model developed for the cost-effectiveness evaluation of early bDMARD treatment. Healthstates [A] to [L].

The health states we modelled are start treatment, discontinuation due to no response treatment, discontinuation due to adverse events (or intolerance), response to treatment, and inactive disease. The patient starts with methotrexate and can then progress to a first bDMARD and then a second bDMARD. As methotrexate and a bDMARD take a while to have effect, a patient always stays the first cycle at the start of treatment of methotrexate **[A]** or bDMARD **[E]/[I]** without any response. After the first cycle a patient can either respond, not respond to treatment, experience an adverse event, or achieve inactive disease. Response to treatment is not precisely defined by any key performance indicator. It simply represents the choice of clinicians to either stop treatment or continue treatment of a specific DMARD. The choice to discontinue due to no response, and the definition of no response, is different per clinician, organization, patient, and region. We assumed

that if a patient responds to treatment the clinician observes satisfactory results in the health outcomes of the patient. In case of no response, it is assumed that the clinician observes unsatisfactory results in the health outcomes of the patient and chooses to switch medication. Therefore, response to treatment results in the patient staying on treatment and achieving small utility benefits which can increase for 8 cycles of consecutive response. How utility is modelled is further explained in Chapter 6 "Model Parameters".

No response to treatment or an adverse event results in treatment discontinuation and a switch to a new treatment (first bDMARD **[E]** if methotrexate is stopped **[B]** or a second bDMARD **[I]** if the first bDMARD is stopped **[F]**). Inactive disease can also result in treatment discontinuation after a set period of time, but this not modelled as it not clear when clinicians discontinue DMARD treatment and what impact this has on the probability of flaring. After the analysis of cohort 3 of the full prospective data, enough data could be available to model the tapering process in a valid fashion. No response resets the patient's utility back to the utility with which the patient entered the model. No response or adverse events for the second bDMARD **[J]** can result in the switch to a third bDMARD. The third bDMARD is not modelled explicitly, instead patients remaining cycles are extrapolated using the cost of the second bDMARD and the initial utility of the patient without any improvement. The reason for this is that it is not certain what the third bDMARD is, and what consequences this has for costs and utility. Furthermore, modelling a third bDMARD has limited effect on overall cost-effectiveness as on average a patient spends 0.1 cycles (3 months per cycle) with a third bDMARD if 24 cycles (6 years) are modelled. The application of a discount factor will further reduce the overall impact of the third bDMARD. A 3-year time horizon is used for simulating the cost-effectiveness of early bDMARD treatment. To see what the effects of a longer time horizon is on the cost-effectiveness a 6-year time horizon is also applied. A short time horizon (3-6 years) was chosen to conduct simulations as a small fraction of children become adults with a short time horizon and only two lines of bDMARDs were modelled.

The Wallace criteria are used for the definition of inactive disease and active disease. Achieving and remaining in inactive disease **[D]**, **[H],** or **[L]** is the main goal of treatment. Utility and costs are improved when a patient achieves inactive disease. Inactive disease without medication is not modelled. A patient remains in inactive disease unless a flare occurs. When flaring, the patient is assumed to remain on the same medication and is returned to the response health state **[C]**, **[G]** or **[K]**. From there a patient can respond, not respond, or achieve inactive disease again with the same probability as before. Death is not modelled as it is very rare event for JIA.

5.3 Treatment Strategy

The model investigates the impact of the early switching strategy compared to the conservative switching strategy from methotrexate to the first bDMARD. If a patient has no response to methotrexate in the first cycle the patient can stay for one extra cycle on methotrexate

(conservative strategy) or switch immediately to the first bDMARD (early strategy). Figure 5 shows how the two switching strategies work using the health states described in Figure 4.

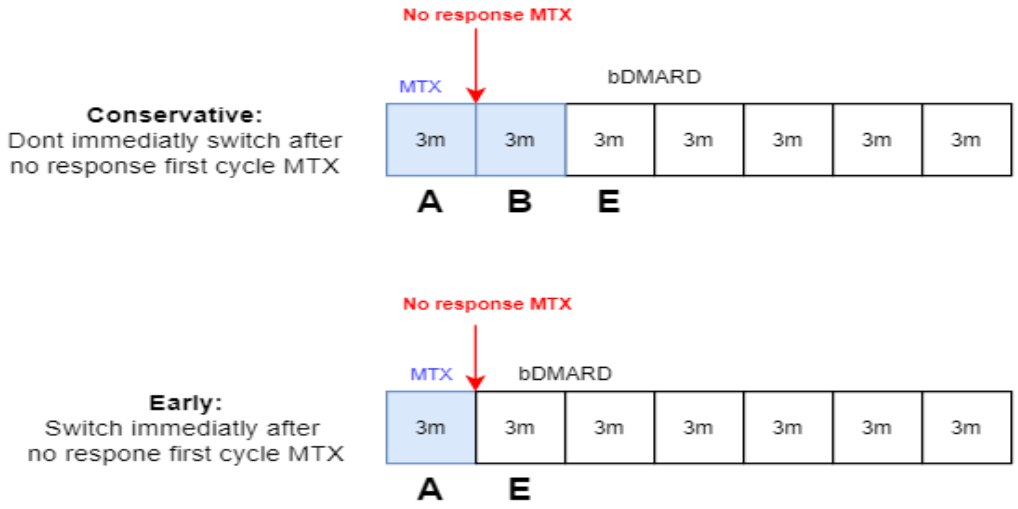

Figure 5: Switching strategies if no response to methotrexate in the first cycle with health states A = Start MTX treatment active disease, B = No response MTX active disease, E= Start treatment first bDMARD.

Start methotrexate treatment **[A]** has the same cost and health impact as no response methotrexate **[E]** as it represents the fact that it takes a couple of months before methotrexate can start having an effect. For no response to methotrexate after the first cycle we model that the patient always switches immediately as we do not investigate since we assume enough time has passed on methotrexate for clinicians to determine if a patient definitively responds or not. Furthermore, we do not investigate the switching strategy of the bDMARDs therefore we assume patients switch immediately if no response to a bDMARD occurs.

5.4 Subtypes

The subtypes enthesitis, oligoarticular extended, oligoarticular persistent, polyarticular RF-, and polyarticular RF+ are modelled. Oligoarticular, systemic, psoriatic, and undefined were excluded. Systemic and psoriatic were excluded due to low number of patients in the data of February 2021. Furthermore, the systemic subtype as well as the undefined, are very different from other subtypes. Oligoarticular was excluded as it should be updated after 6 months to either oligoarticular extended or persistent based on the number of active joints which was not always done.

5.5 Conclusion

Returning to the fourth research question:
"What will a cost-effectiveness model investigating early bDMARD use look like?"
We chose to create an individual based STM instead of a decision tree, cohort based STM, or DES model. A decision tree and cohort based STM were not chosen due to limited ability to model a complex disease such as JIA. A DES was not chosen due the limited study length of the prospective study and studies in literature, which all include multiple follow up visits. This results in a very limited ability to leverage the advantages of a DES over an individual based STM.

We modelled the health states response, no response, adverse event, and inactive disease as a result of a DMARD treatment. The medications modelled are methotrexate as first line DMARD, and the bDMARDs adalimumab and etanercept as second or third line. A cycle length of 3 months was chosen and subtypes polyarticular RF-, oligoarticular extended, oligoarticular persistent, and enthesitis are modelled.

6. Model Input Parameters

In the previous chapter the chosen model was motivated and explained. In this chapter the input parameters and variables required for the model are motivated and explained. The parameters and variables can depend on health state, medication, and patient subtype. First the medication and resource costs are discussed. Then modelling of individual patient utility is explained. Third, transition probabilities are estimated and represented. Finally, the discount factor and model verification are discussed.

6.1 Medication Costs

A key parameter in the cost-effectiveness of early bDMARD use is the cost of medication. As noted by Kip et al. (2020) bDMARDs are more expensive than sDMARDs. The medications modelled are methotrexate, adalimumab, and etanercept, as these are by far the most commonly prescribed bDMARDs in the prospective data and in literature. Other drugs such as NSAIDS, vitamins, or steroids (oral or injection) were not modelled due to a very low-cost impact and lack of data. Monthly medication costs depend on monthly dosage multiplied by the price per dosage. The February 2021 data included medication dosage per month, but not the dosage price. Therefore, dose prices were taken from Kip et al. (2020). Biosimilar medications for adalimumab and etanercept are rare in the prospective data and are assumed to have the same price as the standard medication.

Medication dosage can depend on subtype, body surface, weight, age, and gender. By modelling individual patients, the impact of the aforementioned variables on dosage can easily be implemented especially with weight and age as dynamic variables which increase over the treatment course. However, the relationship between these variables and medication dosage could not be determined and requires further investigation. Therefore, medication dosage was modelled the same for each patient and did not depend on subtype, body surface, weight, age, and gender. Dosage was not modelled as a stochastic variable as no explainable patterns could be detected in the monthly medication dosage for etanercept and adalimumab, although methotrexate showed signs of a normal distribution. Due to the relatively low-cost impact of methotrexate the choice was made to not model it as a stochastic variable. The monthly dosage of etanercept, adalimumab, and methotrexate in the February 2021 data can be found in Appendix A. Monthly medication dosage was thus set as the same average for each patient. The average cost per dosage could not be accurately determined as prices are dependent on the size of a single dose and are dependent on Canadian or Dutch prices. Instead, the average Dutch medication price for etanercept, adalimumab, and methotrexate as reported in the supplementary Table S1 of Kip et al. (2020) were used. Adalimumab and etanercept are often used in combination with methotrexate. This is known as combination therapy and occurs 88% and 80% of the time for adalimumab and etanercept respectively in the prospective data, see Table 11. Estimated methotrexate costs per cycle (€75.60)

are low compared to both etanercept (€1,953.60) and adalimumab (€2,487.84). Adalimumab is the most expensive monthly drug at €2,487.84 excluding combination therapy.

	Estimated monthly dosage (mg)	Estimated costs per dosage (€/mg)	Estimated cycle* costs	Probability combination therapy with methotrexate
Methotrexate	56	€0.45	€75.60	NA
Adalimumab	73	€11.36	€2487.84	0.88
Etanercept	148	€4.40	€1953.60	0.80

*Table 11: Estimated monthly medication dosage, costs, and probability of combination therapy for bDMARDs. *3 months per cycle.*

As medication discontinuation due to inactive disease is not modelled, medication costs do not depend on disease activity. As stated previously, an investigation in how and when medication is discontinued after achieving inactive disease in cohort 3 could provide insight into how this process should be modelled.

6.2 Indirect and Direct Resource Costs

The goal of the model is to estimate the cost-effectiveness from a societal perspective. Therefore, direct and indirect costs were included. The February 2021 data could not be used to estimate these costs instead, the master thesis of Van den Berg (2019) was used. Direct resource costs included imaging, admission, surgeries, laboratory tests, consultations, emergency department (ED) visits, GP visits, medical devices. Indirect costs include non-medical supplements, transportation costs, other out of pocket costs, social care services, and productivity loss of the patient and parent. Annual costs were reported per subtype. Oligoarticular ANA+ and oligoarticular ANA- were classified as oligoarticular persistent. Average costs of all modelled subtypes were €838 per month while oligoarticular persistent had the lowest cost at €803 per month, see Table 12. An overview of the costs per subtype as reported by Van den Berg (2019) can be found in Appendix B.

Subtype	Enthesitis	Oligoarticular Persistent	Oligoarticular Extended	Polyarticular RF-
Mean direct & indirect costs	€845	€803	€858	€861

Table 12: Estimated mean direct and indirect monthly resource costs per subtype.

Van den Berg (2019) did not report on the distribution resource costs had. Furthermore, no standard deviation for indirect costs were reported as these were estimated using literature and no standard deviation was reported for the total direct resource cost per subtype. Resource costs are often right-skewed distributed with the majority of patients having low costs while a minority have relatively high resource costs. This is true for the resource costs of JIA patients according to Thornton (2008). The reported mean and standard deviation for the annual direct costs (including

medication) of JIA were €2,391 and €1,585 respectively. A different study of direct (including medication) and indirect cost of JIA in the UK estimates that the mean total costs are £38,546 with a standard deviation of £28,568 (Kuhlmann, 2016). For reference, mean annual direct costs (including medication) ranged between €2,378 - €7,016, and indirect costs between €1,470 - €2,184 depending on the four subtypes listed above (Van den Berg, 2019). The discrepancy in reported mean and standard deviation costs highlights the heterogeneity of direct and indirect costs which can vary due to methodology and study population (Kip, 2019). Cost distributions need to be further investigated after the full prospective data become available. The standard deviation reported by Kuhlmann (2016) is 74% of the mean costs while it is 66% of the mean costs reported by Thornton (2008). The standard deviation is set at 70% (average of both sources) of the mean direct and indirect costs for all subtypes.

Using the standard deviation and select subtype mean resource costs, the alpha and beta were calculated for use in the gamma distribution using the following two formulas:

$$\alpha = \frac{mean^2}{SD^2} \qquad \beta = \frac{mean}{SD^2}$$

At the start of the model resource costs per patient are drawn from the gamma distribution. This is assumed to be resource cost of active disease for that specific patient. If a patient reaches inactive disease the resource costs are set at 14% of their active disease resource costs as reported by Minden (2004).

6.3 Utility

To measure the quality of life of a patient in a specific health state, utility values (HSUV) are used. Utility values can range between negative infinity and 1. A utility value of 0 indicates death and 1 indicates perfect health while negative values indicate a quality of life worse than death. As observed by Grazziotin et al. (2020) there are critical gaps in literature reporting on utility values of JIA. Therefore, the prospective data will be one of the most complete studies on utility values for patients with JIA. In the prospective data EQ-5D-5L questionnaires are collected. EQ-5D-5L is a simple, generic, and standardized measurement of the health-related quality of life (HRQoL). Five questions are asked about mobility, ability of the patient to look after themselves, ability to take part in usual activities, discomfort, and feeling worried. These five dimensions are rated on a scale of 1 to 5. As EQ-5D-5L is generic and not specific the resulting utility values from the EQ-5D-5L are comparable with different diseases. Utility is calculated from the EQ-5D-Y-5L questionnaires using a value set which is unique for children, and per country. As of April 2021, only the adult version of the EQ-5D-5L value set is available. It is assumed that using the adult value set will yield less accurate but consistent results for the utility values of children compared to using the child value set. It is assumed to be less accurate because the utility values derived from the adult value set is expected to be further from the true or accepted utility values than those that would have been derived from the child value set. Consistency is assumed because it is expected that both the utility derived from the child and adult value set for severe JIA subtypes will be lower

than patients with less severe JIA subtypes. The function eq5d from the R package eq5d version 0.8.1 is used to determine the utility values from the EQ-5D-5L questionnaire found in the February 2021 data. As noted in the Chapter "Prospective Data" the number of EQ-5D-5L questionnaires collected in the February 2021 data were limited and extremely difficult to synchronize with other databases containing medication history, disease status, and patient characteristics. Furthermore, half of the patients did not fill out an EQ-5D-5L questionnaire and those that did fill it, filled it only out twice on average while at least five questionnaires are expected for the full follow up. As a result, only a very limited analysis could be made using the utility values while a more extensive analysis is required to populate the model in a valid manner. EQ-5D-5L questionnaires were filled out by both the child and parent as proxy. As there are more entries available for the proxy reported (215 patients) EQ-5D-5L than the self-reported (87 patients) and parents are moderate to good proxy reporters (Brunner, 2004), the proxy data set is used.

The utility is calculated for all entries of the EQ-5D-5L form of patients with defined subtypes and baseline visits. The utility of patients with active disease (120 patients) per subtype which are not stratified by medication, treatment length or any other variable other than subtype and disease status are shown in Table 13.

Subtype	**Number of patients**	**Utility (mean)**	**Delta from overall mean (Δ)**
Enthesitis	16	0.690	0.065
Oligoarticular *	26	0.663	0.038
Oligoarticular Extended	13	0.654	0.029
Oligoarticular Persistent	13	0.744	0.119
Polyarticular RF-	34	0.542	-0.083
Polyarticular RF+ *	4	0.711	0.086
Psoriatic*	3	0.714	0.089
Systemic*	11	0.461	-0.164
All Patients	120	0.625	0

*Table 13: The mean utility per subtype of all patients with active disease. * Subtypes not included in the model but are mentioned here for validation purposes. RF = Rheumatoid factor.*

Patients with active disease and in subtypes oligoarticular extended, systemic, and polyarticular RF- have the lowest utility values. This is in line with subtype definitions which classifies these subtypes as most severe. Polyarticular RF+ is an outlier but also has a very low entry count. The utility results and comparative delta difference per subtype of the mean utility 0.625 of active disease suggest the utilities values calculated with the adult value set from the EQ-5D-5L questionnaire are at least consistent.

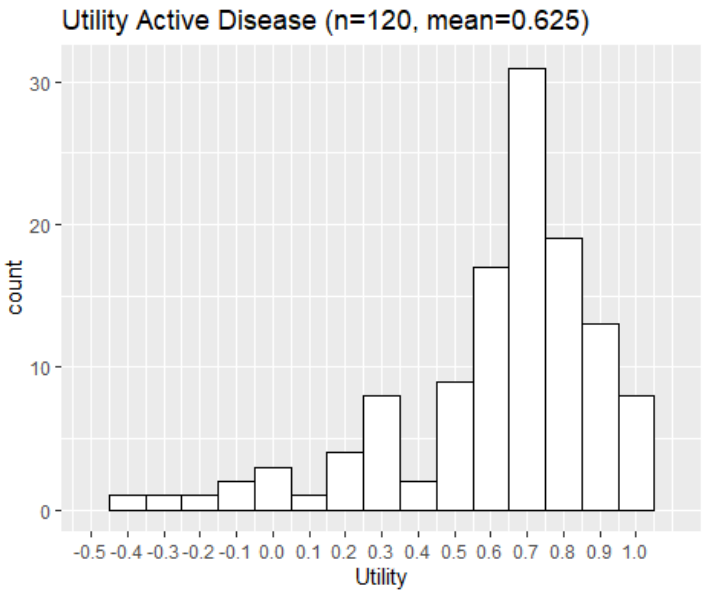

Figure 6: Histogram of the utility of all patients with active disease.

The distribution of utility of all patients with active disease is left-skewed, as shown in Figure 6. Furthermore, a small number of utility values are negative. The choice was made to model utility of active disease with a truncated normal distribution where values cannot not exceed 1 resulting in a left-skewed distribution. A truncated normal distribution was used instead of a beta distribution as it allows for the generation of negative values. For the modelling of the independent or "average" subtype the mean was set to 0.625 and the standard deviation to 0.282 as calculated from all the 120 patients with active disease. To draw the subtype specific utility the mean and standard deviation were calculated from the patients with active disease diagnosed with the respective subtype as presented in Table 14.

Subtype	**Number of patients**	**Utility μ**	**Utility σ**
Enthesitis	16	0.690	0.203
Oligoarticular extended	13	0.654	0.332
Oligoarticular persistent	13	0.744	0.252
Polyarticular RF-	34	0.542	0.324
Independent of subtype	120	0.625	0.282

Table 14: Input (μ,σ) for the truncated normal distribution for the four subtypes.

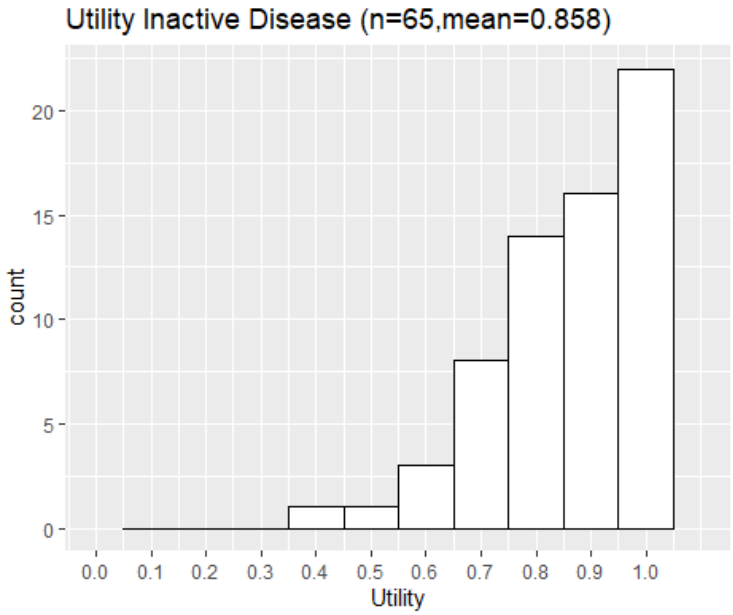

Figure 7: Histogram of the utility of all patients with inactive disease

There were 65 patients whose disease was inactive with a mean utility of 0.858. The distribution is shown in Figure 7. Utility improvement in a health state with inactive disease was modelled by an absolute utility increase of 0.233 based on the difference of the mean utility; 0.625 and 0.858 for active and inactive disease respectively, independent of subtype. There was not enough data to calculate the subtype specific utility increment due to inactive disease. All four subtypes are therefore assumed to experience the same utility improvement due to inactive disease. An absolute bonus of 0.233 was chosen instead of a percentage increase (37%) as this would have resulted in disutility for patients starting with a negative utility. Furthermore, patients with utilities close to 0 would experience little to no increase in utility with a percentage increase. A beta distribution or triangular distribution could have been created from which utility of inactive was drawn. However, this would result in a fraction of patients having lower utility in inactive disease than in active disease. Furthermore, the use of uniform or triangular distributions are not recommended according to the ISPOR Modelling Good Research Practices (Briggs et al., 2012). An alternative for the utility of inactive disease is to set it to 1 as done by Luca et al. (2016), but this is not backed up by evidence. It could be possible that utility in long term inactive disease approaches 1, but this could not be confirmed up by literature nor by the February 2021 data.

Base active utility and inactive utility are assumed to be independent of medication. However, a patient in the health state active disease while on medication plus responding is assumed to experience incremental utility benefits. If there is no utility benefit from medication, it is assumed that the clinician changes medication. The utility benefit of response to treatment could not be estimated using the February 2021 data. Literature reporting on utility improvement is very scarce. The JIA cost-effectiveness models primarily used the study by Prince et al. (2011) reporting on

the HUI3 outcome of 49 patients registered in the Dutch national ABC register from 2003 to 2006. This study investigates the response of polyarticular JIA to etanercept treatment at a 3, 15, and 27 months follow up period. Starting utility was 0.53 which improved to 0.69 after 3 to 15 months (Δ +0.16), to 0.74 (Δ +0.21) after 15-27 months, and 0.78 (Δ +0.25) after 27 months. In the ABC register inactive and active disease patients were included, which is why the utility improvement after 27 months of treatment could exceed the modelled 0.233 utility improvement. It should be noted that the starting utility of 0.53 reported by (Prince et al., 2011) is close to the mean utility (0.542) for patients with active disease and polyarticular RF-in the February 2021 data, see Table 13. For consistency and simplification purposes, it is assumed utility improvement on etanercept is 0.16 for the first 4 cycles (1 year) and 0.21 for the second year (5-8) cycles, see Table 9. Similar utility values for adalimumab could not be found. Shepherd (2016) conducted a clinical effectiveness review on the different efficacy of three anti-TNF bDMARDs (abatacept, adalimumab, etanercept) and tocilizumab and concluded that no clinical difference could be found. Therefore, it was assumed that all four bDMARDs resulted in the same utility value for patients. This assumption was also used in the Roche and Bristol-Myers Squibb submitted to the cost-effectiveness model (Shepherd, 2016). However, the probability of inactive disease, flaring, and discontinuation was not the same for the four anti-TNF bDMARDs investigated. Furthermore, UCAN CAN-DU experts noted that assuming bDMARDs categories, such as anti-TNF bDMARDs, have the same efficacy and thus combining them as "one" medication was not desirable. Nonetheless, due to an absence of alternative utility data it is assumed that utility is the same for etanercept and adalimumab.

No reliable sources could be found for the utility of response to methotrexate treatment. Shepherd (2016) models no utility benefit in methotrexate, while the other models model utility improvement as a result of methotrexate indirectly through achieving ACR pedi response or inactive disease. It is assumed that similar utility improvement for methotrexate in the response health state are experienced as in the first bDMARD health state. A 0.025 utility increment per response cycle is assumed for a maximum of 0.2 utility for 8 consecutive response cycles, see Table 16. As with the etanercept and adalimumab this is assumed to be the same for all subtypes and the utility bonus of inactive disease (0.223) is not exceeded. A slightly slower and smaller total utility increment is chosen to model the improved health effects of a bDMARD over methotrexate as observed in the literature review of early bDMARD use.

First bDMARD	Utility increment	Source
Base* (1st cycle bDMARD)	0	Assumed
Response first 4 cycles	0.160	(Prince, 2011)
Response 4 cycles or more	0.210	(Prince, 2011)
Inactive disease	0.223	Prospective Data

Table 15: Utility improvement response first bDMARD.

MTX	Utility Increment	Source
Base* (1st cycle MTX)	0	Assumed
Response per cycle (max 8 cycles)	0.025	Assumed
Greater than 8 cycle response	0.200	Assumed
Inactive disease	0.223	Prospective Data

Table 16: Utility improvement response MTX.

To conclude, modelling the individual patient's utility values is challenging due to a lack of data and sources. Utility for disease status, subtype, follow up cycles in inactive disease or response related to the three DMARDs needs to be further investigated when the full prospective data become available. Key decisions as to how to model utility improvement due to inactive disease or response could then better be motivated which would greatly improve the validity of the model and leverage the full advantage of the individual simulation approach of the STM model.

6.4 Transition Probabilities

Patients can progress from their current health state to the next health state in each cycle depending on the transition probabilities. For treatment with methotrexate, adalimumab, and etanercept inactive disease, no response, response, or adverse events resulting in discontinuation can occur. In inactive disease a patient can either remain inactive or flare resulting in active disease. To estimate the probability of inactive disease, the February 2021 data could not be used due to the large number of missing data, inconsistent definitions of inactive disease, and challenges with synchronizing the treatment with a DMARD and disease status. In literature, estimating probability of inactive disease is challenging as studies often report on only one DMARD and for one subtype. Studies also often only report on discontinuation due to inactive disease instead of inactive disease irrespective of treatment discontinuation or continuation. Furthermore, different time horizons and different definitions for inactive disease are used.

To estimate the probability of inactive disease the clinical trial, ACUTE, estimating the impact of aggressive bDMARD (Tynjala, 2011) was used as inactive disease was defined using the Wallace criteria and the treatment continuation of methotrexate and infliximab (anti-TNF bDMARD) were investigated. Only early disease course polyarticular patients were included. Tynjala (2011) reported 68% of patients treated with infliximab achieved inactive disease in 54 weeks as opposed to 33% for methotrexate only. As infliximab is an anti-TNF bDMARD and no other sources could be found for adalimumab and etanercept it assumed that the probability of inactive disease of infliximab is the same as adalimumab and etanercept. The probability of achieving inactive disease for a 3-month cycle is set at 17% and 8% for the first bDMARD and methotrexate respectively, see Table 17. A systematic literature review was conducted by Shepherd (2016) of studies reporting on treatment discontinuation due to no response or adverse events, and the probability of flaring for adalimumab, etanercept as well as abatacept and tocilizumab for a model estimating the cost-effectiveness of all four bDMARDs. The model uses a probability of discontinuation of etanercept and adalimumab due to no response of 2.9% and 3.5% respectively per 3-month cycle.

Treatment discontinuation for methotrexate is not reported. In the clinical study (TREAT) conducted by Wallace et al. (2012) 9 of the 43 patients (20.9%) followed for a 12-month period discontinued methotrexate due to no response. For the model the probability of no response for methotrexate 5.2% per 3-month cycle is assumed. Flaring for methotrexate is set at 25% per cycle while it is set to 9% and 14% for etanercept and adalimumab respectively (Shepherd, 2016). The probability of discontinuation due to adverse events is higher for both adalimumab and etanercept compared to methotrexate (1.8%, 1.4%, and 0.5% respectively), (Shepherd, 2016).

Health state	Probability per cycle	Source
Methotrexate		
Inactive	0.080	(Tynjala, 2011)
No Response	0.052	(Wallace, 2012)
Adverse Event	0.005	(Shepherd, 2016)
Response	0.863	Assumed
Methotrexate Inactive		
Flare	0.250	(Shepherd, 2016)
Inactive	0.750	(Shepherd, 2016)
Adalimumab		
Inactive	0.170	(Tynjala, 2011)
No Response	0.035	(Shepherd, 2016)
Adverse Event	0.018	(Shepherd, 2016)
Response	0.777	Assumed
Etanercept		
Inactive	0.170	(Tynjala, 2011)
No Response	0.029	(Shepherd, 2016)
Adverse Event	0.014	(Shepherd, 2016)
Response	0.787	Assumed
Adalimumab Inactive		
Flare	0.140	(Shepherd, 2016)
Inactive	0.860	(Shepherd, 2016)
Etanercept Inactive		
Flare	0.090	(Shepherd, 2016)
Inactive	0.910	(Shepherd, 2016)

Table 17:Transition probability health states per DMARD medication.

The effects of subtype, treatment duration, and health state history (number of flares/achieving inactive disease) on the transition probabilities could not be determined. It is therefore assumed that all transition probabilities are the same for subtype, treatment duration, and health state history. All sources use the subtype polyarticular (RF- & RF+) as the investigated JIA population while enthesitis, oligoarticular persistent, and oligoarticular extended are also used in model.

6.5 Discounting

Discounting is applied for costs and utility after one year. The discount is set at 1.5% for utility and 4% for cost as recommended by Dutch guidelines (Zorginstituut Nederland, 2016).

6.6 Modelling Software

The programming language R, version 3.6.1, was used to model and simulate the STM using the package simmer version 4.4.2.

6.7 Conclusion

In this chapter we answered the research question:
"What data will be used to populate the model?"

To populate the individual based STM, we used data already available from the prospective study in February 2021 and literature. The patient starting utility was modelled using the February 2021 data using a truncated normal distribution and dependent on the patients' subtype. The February 2021 data was also used to estimate the utility increase after achieving inactive disease and the average monthly dosage of adalimumab, etanercept, and methotrexate. Literature was used to model the patients initial direct and indirect resource costs using a gamma distribution which also depended on the patients' subtype. Cost of medication was estimated using Dutch prices. All probabilities of events (no response, adverse events, inactive disease, flaring) for the three medications were based on literature, which all only investigated the subtype polyarticular JIA. Increase in utility due to response for etanercept and adalimumab was also estimated using literature based on polyarticular JIA. Utility improvement for etanercept and adalimumab was assumed to be the same as they are both anti-TNFs bDMARDs. Methotrexate improvement due to response could not be found and we assumed utility improvement was slightly worse than that of etanercept and adalimumab. Utility improvement and probability of events were assumed to be the same for all four JIA subtypes modelled (polyarticular RF-, oligoarticular persistent, oligoarticular extended, and enthesitis), even though the utility improvement and probability of events are only based on the subtype polyarticular JIA.

7. Simulation, methods, and Results

In this chapter the simulation experiments are defined, and results presented. The goal is twofold: 1) to provide insight into the workings of the model and 2) estimate cost-effectiveness outcomes of early bDMARD treatment compared with conservative treatment.

7.1 Simulation Parameters

The variables that can be altered in the simulation model are listed in Table 18.

	Range
Time horizon	0-6 years (3 years or 12 cycles default)
First bDMARD	Etanercept or Adalimumab
Subtype	Polyarticular RF- Oligoarticular persistent Oligoarticular extended Enthesitis
Switch strategy for first bDMARD	Conservative vs Early
No response MTX probability	0-1* (0.052 default)

*Table 18: Experimental parameters that can be changed in the model. *(0 = no patients switch to the first bDMARD, 1 = all patients switch to the first bDMARD.*

A three-year time horizon (12 cycles) is considered as the default time horizon. Subtypes can be set to one of the four specific subtypes. Subtype costs and utility are drawn from the respective distribution (gamma and truncated normal) using the input parameter defined in Section 5.2 "Indirect and Direct Resource Costs" and Section 5.3 "Utility". The probability of events is the same for all subtypes. As the majority of studies used to populate the model are based on only the subtype polyarticular, polyarticular RF- is set as the default subtype for which the majority of scenarios will be run.

The model estimates the cost-effectiveness of early bDMARD use by comparing the two switching strategies, as visualized in Figure 5, only if a patient does not respond to methotrexate in the first cycle. The conservative switching strategy means a patient remains one cycle extra in methotrexate no response before switching to the first bDMARD. The early switching strategy means the patient switches immediately to the first bDMARD after experiencing one cycle of no response on methotrexate. If a patient does not respond to methotrexate after the first cycle it is assumed that they switch immediately (early). The advantages of bDMARD use over methotrexate included in the model are higher probability of inactive disease, lower chance of no response, lower chance of flaring, and better utility improvement over 8 cycles as defined in Chapter 5.

7.2 Methods & Simulation Output

The simulations compare the conservative strategy and early switch bDMARD strategy on costs and effectiveness. The key performance indicators are the incremental cost-effectiveness ratio (ICER), net monetary benefit (NMB), and net health benefit (NHB). The ICER shows the costs of one additional unit of outcome gained using one strategy compared to another and is calculated using the formula:

$$ICER = \frac{(Total\ Costs_A - Total\ Costs_B)}{(Effectiveness_A - Effectiveness_B)}$$

where *A* represent the early switching strategy and *B* the conservative switching strategy. Effectiveness is the health outcome measured using the total quality adjusted life years (QALYs). QALYs are calculated by multiplying the years spent in a certain utility by the utility value. If a patient is in perfect health (utility = 1) for one-year the patient will experience 1 QALY. 2 QALYs if two years of perfect health are experienced. 0.5 QALYs for one year experiencing a utility of 0.5 or half a year of experiencing a utility of 1. The total costs are equal to the medication costs, direct costs, and indirect costs. As the difference between the two strategies is small, the incremental costs and QALYs will also be small. It is beneficial to also calculate the net monetary benefit (NMB) and net health benefit (NHB) (Paulden, 2020). The NMB and NHB are calculated per strategy using the formulas:

$$NMB = Effectiveness \times WTP - Total\ Costs$$

$$NHB = Effectiveness - \frac{Total\ Costs}{WTP}$$

where the effectiveness is also measured in QALYs and WTP stands for the willingness to pay threshold. The WTP threshold indicates what society is willing to pay for an improvement in health and varies between stakeholder and country. In the context of this thesis the WTP is the maximum we are willing to pay for an increase in 1 QALY due to early bDMARD treatment. We use a WTP of €50,000 noting that in the Netherlands WTP commonly ranges from €20,000 to €80,000 with a WTP of €80,000 used for severe diseases and €20,000 used for less impactful interventions such as vaccination programs and prevention (Zorginstituut Nederland, 2015). The NMB indicates the net monetary gain of a strategy by subtracting the cost of treatment from the monetary opportunity cost of funding the treatment strategy. The NHB indicates the net health gain as a result of using a treatment strategy minus the health opportunity cost of funding the treatment strategy and is expressed in QALYs. The highest NMB and NHB indicates that a strategy results in highest monetary gain and highest health gain respectively and can thus indicate which strategy is the most

cost-effective. Furthermore, by calculating the fraction of all runs where the NMB of the early strategy is greater than the NMB of conservative strategy, the probability that the early switching strategy is cost-effective for a given WTP threshold can be calculated. The fraction of positive NHB is exactly the same as the fraction of positive NMB.

The same random number generators and seed order are used per simulation in order to allow for reproducibility and limit artificial variation introduced into the simulation results. For all experiments the time on methotrexate, the number of patients achieving inactive disease, the time in inactive disease, and adverse events experienced in addition to the total costs and total QALYs are presented, as defined in Table 19.

	Description
Time in MTX	Mean time spent of patients in health states with methotrexate (MTX) treatment (Response, no response if treatment strategy 2, and inactive disease on MTX).
Achieved inactive disease	Percentage of patients that achieve inactive disease at least once (MTX or bDMARD).
Time inactive	The mean amount of time a patient spends in the health state inactive disease (MTX or bDMARD)
Adverse Events	Mean number of patients that experience an adverse event resulting in the treatment discontinuation of methotrexate, first or second bDMARD.
Total Costs	The mean total costs of the patients.
Total QALYs	The mean total QALYs representing the health outcome of the patients.

Table 19: Description of outcomes from the simulation.

7.3 Simulation Results

To determine the effect of the number of patients used in the simulation, the base case simulation is run once for 1,000 and 10,000 patients using etanercept as the first bDMARD, polyarticular RF-, the early switching strategy, and with the default methotrexate no response probability.

	1,000 patients		**10,000 patients**	
	Total Costs €	**QALYs**	**Total Costs €**	**QALYs**
Mean	30,029	1.857	29,818	1.815
SD	20,252	0.799	19,439	0.799
SEM	651	0.0253	194	0.008

Table 20: Results of 1 simulation run using etanercept first bDMARD, polyarticular RF-, and early switching strategy on the mean, standard deviation, and standard error of the mean for costs and QALYs.

The mean costs and QALYs estimated by the model are lower for 10,000 patients, as shown in Table 20. As expected, the standard error of the mean for both costs and QALYs is lower for 10,000 patients. A lower standard error of the mean indicates that the estimated mean is closer to the true mean and using 10,000 patients will results in more accurate outcomes. However, computational time increases linearly with the number of patients, and thus increases tenfold when

running with 10,000 patients instead of 1,000 patients. As a result, there is a tradeoff between accuracy and computational time that has to be made. For 1,000 patients the SEM is at around 2% of the total value, which intuitively seems an acceptable level of accuracy. 1,000 is thus an acceptable number of patients, and the only question that remains is whether the additional gain in accuracy for 10,000 patients is worth the additional computation time. When switching to 10,000 patients, SEM decreases with a factor of around 3, while computation time increases with a factor of 10. As computation time increases much more than accuracy, and 1,000 patients already yields an acceptable level of accuracy, we decided to use 1,000 patients for the simulations.

The base case simulation is considered polyarticular RF- with a 3-year time horizon and the default parameters as described in the previous section and Chapter 5.
Four scenarios are run to test the impact of increased probability of no response to methotrexate, subtype, time horizon, and bDMARD as a first line on the model outcomes. For the base case and scenario, 1,000 simulations are run with 1,000 patients each.

Base case: Conservative versus early switching strategy

For the base case simulation, the subtype is set to polyarticular RF- and the time horizon is set to 3 years (12 cycles). The early switching strategy is compared to the conservative switching strategy. Both the impact of etanercept and adalimumab as the first bDMARD on the cost-effectiveness of the two strategies is simulated.

Switching Strategy	Time in MTX *months (%)*	Achieved inactive disease *%*	Time inactive *months (%)*	Adverse Events	Total Costs €	QALYs
Conservative	23.711 (65.9%)	69.5%	7.660 (21.3%)	0.059	€29,742	1.803
Early	23.550 (65.4%)	69.6%	7.750 (21.5%)	0.059	€29,787	1.806
					Δ 45	Δ 0.003

Table 21: Average results base case, etanercept first bDMARD.

Switching Strategy	NMB	NHB	Incremental NMB	Incremental NHB	Probability Positive NMB/NHB	ICER
Conservative	€60,422	1.208	*Reference*	*Reference*	*Reference*	*Reference*
Early	€60,502	1.210	€82	0.02	62.2%	€17,729

Table 22: Cost-effectiveness results base case, etanercept first bDMARD.

Switching Strategy	Time in MTX *months (%)*	Achieved inactive disease *%*	Time inactive *months (%)*	Adverse Events	Total Costs €	QALYs
Conservative	23.711 (65.9%)	69.3%	7.478 (20.8%)	0.065	€30,866	1.802
Early	23.550 (65.4%)	69.5%	7.562 (21.0%)	0.065	€30,940	1.804
					Δ €74	Δ 0.002

Table 23: Average results base case, adalimumab first bDMARD.

Switching Strategy	NMB	NHB	Incremental NMB	Incremental NHB	Probability Positive NMB/NHB	ICER
Conservative	€59,210	1.184	*Reference*	*Reference*	*Reference*	*Reference*
Early	€59,260	1.185	€50	0.01	57.7%	€29,727

Table 24: Cost-effectiveness results base case, adalimumab first bDMARD.

The difference in total costs and effectiveness (QALYs) of the early switching strategy for both etanercept (Table 21) and adalimumab (Table 23) is incredibly small. The small difference is a result of the minimal impact of the early switching strategy on the average time spent in methotrexate before switching to the first bDMARD. This is logical as only one extra cycle is spent in methotrexate for the conservative strategy. An extra cycle of methotrexate is only relevant for patients who have no response to methotrexate in the first cycle, which is a small group as the probability of no response per cycle is 5.2%. The number of adverse events resulting in treatment discontinuation, number of patients with inactive disease, and average time spent in inactive disease also varies little due to the small effect of the switching strategies.

Adalimumab has higher total costs and lower QALYs than etanercept. Moreover, time spent in inactive disease is lower and the percentage of patients achieving inactive disease is lower as well while adverse events are slightly higher. This is due to the higher flare rate of adalimumab compared to etanercept and the higher rate of adverse events resulting in treatment discontinuation. ICER for the early switching strategy is €17,729 and €29,727 for etanercept (Table 22) and adalimumab (Table 24) respectively, but is highly uncertain due to the small difference in QALYs and costs. Both the NMB and NHB for early and conservative strategies is greater for etanercept indicating that etanercept as the first bDMARD is more cost-effective than adalimumab. For both adalimumab and etanercept the early switching strategy results in increased costs and higher QALYs. The ICER for early switching strategy is below the WTP threshold of €50,000 and the incremental NMB as well as the NHB is higher for the early switching strategy indicating that it is more cost-effective to use an early switching strategy for both bDMARDs. However, as the ICER is highly unstable and the incremental NHB and NMB are very small due to the small difference in costs and QALYs between the strategies, this conclusion needs to be treated with caution.

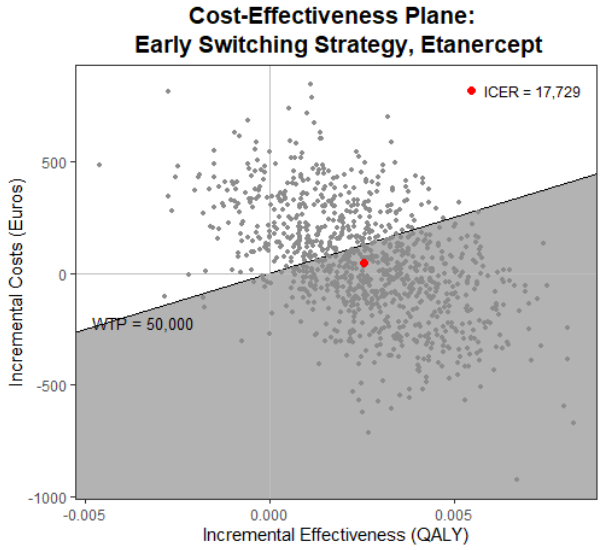

Figure 8: Cost-effectiveness plane early switch strategy etanercept first bDMARD.

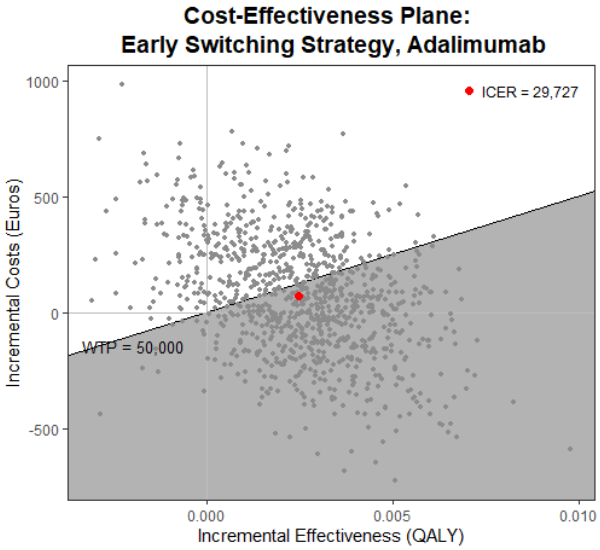

Figure 9: Cost-effectiveness plane early switch strategy adalimumab first bDMARD.

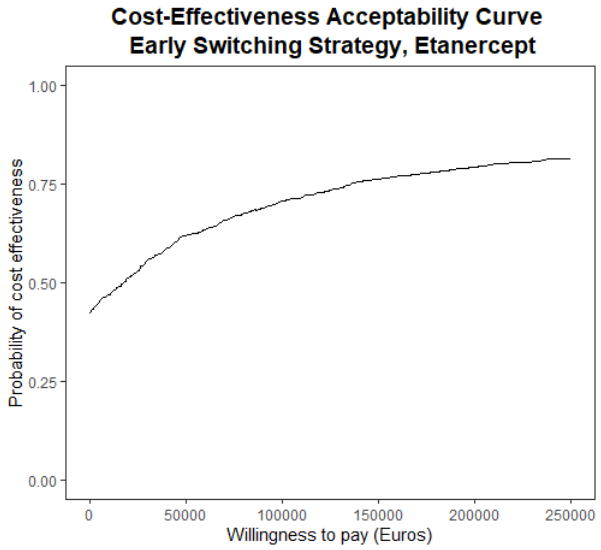

Figure 10: Cost-effectiveness acceptability curve early switch strategy etanercept first bDMARD

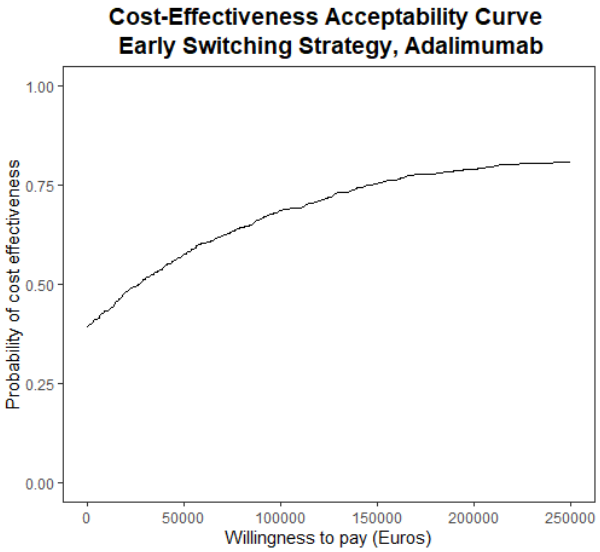

Figure 11: Cost-effectiveness acceptability curve, early switch strategy adalimumab first bDMARD.

The cost-effectiveness plane of etanercept (Figure 8) and adalimumab (Figure 9) show that a majority of the 1,000 simulation runs result in the early switching strategy having a positive incremental costs (etanercept 57.6%, adalimumab 60.9%) and positive incremental effectiveness (etanercept 90%, adalimumab 89.6%). Runs can be found in all four quadrants of the cost-effectiveness plane, which highlights instability of the incremental costs and incremental effectiveness. The majority of runs are below the WTP threshold of €50,000 for etanercept (62.0% Table 22) and adalimumab (57.7%, Table 24), from which we can conclude that the early switching strategy is cost-effective 62.0% of the time for etanercept as the first bDMARD and the 57.7% of the time for adalimumab as the first bDMARD for a WTP of €50,000. The cost-

effectiveness acceptability curve of both etanercept (Figure 10) and adalimumab (Figure 11) show that the probability of the early switching strategy being cost-effective never reaches 100% for any ICER, instead plateauing at 90% for etanercept and 89.6% for adalimumab. From the cost-effectiveness plane and cost-effectiveness acceptability curve, as well as the low fraction of positive NHB/NMB of the early switching strategy, we can conclude that large uncertainty exists for the cost-effectiveness of the early switching strategy.

To gain insight in the number of patients in each treatment line at the end of the model and the average number of cycles extrapolated after the second bDMARD fails, one simulation using 1,000 patients is run for both switching strategies and both bDMARDs. The majority of patients stay in methotrexate until the end of the model (≈60%), see Table 25. The remaining patients receive at least one bDMARD. Around 33% patients only receive one line of bDMARD and 5% a second line bDMARD. A very small number of patients fail the second bDMARD due to a limited 3-year time horizon, consequently the number of cycles extrapolated for both strategies is extremely low; ranging between 0.005 and 0.014. For the early switching strategy, the distribution of patients is slightly tilted towards later cycles. The difference between etanercept and adalimumab is very small.

	Etanercept		**Adalimumab**	
	Conservative	**Early**	**Conservative**	**Early**
Number of Patients				
Methotrexate	609	596	609	599
First line bDMARD	323	349	306	327
Second line bDMARD	61	44	77	66
Extrapolated bDMARD	7	11	8	8
Mean number of cycles extrapolated	0.009	0.012	0.005	0.014

Table 25: Patient progression in treatment lines for the base case (1000 patients and 12 cycles).

Scenario 1: Increased methotrexate no response

As noted in the results from experiment 1 and 2, the average time spent in methotrexate before switching to first bDMARD barely changes due to using the early or conservative switching strategy due to the low probability of no response (0.052). To make this difference more pronounced the probability of no response to methotrexate is increased to 0.2, 0.4, and 0.6. This scenario is not a reflection of current clinical reality or practice, instead it is used to test the model and results from the base case. For this scenario only etanercept is used and the subtype is set to polyarticular RF-.

MTX No response	Switching Strategy	Time in MTX *months (%)*	Achieved inactive disease *%*	Time inactive *months (%)*	Adverse Events	Total Costs €	QALYs
0.2	Conservative	18.975 (52.7%)	73.7%	8.928 (24.8%)	0.066	€32,587	1.811
	Early	18.352 (51.0%)	74.4%	9.291 (25.8%)	0.068	€32,746	1.821
						Δ €159	Δ 0.010
0.4	Conservative	13.761 (38.2%)	78.2%	10.344 (28.7%)	0.074	€35,678	1.822
	Early	12.569 (34.9%)	79.1%	11.046 (30.7%)	0.076	€35,983	1.842
						Δ €305	Δ 0.020
0.6	Conservative	10.037 (27.9%)	81.3%	11.374 (31.6%)	0.079	€37,905	1.832
	Early	8.230 (22.9%)	82.8%	12.443 (34.6%)	0.083	€38,357	1.861
						Δ €452	Δ 0.029

Table 26: Average results scenario 1, etanercept first bDMARD.

MTX No response	Switching Strategy	NMB	NHB	Incremental NMB	Incremental NHB	Probability Positive NMB/NHB	ICER
0.2	Conservative	€57,995	1.160	*Reference*	*Reference*	*Reference*	*Reference*
	Early	€58,995	1.166	€330	0.007	81.4%	€16,245
0.4	Conservative	€55,440	1.109	*Reference*	*Reference*	*Reference*	*Reference*
	Early	€56,106	1.122	€666	0.013	94.0%	€15,702
0.6	Conservative	€53,686	1.074	*Reference*	*Reference*	*Reference*	*Reference*
	Early	€54,694	1.094	€1,008	0.020	99.3%	€15,487

Table 27: Cost-effectiveness results scenario 1, etanercept first bDMARD.

As a result of the increase in probability of methotrexate no response the difference in time spent in methotrexate before switching to the first bDMARD for both strategy increases. A no response probability of 0.2 results in a 0.6-month difference, while a no response probability of 0.6 results in a 1.8-month difference (Table 26) edging closer to the 3-month difference between the two switching strategies. As a result, difference in costs and effectiveness (QALYs) of the two switching strategies also increases, making the effects of the two strategies more pronounced. However, the difference in cost and effectiveness for 0.6 methotrexate no response is still only

€452 and 0.029 QALYs respectively. This highlights the limited impact the switching strategies have on the total costs and effectiveness of JIA treatment using a 3-year model time horizon even when artificially increasing the no response to methotrexate probability. The difference in time in inactive disease, number of patients achieving inactive disease, and adverse events is also more pronounced as methotrexate no response is increased showing that early bDMARD use is more effective in achieving and maintaining inactive disease but results in higher adverse events. The difference in adverse events and overall frequency of adverse events is still very small. For methotrexate 0.2, 0.4, and 0.6 no response probability the early bDMARD strategy is more cost-effective as the NMB and NHB are higher than the conservative strategy, Table 27. Furthermore, the ICER decreases from €16,245 to €15,487 and both the incremental NMB and incremental NHB increase as the difference in months to first bDMARD increases indicating that using the early bDMARD at a WTP of €50,000 is cost-effective. Finally, the probability of the difference in NMB and NHB of the two strategies being positive increases with an increase in methotrexate no response indicating a higher confidence in the early switching strategy being cost-effective at a WTP of €50,000.

Scenario 2: Impact of Subtype

Polyarticular RF- is one of the most severe subtypes of JIA with patients experiencing low utility and high costs. Oligoarticular persistent is a less severe subtype resulting in a higher utility and lower costs than polyarticular RF-. To see what the impact is of subtypes is on the cost-effectiveness of early bDMARD treatment we run the model for oligoarticular persistent and compare the outcomes to polyarticular RF-. Methotrexate no response probability is set to 0.6 instead of the default 0.052 to increase the effects of the treatment strategies. Only etanercept is used, and a time horizon of 12 cycles is used.

	Oligoarticular Persistent		**Polyarticular RF-**	
Switching Strategy	**Total Costs**	**QALYs**	**Total Costs**	**QALYs**
Conservative	€36,434	2.340	€37,905	1.832
Early	€36,938	2.367	€38,357	1.861
	Δ €504	Δ 0.027	Δ €452	Δ 0.029

Table 28: Average results scenario 2, etanercept first bDMARD.

Switching Strategy	NMB	NHB	Incremental NMB	Incremental NHB	Probability Positive NMB/NHB	ICER
Conservative	€80,591	1.612	*Reference*	*Reference*	*Reference*	*Reference*
Early	€81,410	1.628	€819	0.016	97.9%	€19,054

Table 29: Cost-effectiveness results scenario 2: oligoarticular persistent, etanercept first bDMARD.

Switching Strategy	NMB	NHB	Incremental NMB	Incremental NHB	Probability Positive NMB/NHB	ICER
Conservative	€53,686	1.07	*Reference*	*Reference*	*Reference*	*Reference*
Early	€54,694	1.094	€1,008	0.020	99.3%	€15,487

Table 30: Cost-effectiveness results scenario 2: polyarticular RF-, etanercept first bDMARD.

As expected, the subtype oligoarticular persistent results in overall lower costs and overall higher health outcomes (higher QALYs) compared to polyarticular RF- (Table 28) for both switching strategies. The incremental NMB and incremental NHB is higher and the ICER is lower for polyarticular (Table 30) compared to oligoarticular persistent (Table 29) indicating that the early bDMARD strategy is more cost-effective for polyarticular RF-. Both subtypes are cost-effective as both ICERs is below the WTP threshold, and both have a positive incremental NMB and NHB. The difference in cost-effectiveness is due to higher health gain, 0.029 QALYs increase, of the early strategy for polyarticular RF- compared to 0.027 QALYs increase for oligoarticular persistent. Since polyarticular RF- patients have the lowest starting utility in active disease and the maximum utility is capped at 1, the possibility of utility increase due bDMARD treatment is higher. Patients with oligoarticular persistent JIA have a higher starting utility which means the extra utility improvement due to bDMARD treatment is not "included" due to the maximum utility not exceeding 1. The difference in costs of the two treatment strategies is also lower for polyarticular RF- (€452) compared to oligoarticular persistent (€504). This is due to polyarticular RF- having higher direct and indirect costs (excluding medication) than oligoarticular persistent. The early switching strategy increases average inactive disease duration and as only achieving inactive disease reduces these costs (by 14%), polyarticular RF benefits monetarily to a greater extent than oligoarticular persistent. The model thus shows that the early bDMARD switching strategy is more beneficial for severe subtypes with high direct and indirect costs, and low starting utility. Polyarticular RF- and oligoarticular extended thus benefit more from early bDMARD treatment while the less severe subtypes oligoarticular persistent and enthesitis benefit less resulting in better cost-effectiveness for severe subtypes.

Scenario 3: Time Horizon Increase

For this scenario the time horizon is doubled from the default 12 cycles (3 years) to 24 cycles (6 years). Etanercept is set as the first bDMARD, the subtype polyarticular RF- is used, and the probability of methotrexate no response is set to 0.6.

Switching Strategy	Time in MTX *months (%)*	Achieved inactive disease *%*	Time inactive *months (%)*	Adverse Events	Total Costs €	QALYs
Conservative	13.084 (18.2%)	94.3%	31.0 (43.0%)	0.140	€71,388	3.753
Early	11.273 (15.7%)	94.5%	32.0 (44.5%)	0.143	€71,885	3.781
					Δ €497	Δ 0.028

Table 31: Average results scenario 3 (24 cycles), etanercept first bDMARD.

Switching Strategy	NMB	NHB	Incremental NMB	Incremental NHB	Probability Positive NMB/NHB	ICER
Conservative	€116,259	2.325	*Reference*	*Reference*	*Reference*	*Reference*
Early	€117,146	2.343	€886	0.018	84.7%	€17,975

Table 32: Cost-effectiveness results scenario 3 (24 cycles), etanercept first bDMARD.

The doubling of the model time horizon (24 cycles) results, see Table 31, in some logical outcomes when compared to the 12 cycles time horizon for etanercept as the first bDMARD, see Table 26, for a methotrexate no response probability of 0.6. The number of adverse events, percentage of patients achieving inactive disease, total costs, and total health outcome (QALYs) is almost twice as high. What is unexpected is that the percentage of time spent in inactive disease has increased to around 44% from 33%. This is due to a higher percentage of patients reaching a bDMARD and spending more time being treated with a bDMARD for the 25-cycle time horizon. For the 12-cycle time horizon the difference in total costs between both switching strategies is €452 while it is €497 for 24 cycles. The difference in effectiveness of both switching strategies is 0.029 QALYs for 12 cycles and 0.028 QALYs for 24 cycles. As a result, the cost-effectiveness changes little by doubling the time horizon with the ICER changing from €15,487 (Table 27) to €17,975 (Table 32). We therefore conclude that the cost-effectiveness as reported by the model is not sensitive to the doubling of the time horizon.

An overview of number of patients in each treatment line at the end of the 24-cycle time horizon and the number of cycles extrapolated is shown in Table 33. Less than 1% of the patients fail adalimumab (the second bDMARD) and less than 3% of the total cycles are extrapolated

highlighting the minimal impact of the extrapolation after the second bDMARD fails for a time horizon of 24 cycles.

	Conservative	Early
Number of Patients		
Methotrexate	83	92
Etanercept	618	606
Adalimumab	209	216
Extrapolated bDMARD	90	86
Mean number of cycles extrapolated	0.506	0.635

Table 33: Patient progression in treatment lines for scenario 3 (1000 patients and 24 cycles).

Scenario 4: bDMARD first line

Our model investigates the cost-effectiveness of the early switching strategy compared to the conservative switching strategy. With the model we can also investigate what the cost-effectiveness would be if etanercept or adalimumab were used as a first line instead of methotrexate. The subtype is set to polyarticular RF- and 12 cycles are used. For methotrexate first line the early witching strategy is applied while the switching strategy has no impact of on first line etanercept or adalimumab.

DMARD first line	Time in MTX *months (%)*	Achieved inactive disease *%*	Time inactive *months (%)*	Adverse Events	Total Costs €	QALYs
MTX	23.550 (65.4%)	69.6%	7.750 (21.5%)	0.059	€29,787	1.806
ETN	0 (0%)	86.5%	15.593 (45.9%)	0.092	€42,762	1.940
					Δ € 12,974	Δ 0.134

Table 34: Average results scenario 4, etanercept first (ETN) bDMARD.

DMARD first Line	NMB	NHB	Incremental NMB	Incremental NHB	Probability Positive NMB/NHB	ICER
MTX	€60,502	1.210	*Reference*	*Reference*	*Reference*	*Reference*
ETN	€54,232	1.085	€ -6,271	-0.125	0.1%	€96,782

Table 35: Cost-effectiveness results scenario 4, etanercept (ETN) first bDMARD.

DMARD First Line	Time in MTX *months (%)*	Achieved inactive disease *%*	Time inactive *months (%)*	Adverse Events	Total Costs €	QALYs
MTX	23.550 (65.4%)	69.5%	7.562 (21.0%)	0.065	€30,940	1.804
ADM	0 (0%)	86.4%	14.127 (39.2%)	0.119	€48,348	1.929
					Δ €17,408	Δ 0.125

Table 36: Average results scenario 4, adalimumab (ADM) first bDMARD.

DMARD First Line	NMB	NHB	Incremental NMB	Incremental NHB	Probability Positive NMB/NHB	ICER
MTX	€59,260	1.185	*Reference*	*Reference*	*Reference*	*Reference*
ADM	€48,108	0.962	€ -11,152	-0.223	0.0%	€139,133

Table 37: Cost-effectiveness results scenario 4, adalimumab (ADM) first bDMARD.

Etanercept (Table 34) and adalimumab (Table 36) as a first line instead of a second line results in a greater increase in health outcomes (higher QALYs) and a higher total cost. The difference in health outcome is greater for etanercept first line with a 0.134 QALY increase compared to a 0.125 QALY increase for adalimumab first line. Furthermore, the increase in total costs is lower for etanercept (€12,974) than adalimumab (€17,408). As a result of a greater increase in health outcomes and lower increase in total cost the ICER of etanercept first line (€96,782) is lower than adalimumab first line (€139,133) as can be seen in Table 35 and Table 37 respectively. This confirms that in our model etanercept is a more cost-effective bDMARD than adalimumab as also suggested by the results of the base case. Etanercept is more cost-effective due to lower medication costs and a higher effective as a result of a higher probability of achieving as well as maintaining inactive disease, and a lower probability of adverse events compared to adalimumab. Both ICERs are well above the WTP threshold of €50,000, or even €80,000, and the incremental NMB and incremental NMB is negative indicating that first line bDMARD treatment is not cost-effective even when using the highest WTP threshold.

8. Conclusion

To the best of our knowledge this is the first JIA individual based STM and the first model to investigate the cost-effectiveness of early bDMARD treatment using multiple JIA subtypes. We investigated early bDMARD treatment by comparing the early switching strategy and conservative switching strategy to the first bDMARD after a patient does not respond to methotrexate in the first 3 months of treatment initiation. In the conservative strategy a patient waits 3 months before switching to the first bDMARD while in the early strategy a patient switches immediately to the first bDMARD.

We modelled the STM using active disease status and response to DMARD treatment as the primary health states. Patients progressed through three DMARDs starting with methotrexate and adalimumab or etanercept as the second or third DMARD. Patients changed to the next treatment line if the event no response or adverse events resulting in treatment discontinuation occurred. A cycle length of 3 months was used where a patient can respond, achieve inactive disease, flare in inactive disease, not respond, or experience an adverse event as a result of DMARD treatment. For each patient resource costs and starting utility were modelled dependent on the four JIA subtypes; polyarticular RF- JIA, oligoarticular persistent JIA, oligoarticular extended JIA, and enthesitis JIA.

The base case was simulated to investigate the cost-effectiveness of the early switching strategy compared to the conservative strategy using the default parameters. The base case was run for a model time horizon of 3 years using polyarticular RF- and for both adalimumab and etanercept as the first bDMARD. We found that the difference between the treatment strategies was very small. The early switching strategy did result in higher effectiveness and higher total costs than the conservative switching strategy. The resulting ICERs were €17,729 and €29,729 for etanercept and adalimumab respectively, suggesting that the early bDMARD strategy is cost-effective for a WTP of €50,000 and that etanercept is more cost-effective than adalimumab. However, due to the high instability of the ICERs these conclusions should be viewed with caution.

Four scenarios were defined to test the outcomes of the base case. First, we increased the probability of no response to methotrexate from the default of 0.052 up to 0.6 to magnify the impact of the two switching strategies, such that more could be concluded on the cost-effectiveness of the early switching strategy. At 0.6, the difference in cost and effectiveness was still small but resulted in a comparable ICER (€15,487) for etanercept first bDMARD as the base case (€17,729) suggesting that the early switching strategy is indeed cost-effective for a WTP of €50,000. Then we investigated the impact of subtype by comparing the less severe subtype oligoarticular persistent with the more severe subtype polyarticular RF- and showed that it is more cost-effective to use bDMARDs earlier for severe subtypes than for less severe subtypes. For the third scenario we doubled the model time horizon to 6 years for which resulted in minimal changes in the cost-effectiveness of the early switching strategy. Finally, we modelled and simulated etanercept and

adalimumab as a first line instead of methotrexate. The ICERs for etanercept first line was €96,782 and adalimumab first line €139,133, which means that according to our model etanercept is indeed more cost-effective than adalimumab. Both first line etanercept and adalimumab is not cost effective. The results indicate that early bDMARD switching strategy is cost-effective highlighting the need to introduce bDMARDs as soon as patients do not respond to methotrexate. Due to the small difference between the two strategies, high uncertainty of the base case cost-effectiveness outcomes, and the large number of assumptions made in the model this conclusion needs to be viewed with caution.

9. Discussion

In this chapter the results are contextualized by comparing the ICERs to literature. Furthermore, limitations of the research and possibilities for follow up research are described.

9.1 Literature Cost-Effectiveness Adalimumab and Etanercept

The literature study on cost-effectiveness models yielded multiple models which evaluated the cost-effectiveness of methotrexate and adalimumab and or etanercept, see Table 38.

Reference	Time horizon / cycle	Subtype	Range Utility	Original Costs	Strategy	ICER
Luca (2016)	5 years/ 1 month	pJIA	0.53-1.00 Adult version	Direct & Indirect Canada 2008	ETN first vs ETN second	€62,489
Shepherd (2016)	30 years/ 3 months	pJIA	0.53-0.78	Direct (NHS), UK 2013	ADM, TCZ, ETN vs MTX	ADM €49,976 ETN: €42,634 TCZ: €50,670
Simpson (2012)	7 years & lifetime/ 4 months	Not defined	0.18-1.00	Direct & Indirect Russia	ADM vs MTX	7 years: €22,249 Lifetime: €1,850
Haan (2021)	3 years/ 3 months	Oligoarticular Persistent Polyarticular RF-*	-inf – 1.00	Direct & Indirect Netherlands 2020	Early vs Conservative ETN/ADM first line vs MTX first line	ETN: €17,729* ADM: €29,727 ETN: €96,782 ADM: €139,132

*Table 38: Summary of JIA models reporting the cost-effectiveness of etanercept and or adalimumab compared to methotrexate. * Polyarticular RF- subtype used for all four ICERs. pJIA = Polyarticular JIA, ETN = Etanercept, ADM = Adalimumab, MTX = Methotrexate, TCZ = Tocilizumab.*

All models show an increase in total costs and QALYs as a result of adalimumab or etanercept use as opposed to methotrexate. None of the above models are comparable with the cost-effectiveness of the early bDMARD treatment. Comparing the model estimation of the cost-effectiveness of first line bDMARD instead of methotrexate with literature results is only possible for the subtype polyarticular JIA as all other subtypes are not modelled in literature. Our model estimates an ICER of €96,782 and €139,132 for first line etanercept and adalimumab respectively for polyarticular RF- patients. All models in literature report a lower ICER. The ICER €62,489 for etanercept first line reported by Luca (2016) is comparable to the ICER of €96,748 of this model. Adalimumab has a higher ICER than etanercept in the model of (Shepherd, 2016) as well reflecting the high drug price of adalimumab treatment. The ICER for adalimumab first line is far higher than that reported by Shepherd (2016) and Simpson (2012). This could be due to the longer time horizon used and both models modelling the utility benefit of methotrexate treatment less favorable. It should be noted that Luca (2016) and Simpson (2012) explicitly investigated the cost-effectiveness

of a bDMARD as first line compared to methotrexate. The discrepancy in results from all models found, including our own, highlight the lack of consensus in how to model JIA and the effects of DMARDs in a cost effectiveness context.

9.2 Limitations & Possibilities for Further Research

In this section limitation and possibilities for further research are discussed. First the modelling of adverse events, treatment strategy, subtypes, time horizon, and treatment discontinuation are discussed. Then the input utility and costs are discussed. Finally, the expected impact of biomarkers testing, and limitations of the prospective study are discussed

No cost and disutility were modelled for adverse events in our model. Earlier bDMARD use led to an increase in adverse events resulting in patients to switch medication. The difference in adverse events between the early and conservative switching strategy is around 0.0002 events using the base case for both etanercept and adalimumab. No direct disutility nor increase in costs were associated with adverse events. Furthermore, mild adverse events or intolerance to medication not resulting in a discontinuation of medication were not included in the model. Adverse events, whether severe or minor, are rare and data for modelling the utility or cost impact is limited. The models created by Shepherd (2016) and Luca (2016) did include the cost and disutility of adverse events. One cycle disutility of -0.06 for mild adverse events and a -0.19 disutility for severe adverse events was used by Luca (2012) with severe adverse events defined as events requiring hospitalization while mild adverse events did not require hospitalization. The reported utility figures were based on the study of Chiou (2005) which only included adults with RA. The cost of a severe adverse event was set at Can$7,817 based on the cost of a dangerous infection requiring hospitalization. No costs were assumed for mild adverse events. Cost of severe adverse events leading to treatment discontinuation were estimated between £1,073 and £1,993 by Shepherd (2016) while no disutility was modelled due to a lack of data. Mild adverse events or intolerances were not modelled. In both models the difficulty in estimating costs for adverse events was noted due to their low frequency and the variety of adverse events. Furthermore, both did not report that their model was sensitive to adverse events. If the cost reported by Luca (2016) for severe adverse events was included in scenario 4, etanercept first line would result in an extra cost of €506 (0.092 adverse events at $€_{2020}$ 5,500) while methotrexate first line results in an extra cost of €325 (0.059 adverse events). This results in an increase in costs of €187 for etanercept first line as opposed to methotrexate first line which is 1.4% of the cost difference (€12,975) between first line etanercept and methotrexate first line. If the severe adverse events disutility of one cycle was used (-0.19) the health outcome would be lowered by 0.0044 QALYs for etanercept first line and 0.0028 QALYs for methotrexate first line which is a 0.0016 decrease as a result of etanercept first line instead of methotrexate. The difference of 0.0016 QALYs is 1.3% of the difference in health outcome of etanercept first line compared to methotrexate first line (0.125 QALYs). Even though costs and disutility of adverse events are hard to estimate, result in very minimal cost and health

impact, and valid utility figures could not be found, we do recommend including adverse events in the model as they are a clear disadvantage of bDMARD treatment over methotrexate treatment. Further investigation and more data are required to model adverse events in a valid manner.

A literature study was conducted to investigate the impact of the clinical decision of switching early to a first bDMARD. A consensus was found that early bDMARD use is beneficial both short and long term but how this benefit manifests itself in terms of utility and inactive disease is poorly understood. The model only accounted for the benefit of bDMARD over methotrexate use and did not include the additional short- or long-term benefit of early bDMARD use as opposed to conservative bDMARD use.

The subtypes polyarticular RF-, oligoarticular persistent, oligoarticular extended, and enthesitis each impact resource costs (excluding medication) and starting utility of the patient. The impact of the subtype on the probability of events, medication dosage, or utility improvement were not modelled as it is unclear what the relationship is between the four subtypes and these variables. The impact of methotrexate, etanercept, and adalimumab on utility progression and probability of events are primarily based on the studies of Tynjala (2011) and Wallace (2012) using only polyarticular JIA patients. For the other three subtypes it was assumed that the same utility progression and probability of events applied. As a result, the polyarticular RF- outcomes of the model are the most valid of the four subtypes. Early second line bDMARDs after the inadequate response of NSAIDs or a sDMARDs is often recommended for the more severe subtypes polyarticular and oligoarticular extended. However, the February 2021 data showed that patients with the less severe subtypes, enthesitis and oligoarticular persistent, also used second line bDMARDs at the same rate of polyarticular and oligoarticular extended patients. The difference in the treatment pathway before the first bDMARD is used between the more severe and less severe subtypes, was not investigated in the February 2021 data. The impact of subtypes on disease progression needs to be further investigated in both literature as well as in the prospective data.

A limited time horizon of three years and extrapolation after the second bDMARD was used for the model. Most other models use time horizons of 25 years up to lifetime. However, in these models, health improvements of long term bDMARD treatment are assumed to be the same as the first two years of bDMARD treatment. This assumption must be made as the majority of clinical studies investigating the health effects of bDMARDs have a 1- to 2-year time horizon. Additionally, in long term models no distinction is made between patients that are children and patients reaching adulthood with respect to cost and health outcomes. In our model if patients discontinued the second bDMARD the utility and cost of the remaining cycles were extrapolated as no third bDMARD is modelled. Medication costs were set equal to the second bDMARD medication costs. Utility is set equal to the starting utility of a patient with active disease. As explored in the Chapter 7 “Experiment and Results”, the average number of months extrapolated and number of patients requiring a third bDMARD is limited. If the default probability of no

response is used, the average number of cycles extrapolated is around 0.01 for 3 years (12 cycles) and 0.19 for 6 years (24 cycles) which is still very small. We therefore recommend the inclusion of a third bDMARD or a better extrapolation procedure in the model if the time horizon is increased to more than 6 years. Clinical trials investigating the effect of a second line bDMARD or greater are very limited, hence adding a third or even a fourth bDMARD requires the same assumption we made with the second bDMARD in our model. The assumption made was that the effects of the second bDMARD is the same as if it were used as the first bDMARD. If the time horizon is increased the impact of a third bDMARD and the impact of a patient transitioning to an adult on costs, utility, and disease progression needs to be investigated. Extending the model time horizon is key to understanding the full cost effectiveness of early bDMARD treatment. The appropriate model time horizon needs to be investigated and should be based on the requirements of the decision maker and the long-term effects of early bDMARD treatment, which is currently poorly understood.

The only impact of the patient's history included in the model is the number of cycles of response to a DMARD which increases utility. A major advantage of an individual based STM over a cohort based STM is the ability to model the patient's history, which is important because the treatment history can have a major impact on transition probabilities, costs, and utility. In particular, the number of cycles of inactive disease could result in the discontinuation of treatment resulting in lower costs. Medication discontinuation after achieving inactive disease is not included in this model due to a lack of understanding of the process. Clinicians can either taper or abruptly stop medication if a satisfactory duration of uninterrupted inactive disease is achieved. Medication discontinuation in inactive disease can increase the chance of flaring and clinicians can chose to keep a patient on medication for long periods of time after achieving inactive disease. This process and its effects are poorly understood due to the difficulty of capturing the clinical decision process as noted by the systematic literature study on the effects of treatment discontinuation for JIA (Halyabar, 2019). This is further compounded by a lack of a uniform definition of inactive disease which is true for the prospective data as is explored in Chapter 4 of this thesis. The discontinuation of medication after achieving inactive disease could positively impact the cost effectiveness of bDMARDs use as bDMARDs increase the chance of inactive disease compared to methotrexate while being far more expensive.

Utility values for active disease and inactive disease were estimated using the February 2021 data. As the youth value set for converting the EQ-5D-5L questionnaire to utility values was not available the adult value set was used. The utility improvement due to inactive disease is estimated to be 0.233 for all subtypes based on the difference in utility of all patients with active disease and utility of patients in inactive disease. The estimation of active utility per subtype is not stratified for disease progression, treatment duration, or type of medication used.
Improvement of utility as a result of response to treatment was based on the study of health outcomes of polyarticular patients on etanercept (Prince, 2012). Etanercept and adalimumab utility

improvement was assumed to be the same. Utility improvement due to response to methotrexate could not be found in literature and was assumed to be similar, but slightly worse, than etanercept. We recommend that how utility varies for DMARD treatment, disease status, and subtype is further investigated using the full prospective data. The methotrexate utility improvement assumptions, and all other assumptions made in the model impact the outcomes of the model, especially the cost-effectiveness outcomes of the early switching strategy due to the low difference in the switching strategies. The large number of assumptions made highlights the need for caution when making conclusion based on the cost-effectiveness outcomes of both strategies. Furthermore, it also highlights the need for the further development of the model, need for more data, and the importance of conducting extensive sensitivity and scenario analyses.

With the introduction of biosimilar bDMARD, costs are estimated to decrease between 15% and 50% according to the British Columbia Health Agency (Hagen, 2021). However, although biosimilars are widely used in adult RA the use for JIA is limited (Cock, 2017). The February 2021 data also showed that biosimilars were rarely prescribed. bDMARDs are highly complex drugs and there are concerns over whether and when biosimilars are as good as the reference drug. As a result of low biosimilar use for JIA, little data exists about the use of biosimilars compared to the reference drug for JIA (Kearsley-Fleet, 2019). Nonetheless, in Europe, as of October 2020, 8 biosimilars for the expensive adalimumab and 3 for etanercept have been authorized by the European Medication Agency (Biosimilars Nederland, 2020). When biosimilar use becomes more widespread and if biosimilars are as good as the reference drug, early bDMARD use is expected to become more cost effective.

The costs included in the model; medication, direct, and indirect are primarily based on Dutch figures. Direct and indirect costs excluding medication were taken from the master thesis of Van den Berg (2019) who used literature, including no Dutch sources, to estimate. Reported indirect costs such as transportation, social care services, productivity loss of both the caregiver and patient did not vary per subtype. It is likely subtypes do impact indirect costs just as it impacts direct costs, but no literature could be found to confirm this. The prospective data should be used to estimate the relationship between subtype and indirect costs. As noted by Van den Berg (2019) some literature reported higher direct and indirect costs. The study of UK direct and indirect costs of JIA by Angelis (2016) estimated an annual total cost (excluding medication) of €24,876 while Van den Berg (2019) estimated the costs to be €10,374. Early retirement, estimated at a cost of €8,525 by Angelis (2016) is a cost category not included in the study of Van den Berg (2019). As the mean age of the patient population was 38.5 in the Angelis (2016) study it is assumed that all early retirement costs are due to patients retiring early and not the parents. Early retirement costs are therefore not relevant for our JIA model as a short time horizon is used. Furthermore, productivity loss of the parent due to informal care and costs of a professional care were reported higher by Angelis (2016). Estimating indirect costs from multiple sources is challenging. The literature review conducted on cost studies of JIA by Kip (2019) concluded that there was variability in the

methodology for estimating indirect costs including productivity loss and family borne costs which can substantially influence the total estimated costs. We recommend using the prospective data as the primary source for the estimation of the direct and indirect costs for the model for consistency. The prospective data will also yield Dutch and Canadian costs which is useful for country specific cost-effectiveness estimations.

In our model all patients of the four defined subtypes receive a first bDMARD after failing methotrexate. However, not all patients require a bDMARD while others require a bDMARD earlier. It is important to be able to predict which patients would benefit most from bDMARD treatment and which patients would not. With the biomarkers collected in the prospective data, predictions tools will be developed which can help to identify patients that are likely to respond to or benefit from bDMARD treatment which will improve health outcomes. Furthermore, it will reduce over prescription of bDMARDs for patient who do not need a bDMARD thus reducing costs. Personalized bDMARD treatment using biomarkers is thus expected to improve the cost-effectiveness of early bDMARD treatment.

More data is required to leverage the advantages of an individual STM over a Markov cohort STM which is currently the preferred cost-effectiveness model for JIA. Prospective data should provide insight into the relationship between important patient variables such as subtype, direct and indirect costs, utility progression, DMARD medication, age, gender, disease status, treatment response, and treatment duration. The EQ-5D-5L-Y questionnaires collected in the prospective data will provide an extensive overview of utility per patient with possibility of stratification of large numbers of patient and disease characteristics. It will be key for filling in gaps in literature related to utility progression on medication, disutility of adverse events, utility of inactive disease, utility per subtype, and the spillover effect on the utility of parents. We expect that after the evaluation of the full prospective data the estimated parameters of the model (primarily with literature) can largely be based on the prospective data. The greatest restriction of the prospective data is the short follow up period per patient (majority 1 year) as most patients are expected to be enrolled in cohort 1 and 2, while only a small fraction of patients is expected to transit between cohorts. Due to a lack of follow up periods in the prospective study long term consequences of methotrexate and bDMARD use will remain poorly understood. The short follow up per patient could be extrapolated for a longer time horizon using 3-months cycles as is done with our model and all other JIA cost-effectiveness STM models found for JIA. Thus, as there is a lack of long-term data, we recommend using a STM and not a DES model.

Appendix

Appendix A: Literature Review – Early bDMARD Use

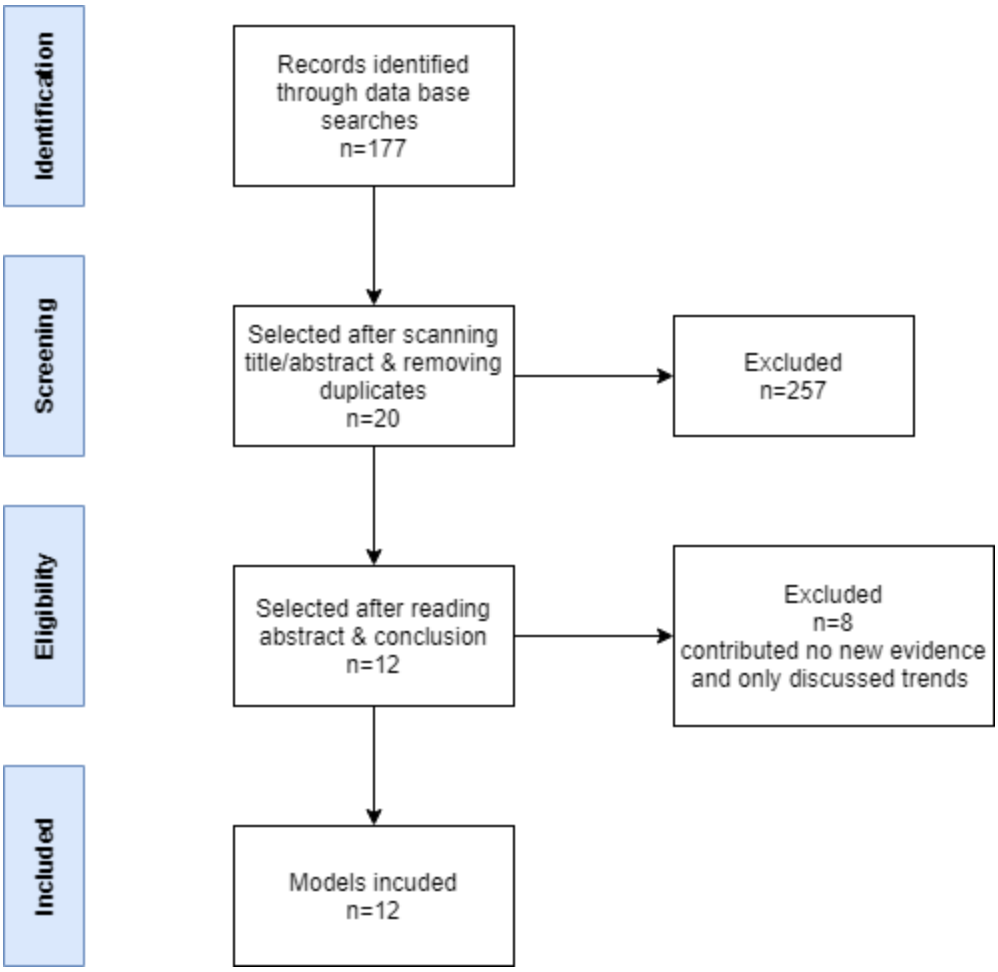

Figure 12: PRISMA flow diagram literature review JIA aggressive bDMARDs.

Search category	Search Terms	Field
JIA terms	JIA	Title
	Juvenile idiopathic arthritis	Title
Medication	bDMARD	Title/Abstract
	Biologic	Title/Abstract
Treatment	Aggressive	Title/Abstract
	Early	Title/Abstract
	window of opportunity	Title/Abstract

Table 39: Search terms for cost-effectiveness models in Pubmed

Appendix B: Literature Review – Decision Analytic Models for JIA

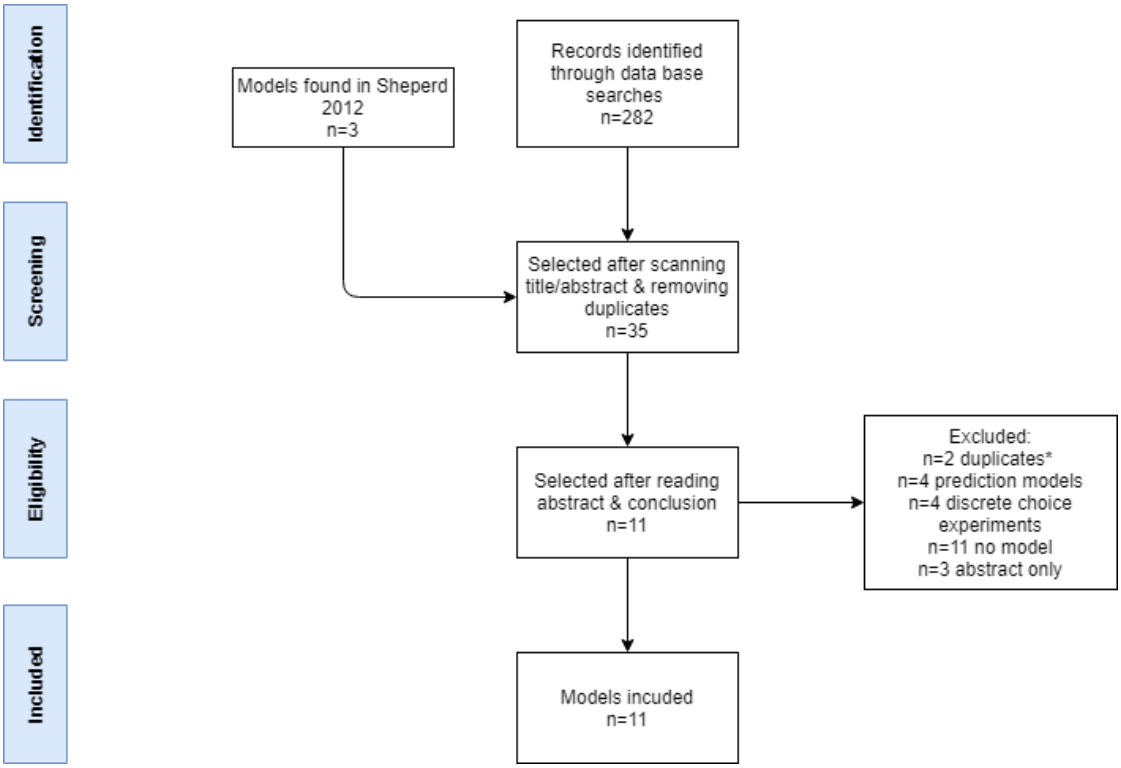

Figure 13: PRISMA flow diagram literature review JIA cost-effectiveness models.

Search category	Search Terms	Field
JIA terms	JIA	Title
	Juvenile idiopathic arthritis	Title
Model terms	Model	Title/Abstract
	Simulation	Title/Abstract
	Markov	Title/Abstract
	Discrete	Title/Abstract
	State transition	Title/Abstract
Evaluation	Cost effective	Title/Abstract
	Cost utility	Title/Abstract
	Health economic	Title/Abstract
	Decision analytic	Title/Abstract

Table 40: Search terms for cost-effectiveness models in Pubmed & google scholar.

Appendix C: Structure DES Model Adult Rheumatoid Arthritis (Literature)

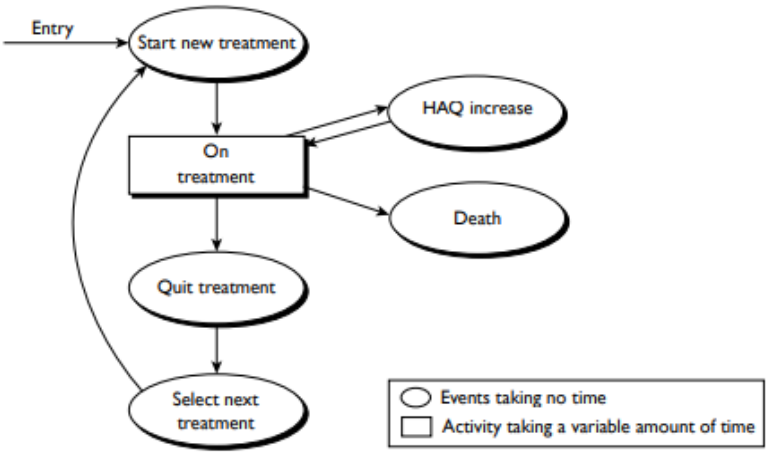

Figure 14: BRAM DES model (Jobanputra, Barton, Bryan, & Burls, 2002).

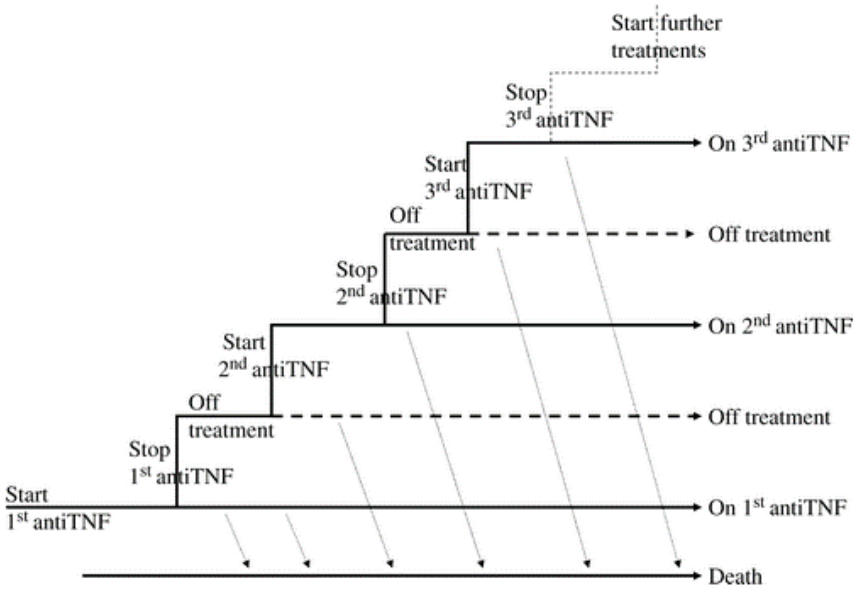

Figure 15: Swedish DES model (Kobelt et al., 2009).

Appendix D: Dosage of Methotrexate, Etanercept and Adalimumab Prospective Data.

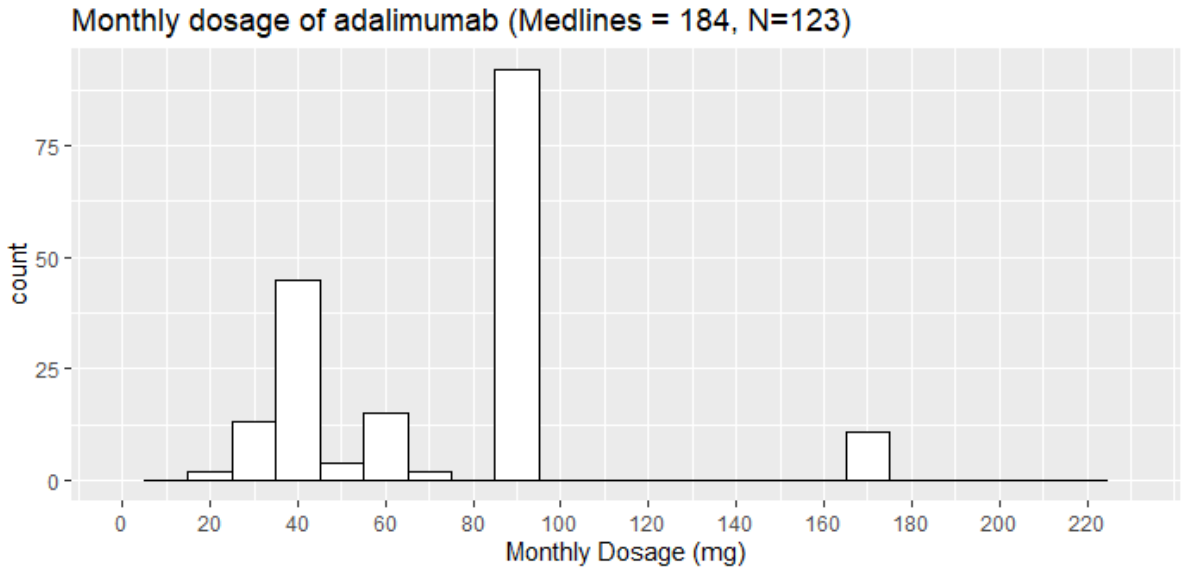

Figure 9: Monthly dosage of adalimumab, with 184 entries for 123 unique patients from the prospective data February 2021.

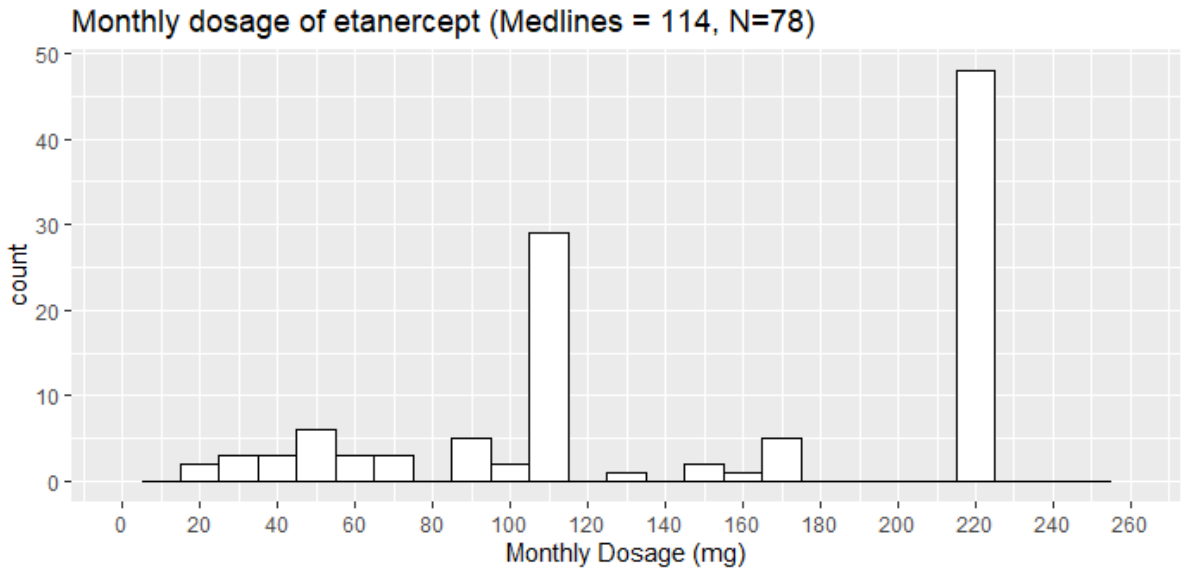

Figure 10: Monthly dosage of etanercept, 114 entries for 78 unique patients from the prospective data of February 2021.

Appendix E. Indirect and Direct Resource Costs as Reported by Van den Berg (2019)

	Systemic JIA		Enthesitis-related JIA		Oligoarthritis ANA +		Oligoarthritis ANA -		Extended oligoarthritis		Polyarticular RF +		Polyarticular RF -		Psoriatic JIA		JIA undifferentiated		JIA uveitis		Reference
	Mean (SD)	Median (IQR)	Mean (SD)	Median (IQR)	Mean (SD)	Median (IQR)	Mean (SD)	Median (IQR)	Mean (SD)	Median (IQR)	Mean (SD)	Median (IQR)	Mean (SD)	Median (IQR)	Mean (SD)	Median (IQR)	Mean (SD)	Median (IQR)	Mean (SD)	Median (IQR)	
Medication	8675 (25,011)	104 (3937)	3226 (5571)	87 (3614)	2821 (15851)	115 (514)	996 (2853)	40 (187)	3326 (4617)	581 (6593)	4934 (5329)	1921 (10,715)	3026 (4661)	343 (4943)	2437 (4597	96 (1230)	93 (205)	27 (46)	2159 (4287)	61 (1501)	Data from WCH
Imaging	294 (654)	59 (255)	359 (499)	173 (401)	100 (147)	64 (105)	151 (326)	41 (113)	237 (260)	183 (197)	361 (441)	229 (329)	245 (311)	141 (241)	168 (333)	86 (111)	211 (276)	154 (265)	60 (130)	5 (58)	Data from WCH
Admissions	2896 (9152)	0 (1073)	211 (792)	0 (0)	316 (909)	0 (290)	382 (2311)	0 (159)	567 (2037)	0 (229)	336 (900)	0 (61)	469 (1331)	0 (253)	147 (532)	0 (0)	278 (880)	0 (0)	506 (1128)	0 (400)	Data from WCH
Operations	121 (516)	0 (0)	79 (286)	0 (0)	89 (287)	0 (3)	50 (222)	0 (0)	115 (416)	0 (23)	39 (161)	0 (0)	94 (365)	0 (4)	15 (80)	0 (0)	102 (235)	0 (0)	612 (1161)	51 (910)	Data from WCH
Laboratory tests	516 (822)	177 (601)	299 (597)	136 (186)	118 (199)	82 (123)	97 (216)	41 (86)	216 (236)	132 (186)	328 (357)	223 (175)	239 (433)	129 (204)	161 (255)	92 (128)	116 (157)	39 (198)	176 (188)	126 (184)	Data from WCH
Consultations	1013 (864)	735 (1273)	872 (543)	836 (729)	763 (553)	664 (752)	671 (706)	484 (661)	893 (434)	907 (525)	961 (550)	833 (747)	865 (534)	797 (643)	743 (579)	617 (809)	1060 (1351)	537 (1477)	675 (449)	617 (401)	Data from WCH
Emergency department visits	33 (134)	0 (0)	59 (416)	0 (0)	4 (33)	0 (0)	4 (28)	0 (0)	10 (59)	0 (0)	30 (77)	0 (0)	67 (709)	0 (0)	2 (12)	0 (0)	0 (0)	0 (0)	25 (112)	0 (0)	Data from WCH
Literature	Mean		Mean		Mean		Mean		Mean		Mean		Mean		Mean		Mean		Mean		
Visits to GP	27		27		27		27		27		27		27		27		27		27		(15)
Medical devices	88		88		88		88		88		88		88		88		88		88		(1, 3, 15)
Supplements	52		52		52		52		52		52		52		52		52		52		(13)
Transportation	219		219		219		219		219		219		219		219		219		219		(3, 13)
(Other) out-of-pocket costs	23		23		23		23		23		23		23		23		23		23		(13)
Social care services	1467		1467		1467		1467		1467		1467		1467		1467		1467		1467		(3)
Productivity loss caregiver	6386		6386		6386		6386		6386		6386		6386		6386		6386		6386		(1, 3, 13)
Productivity loss patient	123		123		123		123		123		123		123		123		123		123		(3)

Table 41: *Overview of resource costs per subtype. Copied from Van den Berg, 2019), page 19.*

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