Globalize the evidence, Localize the Decision

''A comparative analysis of factors responsible for differences in cost effectiveness of Relapsing Remitting Multiple Sclerosis therapy between Norway and its price referenced countries''.

Ibi Fredrick

University of Oslo, The Faculty of Medicine, Department of Health Management and Health Economics.

University of Oslo

July, 2020

Title Page	
Title:	**Globalize the Evidence, Localize the Decision**
Subtitle:	A Comparative analysis of factors responsible for differences in cost effectiveness of Relapsing Remitting Multiple Sclerosis therapy between Norway and its price referenced countries.
Author:	Ibisayo Fredrick
Learning Arrangement:	Master Thesis
Class:	Economic Evaluation
Student Number:	515610 EUR – 618964 UiO
Cohorts:	2018-2020
University Supervisor:	Knut Reidar Wangen
Study Phase:	Graduation Phase ''4th Semester''
Academic Year:	2020
Institute:	University of Oslo
Course of Study:	European Masters in Health Economics
Course Code:	EMHEM5500
Period of Study:	September 2018 – March 2020
Date of Completion:	31st, July 2020
Confidentiality Status:	Not Applicable
Place:	Oslo
Language:	American English
Word Count:	19,719

Abstract

Background; as a result of the centralized marketing authorization of pharmaceutical therapies by EMA, whereby Quality, Safety and Efficacy is assessed, it is assumed that the biological effect of therapy are the same across countries. However, there are factors that are unique to the individual countries such as differences in epidemiology, differences in analytic Approach and Methodological requirement etc. These mentioned factors contradict EMA centralized assumptions, which prompts the individual countries to require a cost effectiveness study before such therapy is granted market access and reimbursement.

In other words, as a result of these factors, the cost effectiveness therapies across the individual countries vary. These variations eventually are one of the reasons why Ocrelizumab, a new and only authorized treatment for MS patients ''85% RRMS and 15% PPMS'' is not reimbursed in Norway.

Objective; the objective of this research is a comparative analysis of these factors between Norway and the price referenced countries to see how these factors vary among them to refute EMA assumption, what could be transferred and if Norway decision not to reimburse would change or not in light of new evidence.

Methods; the method used is to compare and contrast the factors that limit transferability of economic evaluation data as published by Drummond and Pang. To enable use the method, a clear problem statement of why Ocrelizumab is not reimbursed in Norway is stated. In addition, the problem statement is further broken down in series of questions that enable how those factors vary among countries. Hence, how it impacts the cost effectiveness study of Ocrelizumab. The focus of the research is only on RRMS patients.

Result; after careful and thorough analysis, research findings shows that, as a result of the variation among those factors and its impact on their respective cost effectiveness study, as well as the fact that economic evaluation interpretation is subjective and sometimes seen as a tool of manipulation, generalizability assumption assumed by EMA is indeed not valid across countries. Finally, research also shows that cost effectiveness result does not always capture values, perhaps Norway should rethink the decision not to reimburse.

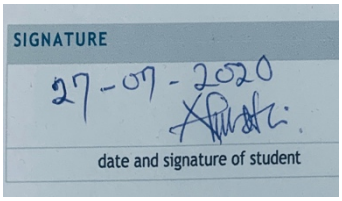
Preface

This is my Master's Thesis for the program European Masters in Health Economics and Management. I started my first Semester in Innsbruck, Austria, where I was impacted with the knowledge of the relevance of Healthcare Management and Statistics. Thereafter, I did my second Semester at the Erasmus University in Rotterdam, where I was introduced to Pharmaceutical pricing, Health Innovation Science, Market Access and Reimbursement, healthcare Ethics, Health Economics Development Policy and Evaluation, as well as Advance Economics Modelling. After that, I came to Oslo, Norway for my third and final semester. While in Oslo, I am also impacted with the knowledge of Advance Economics Modelling Part II, Method for Effectiveness in Healthcare ''with an introduction to Python'', Priority Settings in Healthcare, Research Design as well as Introduction to Norwegian Course A1 to A2 Level.

This thesis will not be completed without the adequate knowledge of those courses mentioned in the above paragraph. Therefore, I want to use this opportunity to thank Sara Repo ''our go to person'' and of course Prof. Siegfried Walch, as well as Dr. Armin Fidler and the rest of the professors and staffs in Innsbruck. In addition, I will like to thank the Rotterdam team, especially Victoria Lorenzo Sanchez, Mireille Bourne, Benno Arentsen who are always there to support us, even when it is not convenient. Of course, huge thanks to Prof. Maureen Rutte-Van Mölken, Matthias Rieger and Marc Koopmanschap who impacted not only the knowledge needed to execute this thesis, but also inspired me to challenge some of the status quo in Economic Evaluation.

Moreover, a huge thanks to the Oslo team, especially to Ola Anders Magnusson whose assurance you can always count on. Also, a huge thanks to Eline Aas, who saw a potential in my thesis topic right from the onset and helped redirect the path towards the execution. Eline, thank you for making one of the most difficult subject in Economic Evaluation easy – your mode of teaching is superb. In short, this report would not have been made possible without the help of Knut Reidar Wangen whose support, guidance and advice polished this thesis to what it is today. In short, in every meeting with Knut, the first thing he would like to know is my wellbeing – that goes a long way to assuage the impact of COVID-19 among other difficulties.

This has really been an important milestone in my life and I hope I will be able to translate the knowledge and kindness you have all shown me and impact this generation as well in return. To those whose names I might have skipped, especially to my friends, it is not intentional. Thank you.



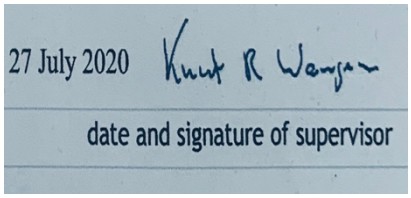


Table of Content

Glossary	
EMA	European Medicine Agency
PML	Progressive Multifocal Leukoencephalopathy
AMNOG	Pharmaceuticals Market Reorganization Act
AIP	Pharmacy Purchasing Price in Denmark
DMTs	Disease Modifying Therapies
AR (Absolute Risk)	The number of events (good or bad) in treated or control groups, divided by the number of people in that group ARC = the AR of events in the control group ART = the AR of events in the treatment group
ARR (absolute risk reduction)	= ARC – ART RR (relative risk) = ART / ARC RRR (relative risk reduction) = (ARC – ART) / ARC RRR = 1 – RR NNT (number needed to treat) = 1 / ARR
CMA	Cost Minimization Analysis
Ex-factory Price	The ex-factory price means the price at the factory, and does not include any other charges, such as delivery or subsequent taxes
EDSS	Expanded Disability Status Scale
G-BA	Highest decision maker for therapies in Germany
IQWiG	Institute for Quality and Efficiency in health Care
NHS	National Health Service (U.K.)
NOMA	Norwegian Medicine Agency
OTC	Over the Counter Medicine
PPP	Pharmacy Purchasing Price
RAD	Regional Health Authorities
RHAs	Regional Health Authorities

Reliability	Degree to which measurement is free from measurement error
Validity	Degree to which the instrument measures the construct it purports to measure
Responsiveness	Ability of a measure to detect checnge over time
Relative risk definition	Difference between the treatment group and the control group
TLV	The Swedish Dental and Pharmaceutical Benefits Agency
Lesion	A brain lesion describes damage or destruction to any part of the brain
Contraindicated	(of a condition or circumstance) suggest or indicate that (a particular technique or drug) should not be used in the case in question.
Adjunctive Therapy	Clinical Intervention
CUA	Cost Utility Analysis
RRMS	Relapsing Remitting Multiple Sclerosis
PPMS	Primary Progressive Multiple Sclerosis
SPMS	Secondary Progressive Multiple Sclerosis
NIPH	Norwegian Institute of Public Health
JCV	John Cunningham Virus
NCPE	National Center for Pharmaco-economics
LIF	Danish Association of the Pharmaceutical Industry
SAE	Serious Adverse Events
TWSAE	Treatment Withdrawal Due to Serious Adverse Events

Differential Pricing	Selling the same medicine to different countries according to their ability to pay at different pricing, when cost is the same.

1. Introduction

In this chapter, a distinct explanation of the common ground, statement of research problem, Solution to the research problem and the project structure will be explored.

1.1. Common Ground

To start, the European Medicines Agency (EMA) is responsible for the scientific evaluation of centralized marketing authorization applications ''MAA''. Once granted by the European Commission, the centralized marketing authorization is valid in all European Union (EU) Member States, Iceland, Norway and Liechtenstein (EMA, 2020).

The process of marketing authorization as described by EMA in the above paragraph assessed the Quality, Safety and Efficacy of a pharmaceutical therapy. If those criteria are found sufficient, approval to sell such therapy is granted in the countries listed under the European commission. Meanwhile, it is imperative to know that EMA assumption of centralized procedure assumes that the biological and cost effectiveness of the drug should be the same irrespective of the countries where the patient is undergoing treatment. Indeed, this might not always be true as a result of a variety of unique factors peculiar to each country. Factors such as **''country specific differences in demography in patient population, healthcare system design, analytic approach and methodological requirement, to mention a few''.** So, for the EMA centralized assumption to hold true, estimates of these factors among countries should be similar. Hence, generalizability assumption as described in the next paragraph can be upheld.

In addition, the process described in the later part of the above paragraph can be termed as generalizability or external validity - it is described as the extent to which the result from a given study holds true in another setting. On the other hand, the term Transferability ''which will be used in the paragraph below'' is the extent to which the result from a given study can be adapted to be applied in another setting (Drummond & Pang, 2001).

Having established the above, as a result of the fact that generalizability assumption does not always hold true, the pharmaceutical companies are compelled by each country in the European commission to provide the country's individual cost effectiveness data/analysis. The provided data or analysis is assessed nationally to see if the therapy is cost effective in comparison to the standard treatment or most efficient alternatives. Hence, market access and reimbursement for each country is determined. Meanwhile, as a result of those factors mentioned in the second paragraph, the results of cost effectiveness study vary among countries. Therefore, the studies are not necessarily transferable to another country (Maureen Rutten, 2018).

1.2. Statement of Research Problem

In light of the above paragraph, the issue surrounding the provision of the country specific cost effectiveness data/analysis as described gives credence to the situation surrounding the non-reimbursement of Ocrelizumab for the RRMS patients in Norway. Ocrevus, ''with an active ingredient '' Ocrelizumab'' is the new medicine, developed and manufactured by Roche pharmaceuticals and was approved by Norwegian Medicine Agency ''NOMA'' since January

2018 for the treatment of both Relapsing Remitting Multiple Sclerosis ''RRMS'' and Primary Progressive Multiple Sclerosis ''PPMS''**.** It has a market authorization to treat both RRMS and PPMS with mild adverse effects, i.e., clinical trials have shown efficacy in patients with strokes. In addition, the approval of the therapy has raised the long awaited hopes of MS patients that Ocrelizumab would be reimbursed by October 2018. However, the hopes of the patients were dashed by decision from Norwegian Medicine Agency ''NOMA'' with the assertion that **''although, Ocrelizumab has proven effective and probably at the topmost of what can be considered as a cost effective treatment, but we cannot reimburse it because the price is high''** (Dagensmedisin, 2018), (NIPH, 2019) (Roche, 2018)

Moreover, it is important to know that the guideline for price settings for medicine in Norway according to the NOMA is by referencing the following countries namely; Sweden, Finland, Denmark, Germany, UK, Netherlands, Austria, Belgium and Ireland. It is said further that ''in a situation where market prices exist in three of the lowest market prices of the product in a selection of countries, the price will be set as the average price of the existing prices (NOMA, 2020).

In light of the statement in the last paragraph, the statement of research is formed as follows; if Ocrelizumab is approved, marketed and reimbursed for treatment of MS in Sweden, Denmark, Finland and few other pricing referenced countries, why is it not marketed and reimbursed in Norway? More importantly, why does the cost effectiveness of a therapy varies among countries and what are the factors responsible for the variation in cost effectiveness between Norway in comparison to the referenced countries? Most importantly, will the decision to reimburse Ocrelizumab change or remain the same in light of new evidence, i.e., if there are some patient group that are cost effective **OR** if transferability is applied, i.e., adapting the cost effectiveness study in one of the aforementioned referenced countries to be applied in Norwegian settings (Welte, R., et al., 2004). The questions below are the problem questions;

1.2.1. What are the decision made on reimbursement or non-reimbursement of Ocrelizumab in Norway and the referenced countries?

Question 1.2.1., will first elaborate which country among the referenced countries currently reimbursed the therapy. More so, it will enable the author gain preliminary insights to some of the reasons why the therapy is not reimbursed in Norway as outlined in the subsequent subchapters. Therefore, the reimbursement decision will first be stated in this chapter (NIPH, 2019) (NICE, 2018) (Medicinraadet, 2018) (NCPE, 2019) (Jarosławski, S., & Toumi, M., 2011).

1.2.1.1. Based on the decision as outlined in chapter 1.2.1, Is the cost effectiveness result enough for the reimbursement decision in the referenced countries?

This question is important because is it widely known that economic evaluation is not an end in itself, but a means to an end. This implies that it is a basic tool to inform decision about which of the therapies to recommend in the face of alternatives (Drummond et al., 2015).

1.2.1.2. What are the factors responsible for the reimbursement decision of the therapy in the countries where it is currently reimbursed?

This question is important to see if Norway decision not to reimburse will change or remain the same in light of evidences from other countries or new evidences that is avoided in

Norway's economic evaluation result. Also, the question delves further into the blanket statement ''economic evaluation is a tool to inform decision'' as mentioned in chapter 1.2.1.1. The usage of the statement is subjective because economic evaluation can be used to inform decision about pricing, access, coverage etc. (Drummond et al., 2015). Therefore, this question will help gain further insights into other criteria for decision making in the aftermath of the economic evaluation results in the respective countries with similarity or differences in their characteristics of pharmaceutical products reimbursement. (Gregson N et al, 2005) (Kolassa, E. M., 2009) (Sussex J et al., 2013) (Jarosławski, S., & Toumi, M 2011).

1.2.2. What are the factors responsible for the variation in cost effectiveness of the therapy among these countries and Norway?

As discussed previously in the introduction chapter, market authorization done by EMA assessing the quality, safety and efficacy of a pharmaceutical product for all the EU member states, Iceland, Norway and Liechtenstein. EMA assumption however assumes a centralized procedure and neglects the factors that are unique to individual member states that cause variation in cost effectiveness across member states. To insulate these factors, each member state requires a cost effectiveness analysis before the pharmaceutical therapies are granted market access and reimbursement (EMA, 2020) (Maureen Rutten, 2018).

Therefore, this question is important. This is because it investigates some of the mentioned unique factors as it varies across countries vis-à-vis its effect on cost effectiveness of therapies. For instance, assuming the clinical effectiveness endpoints of a similar intervention for an indication that is compared with a similar comparator between country A and country B. After comparison of outcomes, there is a likelihood of a huge differences in their primary and second endpoints ''irrespective of the same molecular structure present in the active ingredient''. As a result of the differences in outcome of these endpoints, the cost effectiveness result will also be different (EMA, 2020) (Drummond, Pang, 2001) (Briggs et al., 2006).

1.2.2.1. In light of new evidence, would the decision to reimburse change or remain the same in Norway?

This question is self-explanatory and its import because it will help scrutinize the decision for reimbursement in the referenced countries that have some of those similar factors that cause variation in the cost effectiveness study as Norway. For example, Norway may perhaps opt for a separate analysis for subgroups that is found cost effective in any of the reference country. In addition to that is if Norway may be willing to consider adopting any of those factors for reimbursement decision as described in chapter 1.2.1.2. (Eunethta, 2015)

1.2.2.2. Can the cost effectiveness of any of the countries be adapted to be applied in Norwegian settings?

This question is important because in the face of obvious fact that EMA generalizability assumption does not hold true in all the countries, it may be interesting to see if Norway has some characteristics in common with other referenced countries that might challenge the status quo. Hence, transferability can be applied, i.e., adapting the cost effectiveness study in one of the aforementioned referenced countries to see if it is applicable in Norwegian settings (Knies, S., et al., 2009).

1.2.2.4. Scope of the Project

Having established the above, the scope of this project will only be limited to the RRMS category of Multiple Sclerosis. More so, some countries will be filtered out in the analysis. In practical terms, due to lack of available data, Belgium, Finland, Austria are filtered out from the list of NOMA price referenced countries to be analyzed. Therefore, the health system and criteria for pharmaceutical reimbursement of Germany, the U.K., Ireland, the Netherlands, Sweden, Denmark and Norway will be elaborated.

Furthermore, in the analysis of factors that are responsible for variation in cost effectiveness studies in chapter 3, Germany, the Netherlands and Sweden are also filtered out. This is as a result of a peculiar pharmaceutical reimbursement criteria that characterizes Germany, as well as lack of HTA studies for the Netherlands and overly redacted HTA studies from Sweden. Therefore, only Ireland, the United Kingdom, Norway and Denmark will be further analyzed.

More importantly, due to several missing information when it comes to incremental costs and QALYs from the respective countries and due to the fact that not all the countries adopt a CUA analysis whereby the effect is expressed in QALYs, the ICERs therefore, will not be compared. Additionally, the budget impact will also not be compared as a result of lack of information.

1.3. Proposed Solution to the Research problem

This chapter proffers solution to the question raised in chapter 1.2.

1.3.1. What are the decision made on reimbursement or non-reimbursement of Ocrelizumab in Norway and the referenced countries?

To answer the first question, the reasons for reimbursement or non-reimbursement of Ocrelizumab in Norway and the referenced countries will be stated. The statement will be sought from the cost effectiveness analysis of the respective countries (NIPH, 2019) (NICE, 2018) (Medicinraadet, 2018) (NCPE, 2019).

- **Based on the decision as outlined in chapter 1.2.1, is the cost effectiveness result enough for the reimbursement decision in the referenced countries?**

To answer this sub question, the connection between the decision that was made after being informed by the economic evaluation and the actual recommendation of economic evaluation will be compared to see how both deviate from each other. The data from the cost effectiveness study of the respective countries will be used (Drummond et al., 2015).

- **What are the factors responsible for the reimbursement decision of the therapy in the countries where it is currently reimbursed?**

To answer this sub question, the content of chapter 2, the deviation found in the first sub question of chapter 1.3.1, as well as various characteristics of each country reimbursement decision will help provide answer to this question (Gregson N et al, 2005) (Kolassa, E. M., 2009) (Sussex J et al., 2013) (Jarosławski, S., & Toumi, M 2011).

1.3.2. What are the factors responsible for the variation in cost effectiveness of the therapy among these countries and Norway?

To answer this question, factors associated with differences in **Burden of Disease, Basic Demography and Disease Epidemiology** such as disease prevalence and severity will be compared. In addition, factors associated with **Differences in health System Design and Variation in Clinical Practice** such as Differences in Relative Prices and Costs and Differences in Choice of Comparators as it affects the Clinical Effectiveness, Safety and their Respective Cost Effectiveness will also be compared. Moreover, factors associated with **Differences in Analytical Approach and Methodological Requirements** such as the Analysis of Subgroup in Economic Evaluation, Differences in Types of Analysis Used ''CEA/CUA/CCA/CMA etc., Differences in Choice of Perspectives on Costs and Outcomes, Differences in Choice of Discount Rate and Time Horizon, Differences in Costing Method, Differences in Utility Value Used, Differences of Willingness to Pay Threshold, Differences in Choice of Currency Conversion. (Drummond et al., 2015) (EMA, 2020) (Drummond, Pang, 2001) (Briggs et al., 2006).

- **In light of new evidence, would the decision to reimburse change or remain the same in Norway?**

To answer this sub question, the reimbursement decision as discussed in the sub question of 1.3.1. will be used. Also, the characteristics of Norwegian health system regarding the reimbursement of pharmaceutical product in chapter 2.5.7. will be used. In addition, the cost effectiveness data of Ocrelizumab and Rituximab will be investigated will be investigated to enable determine additional consideration beyond the recommendation of cost effectiveness analysis i.e., the inclusion of the pricing, market access and reimbursement strategy explained in chapter 2.6, chapter 2.7 and chapter 2.8 respectively. (NIPH, 2019)

- **Can the cost effectiveness of any of the countries be adapted to be applied in Norwegian settings?**

To answer this sub question, the cost effectiveness study of any of the countries with similar characteristics and healthcare architectural design as Norway will be looked into to see what can be adapted to Norwegian settings in terms of factors that contribute to an efficient and effective use of resources that will eventually impact the cost effectiveness.

1.4. Project Structure

This project is divided into Five chapters. Chapter 1 is the introduction which comprises Common Ground, Statement of Research Problem, and Project Structure. Thereafter, Chapter 2 is the Theoretical Framework which comprises of a short overview of Multiple Sclerosis ''MS''. In addition to that is the explanation of the instrument for diagnosis and measuring MS. After that is the MS background and prevalence in Norway. Then, Norwegian Medicine Agency guideline.

Thereafter is the healthcare system regarding the market access and reimbursement of pharmaceutical therapies in Norway and the referenced countries, as well as various Pricing, Market Access and Reimbursement strategy. Chapter 3 comprises of the Theoretical

Framework, whereby the question raised in the first chapter is answered. Chapter 4 reveals the result of the analysis of the previous chapter, while Chapter 5 comprises of the Conclusion and the Discussion.

2. Theoretical Framework

This chapter will give a comprehensive background on Multiple Sclerosis, the instrument for measuring and diagnosing MS, its trend and its treatment in Norway, as NOMA guidelines regarding pharmaceutical reimbursement. In addition, various market access strategy, pricing models and reimbursement strategy. Finally, the health systems regarding the market access and reimbursement of pharmaceutical products in Norway and the price referenced countries.

2.1. Multiple Sclerosis

Multiple Sclerosis ''MS'' is an autoimmune condition that occurs when the immune system attacks the myelin sheath that stands as the insulation and supports the nerve cells in an abnormal manner. Hence, the brain and the spinal cord are affected. As a result, the quality of life due to problems with vision, arm or leg movement, sensation and balance are compromised. More so, it affects about 2.3 Million people globally and the overall life expectancy of an MS patient is reduced. MS can develop in any age, but the disease is commonly diagnosed in people in their 20s and 30s and the disease is two to three times more common in women than in men (NHS, 2018).

More so, MS has no cure. There are two types of MS namely, Relapsing Remitting MS ''RRMS. It is the most common form as it affects about 85% of the MS patients. The majority of RRMS patients eventually transition to Secondary Progressive MS ''SPMS'', whereby the symptoms become worsened typically without relapses or periods of remission. Eventually, relapsing forms of MS ''RMS'' is characterized with RRMS and people with active SPMS which continue to undergo relapses. Over a period of time, some MS patients ''approximately 5% can live for decades without any form of disabilities. These groups are referred to as having a Benign MS (F Hoffmann, 2019) (Roche, 2019).

2.2. Instrument for Diagnosis and Measuring Disease progression in MS

Magnetic Resonance Imaging ''MRI'' is the preferred and most non-invasive instrument used to diagnose and measure the disease progression in the brain, spinal cords and other parts of the body. More so, Expanded Disability Status Scale ''EDSS'' is one of the standardized ways of measuring the effect of MS on patients (MS Society, 2020). There are four different kinds of MRI scans namely; T1-weighted Scan, T2-Weighted Scan, Fluid Attenuated Inversion Recovery ''FLAIR'' and Spinal Cord Imaging (confer glossary for definition). T2-weighted Scan is the most common MRI scan used to diagnose MS and to detect areas of both new and old myelin damage in the brain and spinal cord and it is later used as the secondary endpoint in this report (Multiple Sclerosis Today, 2020)

The result from MRI is analyzed and measured by a neurologist using EDSS. The measurement shows how MS impacts the patient's body functions through muscle weakness, eyesight, thinking memory etc. The scores derived are used to determine the types of patients who can use Disease Modifying Therapies ''DMTs''. The points on the scale start from 0.0 until 10. While 0.0 score implies that the examination shows everything is normal, 10 means death due to MS. A score above 6.5 implies that a patient uses a wheelchair most of the time. In that case, such patients do not qualify for DMT because the previous studies have shown that the DMTs do not have enough benefits for patients at that level of disabilities. However, it has

been discussed that EDSS is more physician focus than patient focus as a result of the fact that it does not measure the full extent of MS symptoms that are not visible, such as pain, fatigue, depression etc. Hence, another standardized instrument might be appropriate (MS Society, 2019).

2.3. Multiple Sclerosis – Background and Prevalence in Norway

Moreover, MS prevalence in Norway as at 2013 is about 10,600 patients with a rough estimation of 203 patients per 100,000 incidences as at 2014. MS can either start with individual relapses (attack or exacerbation) or with gradual progression. About 85% of MS are Relapsing Multiple Sclerosis ''RMS''; which comprises of episodes of new or worsening symptoms known as relapses. In the same vein, about 10% to 15% of cases of MS are Primary Progressive Multiple Sclerosis ''PPMS'' – consists of gradually worsening symptoms which accumulates over several years with no period of remission (NIPH, 2019).

In light of the above paragraph, there is currently no cure for MS. In august 2019, Norwegian Institute of Public Health ''NIPH'' conducted a Health Technology Assessment ''HTA'' including a network meta-analysis on 11 different medicines for RRMS. In the study, it was established that one important acknowledged risk of DMT is Progressive Multifocal Leukoencephalopathy ''PML''. PML is caused by the infection of the brain with John Cunningham Virus ''JCV'' which destroys the myelin sheaths of nerves in patients with decreased function of the immune system. Hence, approximately 25% of patients die within 6 months and the survivors have increased long-term disability (NIPH, 2019). (Nina Grytten et al., 2015)

Alternatively, Ocrelizumab is the first and the new active ingredient that has a market authorization to treat both RMS and PPMS with mild adverse effects. Clinical trials have shown efficacy in patients with strokes. Even though it's been approved since January 2018 by the Norwegian Medicine Agency, it's market access and reimbursement is not allowed. This is because Ocrelizumab is 14 times more expensive than its off-label comparator ''Rituximab'' (NIPH, 2019).

Moreover, while Ocrelizumab is not yet reimbursed, the hospitals in Norway are granted exceptions from the regional medical directors to treat MS patients with Rituximab. Although, Rituximab holds market authorization for several autoimmune diseases such as rheumatoid arthritis, B Cell non-Hodgkin's Lymphomas and few other types of cancer, it does not have a market authorization for the treatment of MS. Hence, it is used as an off-label medicine to treat only RRMS. The justification is that one year of treatment with Rituximab cost about NOK 20,000, while that of Ocrelizumab is estimated to be NOK 290,000. (Dagensmedisin, 2018), (NIPH, 2019).

2.4. Norwegian Medicine Agency Guideline regarding Pharmaceutical Products

To start, Noma determines the price of therapies through international price comparison. More precisely, the prices of therapies in countries such as Sweden, Finland, Denmark, Germany, Netherlands, United Kingdom, Austria, Belgium and Ireland are referenced. It is further stated that in situations where market prices exist in three or fewer of these countries, the price will be set as the average price of the existing prices. NOMA price referencing is done on the basis of the actual market prices ''the maximum price that the majority of the market pays for the therapy'' in the referenced countries.

Furthermore, the only justification to price a therapy at a higher maximum pharmacy purchasing price is the following. First, there is a major risk that the therapy will not be available in the market if the maximum price is implemented. Second, the absence of the therapy in the market could have negative consequences for the availability of other cost effective medicines. In the event of the above two factors, NOMA will consider using a discretionary price settings judgement by documenting the production costs and special circumstances regarding the basis for price calculation. Finally, new prices are set within 90 days after receiving a price application (NOMA 2020).

2.5. Healthcare systems in the referenced countries and Norway regarding the market access and reimbursement of pharmaceutical therapies.

As a result of differences in the healthcare system of the individual countries, there is also differences in the reimbursement of pharmaceutical among the countries. Therefore, below is the overview of the health system as it allows the market access and reimbursement of pharmaceutical therapies in the referenced countries and Norway.

2.5.1. The Netherlands

The Dutch healthcare system is a comprehensive system with universal coverage, i.e., social basic benefit package health insurance. It is financed through subsidies from general taxation and reallocation of payroll levies among insurers via risk adjustment system (The Commonwealth Fund, 2020). Therefore, it is a compulsory health insurance in combination with competition among private health insurance providers which are required to accept everyone in the risk pool irrespective of their pre-existing condition. (Ispor.org, 2020).

For some pharmaceuticals, specific criteria must be met before reimbursement. Therefore, such pharmaceuticals are included in Appendix 2 of the Health Insurance Regulation. This implies that the pharmaceutical therapies in appendix 1A and 1B can also be on Appendix 2, but their reimbursement is subjected to certain conditions – for instance, that the therapies are not administered on an entire group of patients, but only to specific patients. Hence, the reimbursement is not cost effective at the population level. Ocrelizumab for the treatment of multiple sclerosis is categorized as one of those therapies in Appendix 2. Therefore, it's not reimbursed (Seigraaf, 2020) (ZIN, 2020) (farmacotherapeutischkompas, Netherlands, 2018)

2.5.2 United Kingdom

The NHS, National Health Services is a government funded medical and healthcare services in the United Kingdom. Unlike the healthcare delivery system in the Netherlands that is run by a chain of private insurance companies, the NHS provides healthcare service free of charge at the point of use. NHS is funded through general taxation i.e., ''about 80%'' of the NHS budget and National Insurance Contributions ''about 20% of the NHS budget'', as well as patient's prescriptions and dentistry. Medicinal products are classified into three groups namely; the Prescription Only Medicine ''POMs'', General Sales Medicines - which implies consumers may purchase without a prescription and the Pharmacy Medicine, whereby consumers may also purchase without a prescription, but only from a pharmacy. NHS reimburses the three

categories of the medicinal product, but as a way to dissuade the public from purchasing over the counter medicine, NHS focuses more on the POMs (GLI, 2019).

Meanwhile, NHS England to provide centralized funding for a high cost medicinal product that the CCGs might be reluctant to fund. However, guidelines from NICE over the clinical and cost effectiveness plays a significant role in determining if NHS should fund a medicinal product in both primary and secondary care (GLI, 2019).

Having established that, Ocrelizumab was previously not recommended for reimbursement by NICE in 2018. However, the parties involved, namely Roche Pharmaceutical and NICE reached a compromise with commercial agreement strategy in 2019 where the medicine is recommended for the treatment of early RRMS and PPMS with imaging features characteristic of inflammatory activities in adults (NICE, 2018).

2.5.3. Ireland

Irish healthcare policy and expenditure are determined by the Department of Health and Children and administered through the Health Service Executives ''HSE' (GLI, 2019). The healthcare system is divided into two namely, the public and the private healthcare system. The public healthcare system is funded by 75% general taxation and social security contributions, while the private healthcare system is funded by 11% private funds and private insurance schemes and the remainder is funded by patient's co-payments. (Michael Barry et al, 2004).

In addition, Long Time Illness Scheme ''LTI'' is similar to DPS and it is administered irrespective of the patient's income. More importantly, it is applied to provide medicine for specified long term illness like Cystic Fibrosis, Multiple Sclerosis etc.

However, the HSE requests that the National Center for Pharmaco-economics ''NCPE'' to conduct an HTA assessment. For products that the value for money is not well proven and according to 2013 ACT and 2016 agreement, medicinal product must be priced at the currency adjusted average ex-factory price in the 14 reference EU member states (GLI, 2019) and if the product is not available in all 14 member states, the average ex-factory price in the countries the medicine is available is used. Moreover, reimbursement is decided on forum factors namely; cost effectiveness, safety and budget impact (NCPE, 2018)

Having established that, NCPE Ireland recommends Ocrelizumab may be used as a first line treatment for RRMS, but should not be considered for reimbursement unless the cost effectiveness can be improved relative to existing treatments. (NCPE, 2018). After a confidential negotiation between HSE and Ocrelizumab manufacturer, it was published that the HSE has approved reimbursement on a confidential price agreement for only RRMS (NCPE, 2018)

2.5.4. Germany

Just like in the Netherlands, health insurance is also mandatory in Germany. About 90% of Germans get coverage from statutory health insurance ''SHI'', while the remaining 10% are covered via private insurance special programs. The content of what is covered by SHI is determined at the national level by the Joint Federal Committee called Gemeinsamer

Bundesausschuss ''G-BA''. While the Private health insurance covers more or less the same basket as SHI, it does permit to extend or restrict benefits. The basket of reimbursed pharmaceuticals is defined by statutory exclusion of various categories ranging from OTC, lifestyle medicine and minor ailments. More so, about 84% of medicine used in outpatients are covered by health insurance, while the remaining amount is covered through co-insurance payments or OTC (OECD, 2018).

Since 2011, the pharmaceutical market has been reformed ''Neuordnungsgesetz – AMNOG''. As a result, the pharmaceutical is kept at free pricing at lunch. However, the price is renegotiated 12 months after medicinal product launch, through a systematic and assessment of the added therapeutic value by the Institute for Quality and Efficiency in health Care ''IQWiG''. After the cost benefit assessment, if the therapy is found to have an added therapeutic value more than the standard treatment, a reimbursement price is negotiated.

Meanwhile, IQWiG in Germany recommended the use of Ocrelizumab as a best supportive care for adult with PPMS (IQWiG, 2018) (G-BA, 2018).

2.5.5. Sweden

Sweden's healthcare system is a shared responsibility between the states, counties and the municipalities. While the state responsibility is health and medical care policy, the county responsibility is the provision of healthcare services. The Swedish national health services cover every Swedish residence. The goal of the Swedish healthcare system is that care should be given in respect to equality or rights to all and individual dignity. In 2002, Sweden abolished the price referencing system for pharmaceuticals reimbursement and introduced a value-based and reimbursement system that is embedded in the cost effectiveness analysis in determining the reimbursement decision (GLI, 2019).

The Swedish Dental and Pharmaceutical Benefits Agency ''TLV'' decides which pharmaceutical product should be reimbursed. (GLI, 2019). However, it is imperative to know that PPMS is about 15% of all MS cases, so after a careful assessment of some age groups based on ethical evaluation that is opined on human dignity principle, solidarity principle and of course, cost effectiveness principle, it was discovered that Ocrelizumab is cost effective for patients aged 55 and below. The ethical evaluation is further operationalized in the following four dimensions namely; the severity of the condition, effect size of the measure, rarity of the condition and the cost effectiveness of the measure. Therefore, the therapy is reimbursed (Janusinfo, 2018).

2.5.6. Denmark

Denmark has a public healthcare system that is run by the national states institutions, regional and municipalities. The stakeholders elected in the three levels of government are democratically elected, which gives room for a decentralized management for the regions and the local municipalities. The state level organizes the overall healthcare legal framework, as well as coordinating and supervising the healthcare delivery at the regional and municipalities levels. The regions are responsible for both primary and secondary healthcare delivery and while the hospitals doctors are paid by the region, the general practitioners and other practicing specialists are privately employed (ISPOR, 2015).

The agreement between the Danish Association of the Pharmaceutical Industry 'Lif'' and the Danish Ministry of Health restricted the pricing of the pharmaceutical product and introduced a pharmaceutical pricing cap. Therefore, the pricing of the pharmaceuticals requires that the Danish Health and Medicine Agency is notified about the Pharmacy Purchasing Price ''PPP''. Hence, the price will be used to derive the consumer price, which has a basis with the wholesales resales price to the pharmacies. In the primary sector, prices can be changed every two weeks (ISPOR, 2015).

In regards to the reimbursement of Ocrelizumab, the board recommends Ocrelizumab as a standard treatment for RMS, including patients with activities that have not been previously treated. The board also asserted that there is a reasonable clinical added value and it is cost effective in some patient categories (Medicinraadet, 2018).

2.5.7. Norway

Norwegian healthcare system is founded in three tenets namely, on the principle of universal access, decentralization and free choice of provider. It is financed by taxation which also includes contracts with private entities that are financed by private healthcare insurances. For instance, about 10% of Regional Health Authorities ''RHAs'' expenditure to purchase private healthcare service delivery. In addition, some out of pocket payments are also an additional source of funding, while the dental care is mainly funded by private expenses (PPRI, 2018).

Similar to the Danish healthcare system, the Norwegian healthcare system is also categorized in three levels namely; the central state, the four regional levels and 422 municipalities level. Regarding the pricing and reimbursement of the pharmaceuticals, primary care and specialist care becomes relevant i.e., outpatients medicine or the ''H-Prescriptions'' are reimbursed by the specialist care sector ''RHAs'', but dispensed in the community's pharmacies. More so, the Norwegian Health Economics Administration ''HELFO'' is responsible for the reimbursement of all services, including pharmaceuticals that are covered by NIS (PPRI, 2018).

It is established that the health intervention should be evaluated based on the benefit, the resources available and the severity criteria. Therefore, reimbursement is only pre-approved if the relationship between the resources and benefits is reasonable. To determine that, the Cost Effectiveness Acceptability Ratio is weighted against disease severity (PPRI, 2018). In the case of Ocrelizumab, the benefit, resource availability and the severity criteria was not met as the therapy is deemed not cost effective when compared to its comparator (NIPH, 2018).

2.6. Market Access Strategy

To start, to enable minimize the challenges faced by payers such as; uncertainty related to the effect of the therapy and its costs, cost of non-responders, enhance political reputation, minimization of inappropriate use of therapy (off-label), budget constraints and many more, and that pharmaceutical industries, a compromise is sometimes reached with the pharmaceutical companies to enable the necessary healthcare delivery to the citizens (Anneloes van Walsem, 2019). Therefore, three types of Market Access Agreements will be discussed namely; Commercial Agreement, Payment for Performance Agreement and Coverage with Evidence Agreement (Maureen Rutten, 2018).

2.6.1. Commercial Agreement

To start, commercial agreement is a discount based, payer perspective contract type that helps to reduce the pharmaceutical expenditure for the payers. A separate analysis and collection of patient health outcome data by the payer is not applicable. Examples are flat price per patients regardless of the number of doses administered, Cost sharing agreement, Rebate and Discount. The time frame of the agreement is permanent and it is currently known that the U.K. reimbursement decision is as a result of the commercial agreement, but the specifics are not revealed (NICE, 2018) (Jarosławski, S., & Toumi, M 2011).

2.6.2. Payment for Performance

Payment for Performance is a form of outcome guarantee or insurance contract based. It is a permanent risk-sharing agreement that is applicable per patient treated. In addition, per patient analysis and collection of health outcomes data is applicable. The underlying concept is to avoid inefficient healthcare expenditure of treating patients who do not respond to the expected efficacy of the therapy. Also, the time frame of the agreement is permanent. Examples are Payment for Performance and Pay back for non-Performance (Jarosławski, S., & Toumi, M 2011).

2.6.3. Coverage with Evidence Development

Coverage with evidence development is a provisional agreement until a new sets of evidence is developed from the cohorts of patients. The analysis and collection of cohorts of patient's health outcome is applicable. The time frame of the agreement is temporary and provisional until the final decision making is reached and guided by new evidence.

In addition, its underlying concept is that it reduces the uncertainty about the real life effectiveness of the therapy. Therefore, with the help of the HTA analysis, final reimbursement decision can be tied to the pricing decision made as a result of coverage with evidence. Examples are; Temporary coverage on a condition that the uncertainty about a specified health outcome will be reduced with new evidence, real life effectiveness, higher efficacy following the analysis of a pre specified patient's subgroup, long term effect, reduction in the rate of healthcare resources use e.g., reduction in the rate of hospitalization (Jarosławski, S., & Toumi, M 2011).

2.7. Pricing Models

The pricing models that would be discussed in this chapter includes but not limited to the following; Cost Plus Pricing, Willingness to Pay Pricing, Value Based Pricing, price benchmarking and Mixed-Model Pricing (Gregson N et al, 2005). However, only Value Based Pricing and Price benchmarking or Price Referencing Strategy will be elaborated in this project. The few others can be found in the glossary.

2.7.1. Price Benchmarking/Price Referencing Systems

Price benchmarking is used when there is already an existing therapy with similar efficacy in the markets and mostly when the mentioned existing therapy has been launched in another country. More importantly, an innovative therapy is clustered among other therapies of equivalent efficacy (Gregson N et al, 2005). In addition, Price Referencing System can be categorized into three namely; Internal Price referencing, External Price Referencing and the combination of both internal and External price referencing.

Moreover, Internal Referencing Pricing is used when a new innovative therapy is compared with cluster of a similarly efficacious therapy. In the same vein, an External Referencing Pricing is used to compare the price of a new innovative therapy to the therapy launch prices in a group of countries. A typical example of an external referencing pricing is NOMA pricing guidelines explain in chapter 1.2. Finally, the combination of both Internal and External Price Referencing implies that the new innovative therapy is compared to both the group of products in other countries and the respective launch price. The lower of both prices in used (Gregson N et al, 2005).

2.8. Reimbursement Strategy

Reimbursement strategy is a combination of market access strategy and pricing models that is locally tailored to meet the health needs of a locality, region or state. Therefore, various reimbursement Strategy includes, but not limited to Price Volume Agreement, Discount, Claw-back, Rebate, Out of Pocket, Prioritization, Local and Region Reimbursement, One-on-One Reimbursement.

Price Volume Agreement is reached when the pharmaceuticals pay a portion of sales volume of a specific threshold or pays rebate to the payer on an agreed sales quota (Kolassa EM, 2009). In addition, a Discount is a reduction in the price that is intended to increase the sales volume. Claw-back is the amount the industry has to return to the payer in instances where the public spending exceeds the budgeted, while a rebate is a form of price volume agreement whereby some amounts is refunded to the payer when a certain volume of the therapeutic is purchased.

Moreover, out of pocket spending is a supplementary healthcare expenses paid by the patients. Prioritization is a form of rationing the therapy to a subgroup of patients according to their level of needs. Local and Regional Reimbursement happen mostly in countries where reimbursement is usually from the states level and as a result of scarce resources in the midst of a costly therapy, consensus is given to the local or regional level if their budget could fund the said therapy. Finally, one-on-one reimbursement is when individuals pays the healthcare expenses out of their own pocket (Maureen Rutten, 2018).

3. Research Methods

This chapter will provide answers to the framework illustrated in Chapter 1.3., and to the research problems raised in chapter 1.2.

3.1. What are the decision made on reimbursement or non-reimbursement of Ocrelizumab in Norway and the referenced countries?

To start, some of the content of chapter 2.5 will be used. In other words, the recommendation of the referenced countries and Norway will be stated.

In light of that, NICE recommends Ocrelizumab as an option for treating RRMS in adults with active disease defined by clinical image on two condition. First, only if Alemtuzumab is contraindicated or not suitable. Second, if the manufacturer provides the therapy according to commercial agreement (NICE, 2018).

For Ireland, it is established in chapter 2.5.4., that ''the HSE has approved reimbursement of Ocrelizumab following a confidential price negotiation for this indication RRMS only'' (NCPE, 2019)

For Denmark, the Danish Medicine Agency after entering in a pricing agreement with the manufacturer at a lower price than AIP, it is estimated that there is a reasonable relationship between the clinical added value and the costs associated with the treatment with Ocrelizumab for all three populations (Medicinradet, 2018)

For Norway, the Norwegian Medicine Agency as written in chapter 1.2. concluded that although, Ocrelizumab has proven effective and probably at the topmost of what can be considered as a cost effective treatment, but we cannot reimburse it because the price is high'' (Dagensmedisin, 2018) (NIPH, 2019).

3.1.1. Based on the decision as outlined in chapter 1.2.1, is the cost effectiveness result enough for the reimbursement decision in the referenced countries?

To start, the recommendation of the economic evaluation done in June 2018 by NICE was that Ocrelizumab is not recommended for the treatment of RRMS in adults with active disease defined by clinical or imaging features. The reasons being that although Orelizumab slows the disease progression in the respective comparators, the committee is skeptical about the result of the indirect comparison of Ocrelizumab to the comparators. In other words, there is no direct evidence comparing Ocrelizumab to other treatments when it comes to the results the primary endpoints of ARR and CDP (NICE, 2018). However, in July 2018, NICE reimbursed the same therapy with the same comparators, as well as the same values of endpoints.

Therefore, between the recommendation and the decision in June 2018 and that of July 2018, the only difference is the ''commercial agreement clause'' added to the 2019 reimbursement decision. Hence, it shows that the cost effectiveness result is not enough for the reimbursement of Ocrelizumab in the U.K. (NICE, 2018).

For Ireland, it is also a similar trend with the U.K. This is because in 2018, the NCPE recommended that Ocrelizumab is not to be considered for reimbursement unless its cost effectiveness is improved against the alternative treatments. A year after, the therapy becomes reimbursed, even with the same comparators and the same endpoints values from

2018. The only difference is that the condition necessary for reimbursement is the ''confidential price negotiations'' (NCPE, 2018) (NCPE, 2019)

For Denmark, as would be seen later in chapter 3.2, Ocrelizumab is only cost effective with Alemtuzumab for P3 i.e., for patients where neither Natalizumab nor Fingolimod is a possible treatment. More so, Ocrelizumab may be considered cost effective because it has more clinical value than Alemtuzumab and only if subject to 2-year time horizon. However, it is interesting to see that, even though the Danish Medicine Agency concluded that there is ''no clinical value'' of Ocrelizumab when compared to the comparators for both P1 and P2, except a little clinical value for P3 (see Appendix 1). The committee still concluded that there is a reasonable relationship between the clinical added value and the costs associated with the treatment with Ocrelizumab for all three populations P1, P2 and P3 (Medicinraadet, 2018).

3.1.2. What are the factors responsible for the reimbursement decision of the therapy in the countries where it is currently reimbursed?

In a nutshell, the factors responsible for the reimbursement of Ocrelizumab in the referenced countries are beyond the cost effectiveness analysis evaluation, rather as a result of pricing, market access and reimbursement strategies as elaborated in chapter 2.6, chapter 2.7 and chapter 2.8. The author of this report is not able to go deeper on the type of specific strategy each country used because the content of those respective agreement is confidential (NICE, 2018), (NCPE, 2019), (Medicineraadet, 2019)

3.2. What are the factor responsible for the variation in cost effectiveness of the therapy among these countries and Norway?

The factors listed in chapter 1.3.2. will be investigated, elaborated, evaluated and compared between Norway and the referenced countries.

3.2.1. Differences in Burden of Disease, Basic Demography and Disease Epidemiology

The burden of disease is described as death and loss of health due to disease, injuries and risk factors and it is estimated by adding together the number of years an individual loses as a result of an early death, this is termed as Years of Life Lost ''YLL''. In addition to that is also the number of years of life an individual life with disability that is caused by that disease. It is termed as Years of Life Lived with Disability ''YLD''. Meanwhile, the sum of YLL and YLD gives a single estimate of burden of disease and it is termed as Disability Adjusted Life Year ''DALY'. Therefore, one DALY represents the loss of one year of life lived in full health (WHO, 2020).

Having established the above, MS is one of the costliest neurological diseases as a result of its early onset, long duration and its adverse effects it has on work and daily activities. It is established that about 700,000 people are living with MS in Europe, with which about 70% of them are diagnosed during prime working years ''between 20-40''. Alongside, with the additional 9 million people with neurodegenerative disease, the cost of neuron condition is approximated to about €800 Billion (EMSP, 2015).

In addition, Norway and the reference countries differ in basic demographic and epidemiology such as the patient population, Mortality, severity and prevalence of Multiple Sclerosis. The differences among these factors across countries will affect the cost effectiveness of Ocrelizumab. Having established that, the percentage of the patient population in comparison

to the population of Norway and the reference countries falls within 0,001 and 0,002. This indeed explains the rarity of MS (both RRMS and PPMS).

Table 1. MS Prevalence and Severity

		Death (95% uncertainty interval)		Prevalence (95% uncertainty interval)		DALYs(95% uncertainty interval)	
Country	**Patient Population**	**2016 Counts**	**% change in age-standardized rates between 1990 and 2016**	**2016 Counts**	**% change in age-standardized rates between 1990 and 2016**	**2016 Counts**	**% change in age-standardized rates between 1990 and 2016**
Netherlands	**25,197**	**219**	**-13%**	**25,197**	**16.7%**	**12,190**	**0.6%**
U.K.	**106,454**	**1,290**	**8.1%**	**106,454**	**28.5%**	**60,333**	**12.4%**
Ireland	**8,054**	**52**	**-14.5%**	**8,054**	**26.1%**	**3,536**	**4.9%**
Germany	**111,970**	**1,165**	**-7.3%**	**111,970**	**21.4%**	**57,865**	**2.5%**
Sweden	**20,304**	**126**	**7.2%**	**20,304**	**50.9%**	**8,138**	**27.2%**
Denmark	**11,673**	**112**	**-15.4%**	**11,673**	**18.5%**	**5,812**	**-3.3%**
Norway	**7,518**	**88**	**6.0%**	**7,518**	**7.7%**	**4,224**	**3.9%**

Source; (Wallin, M. T. et al., 2019)

Moreover, as shown in Table 1, Denmark, Ireland, the Netherlands and Germany have the lowest mortality rate as a result of Multiple Sclerosis with the percentage change in age standardized mortality rates between 19990 and 2016 of -15.4%, -14.5%, -13%, and -7% respectively. On the other hand, the United Kingdom, Sweden and Norway have the highest mortality rate of patients with MS with 8.1%, 7.2% and 6.0% respectively (Wallin, M. T. et al., 2019). Nonetheless, on a scale of small, moderate, large and very large, the impact of death according to MS is small, which explains one of the reasons why none of the countries reimburse the pharmaceutical therapies of MS due on the mortality rate (Wallin, M. T. et al., 2019) (Drummond et al., 2015)

In the same vein, Sweden, United Kingdom, Ireland and Germany have the highest number of MS prevalence with percentage change in age standardized prevalence rate between 1990 and 2016 of 50.9%, 28.5%, 26.1%, and 21.4% respectively. Moreover, Denmark, Netherlands and Norway have the least number of MS prevalence with percentage change in age

standardized rate between 1990 and 2016 of 18.5%, 16.7% and 7.7% respectively (Wallin, M. T. et al., 2019).

Furthermore, the severity of MS as expressed in DALYs is the highest with Sweden, United Kingdom, Ireland and Norway with percentage change in age standardized DALYs rates between 1990 and 2016 of 27.2%, 12.4%, 4.9% and 3.9%. On the other hand, Germany, the Netherlands and Denmark have the least severity of MS with percentage rates of DALYs between 1990 and 2016 of 2.5%, 0.6% and -3.3% (Wallin, M. T. et al., 2019).

3.2.1.1. Mortality Rate

It is established that the United Kingdom, Sweden and Norway have the highest mortality rate (Wallin, M. T. et al., 2019). Also, the effect of MS mostly reduced quality of life. Nonetheless, the effect of death according to MS on the scale of small, moderate, large and very large is small. Hence, none of the countries cost effectiveness analysis is affected by the mortality rate, but life lost due to disability.

3.2.1.2. Disease Population

It is common knowledge that the health interventions that are delivered on the population level are mostly cost effective. As a result, MS is the most common neurological disorder that often result in being handicapped (Foundation Charcot, 2014). Therefore, although MS is a rare disease, but there is a likelihood that a therapy for RRMS might be cost effective.

Interestingly, as explained in chapter 2.5.5., Sweden digressed a bit from its usual value based reimbursement requirement and include ethical issues that emphasizes human dignity as a part of the assessment criteria. In doing so, the rarity of PPMS, which comprises about 10%-15% of MS is considered as a criterion for reimbursement (Janusinfo, 2018). In addition to the U.K. clinical and cost effectiveness criteria for reimbursement, NHS also cited an ethical reason for reimbursement of Ocrelizumab for the treatment of RRMS i.e., ''other than Ocrelizumab, there are currently no disease-modifying treatments with a marketing authorization for RRMS''. Hence, its reimbursement (NICE, 2018) (Drummond & Pang, 2001).

In addition, the age group of the patient's subgroup with PPMS that Ocrelizumab is highly efficacious are patients younger than 45 years. Therefore, the fact that the patients older than 55 will have hard time coping with the adverse effects of the therapy limit the target user age group to 55 years and below. In other words, the patient subgroup that is cost effective for Ocrelizumab to be reimbursed in Sweden are patients 55 years old and below (Janusinfo, 2019).

3.2.1.3. Disease Prevalence

More so, is it established that intervention is likely to be cost effective where the prevalence is high. Having noted that, Sweden, the United Kingdom, Ireland and Germany have the highest prevalence rate. Ocrelizumab is indeed reimbursed in the four countries. Well, according to chapter 2.5.3 and chapter 2.5.5, prevalence rates are not the major criteria used in the reimbursement of pharmaceuticals in Sweden and Ireland. Swedish TLV uses a value based pricing model to assess market access and reimbursement of pharmaceuticals, while cost and efficacy are the main concern for HSE Ireland (GLI, 2019). However, Sweden grants

market access and reimbursement to Ocrelizumab on ethical reasons. One of the elements included in the ethical ground is the prevalence of PPMS as a condition for reimbursement (Drummond & Pang, 2001).

Using the same criteria, it was established in the last paragraph of chapter 2.5.7. that Norway reimbursement criteria is the benefit of the therapy, availability of resources and severity criteria. Therefore, level of prevalence does not affect cost effectiveness of Ocrelizumab in Norway i.e., it's not a criterion for Norway to reimburse a pharmaceutical product. Even if it is, the prevalence rate is low if placed on the scale of low, moderate, high and very high. In short, Norway also has one of the least/lowest prevalence rates among the referenced countries (PPRI, 2018) (Wallin, M. T. et al., 2019) (PPRI, 2018).

3.2.1.4. Disease Severity

As elaborated in Table 1, Sweden, the U.K., Ireland and Norway have the highest disease severity with DALYs of 27.2%, 12.4%, 4.9% and 3.9%. Indeed, the severity clause impacts the cost effectiveness of Ocrelizumab in Sweden, because it is cited as one of the elements considered for its reimbursement. As a matter of fact, one of the four operationalized dimensions of Swedish human-dignity ethical requirements is also the severity of the condition. In other words, on a severity scale of low, moderate, high and very high, Swedish HTA body categorized the PPMS severity as high.

The body further stated that MS is a disease that leads to disability and shortened life expectancy. More importantly, that MS disability also leads to hospitalization which has a negative impact on the patient's quality of life and occasionally involves an increased risk of dying prematurely (Janusinfo, 2019).

More so, one of the criteria for Norway pharmaceuticals reimbursement is the disease severity, so one would expect that the therapy would be reimbursed. More importantly, according to the Norheim commission which proposed measuring severity with a health loss criterion. Furthermore, it was recommended that the severity criterion should be presented in two forms, namely; the description as used in **clinical practice** and the operationalized form used in quantifying **severity in HTAs at the group level** (Regjeringen, 2017).

To test the HTA context, assuming the patients are 30 years old, these patients would have a quality adjusted life expectancy of approximately 11.0 QALYs. A 30 years old person, not suffering from RRMS, has a quality adjusted life expectancy of 43.1 QALY. Compared to the normal population, a patient 30 years old receiving current treatment would have expected health loss of 43.1-11-0=32.1 years in good health measured in QALYs (NIPH, 2019).

Furthermore, the latter clause of severity criteria implies quantifying severity by measuring the number of lost healthy life years provided the treatment is not made available. (Regjeringen, 2017). Having established that, as explained in chapter 2.2., the patient with EDSS scores higher than 3.5, but below 6.5 meet the clinical level severity criteria. Especially, in the subgroups of highly active and rapidly evolving severe patients within the RRMS. Therefore, the severity criterion is met (MS Society, 2020).

Finally, among the criteria enumerated in basic demography and epidemiology, Norway varies in the entire criteria in comparison to the reference countries. Disease severity however is the only criteria that Norway has a similarity with the referenced countries.

3.2.2. Differences in Health System Design and Variation in Clinical Practice

This subchapter will show how the health system design and variation of clinical practice differ between Norway and the reference countries. More importantly, how the differences in choice of comparators in its clinical effectiveness and safety impact the cost effectiveness. Also, how the differences in their respective relative cost, incentives and healthcare payment structure affects the cost effectiveness of Ocrelizumab for the treatment of MS patients (Drummond & pang, 2001).

As already established, the variation in clinical practice patterns among countries also explains the variation in the cost effectiveness among those countries. It is imperative to know that except Cladribine and Ocrelizumab, the remaining current DMTs do not have market authorization for RRMS (NIPH, 2019) (Eunethta, 2015).

3.2.2.1. Variation in Clinical Practice as it relates to Differences in Relative Prices and Costs

When it comes to recommendation as a result of sources for data on costs, Ireland opts for sources included in the RTCs, observational studies, clinical practice guidelines, local administration and accounting data, expert opinion. For U.K., the sources for costs Healthcare Resource Group HRG of public list prices, patient access scheme, national average unit costs. For Norway, market prices are used as a proxy for costs. For Denmark, the source for costs is a Diagnostic Related Group DRGs of clinical and epidemiology data on use of resources. Finally, (Eunethta, 2015).

In addition, in cost effectiveness analysis between countries, the differences in their relative costs of healthcare resources like the drug prices, physician's consultation, inpatient hospital costs etc., also lead to the differences in their respective cost effectiveness (Drummond &Pang, 2001).

In light of the previous paragraph, elaboration of cost comparison between Norway and Denmark will be done. To start, the hospital cost constitutes the following; the starting cost i.e., initial patient's consultation with doctor or nurse, the administration costs, Control and Lab Test, MRI scan and the handling cost of SAE ''only listed for Denmark''. Therefore, the administration costs of NOK9.483 in Norway is almost 35% higher than 6,207 in Denmark. The reduction in the respective relative costs in Denmark is as a result of the country's usage of DRGs which has advantages in reducing the length of stay, as well as avoiding the delivery of unnecessary services that may incur additional costs. In other words, DRG payment as it affects the relative price, in turn affects the relative cost effectiveness of Ocrelizumab between Norway and Denmark (EuroHealthSUmmit, 2012) (Drummond & Pang, 2001) (Drummond et al, 2015).

Additionally, the inclusion of Rituximab whose list price is NOK29,599 and about 86% cheaper than the list price of Ocrelizumab NOK217.295. More importantly, Rituximab is not included as one of the comparators in Denmark. The inclusion or exclusion, as well as the low cost list price of Rituximab will have an impact on the total costs and affects the incremental cost that

eventually explains part of the variation in ICERs for the respective countries (NIPH, 2019) (Medicinraadet, 2018).

3.2.2.2. Variation in Clinical Practice as it relates to Choice of Comparators

To start, as a result of problem associated with the DMTs as an unauthorized ''except Cladribine and Ocrelizumab'' therapy for RRMS, a Placebo comparison is relevant, especially when the new therapy is intended as adjunctive therapy or a substitute for an existing therapy that is the current standard treatment.

Therefore, all therapies from each country is compared to placebo to enable derive the critical endpoints needed. Then, the respective derived data of the comparators for each critical endpoint are compared to the intervention of Ocrelizumab (Drummond et al, 2015).

Additionally, For the United Kingdom, technologies that are currently used in clinical practice or recommended in current NICE guidance are permitted to be used as comparators. Cladribine is excluded because the trial started before the recommendation by NICE. Therefore, the relevant comparators are Alemtuzumab, Interferon beta-1a, Dimethyl Fumarate and Fingolimod for highly active disease, while Glatiramer Acetate, Natalizumab and Teriflunomide are for the rapidly evolving severe disease. So, the alternatives are compared individually to Ocrelizumab. More so, it is concluded that Interferon beta-1a and Glatiramer Acetate could be considered similar in terms of effectiveness, but not in terms of cost effectiveness. Therefore, Interferon beta-1a is compared with Ocrelizumab (Eunethta, 2015) (NICE, 2018).

In addition, Ireland requires routine care as the comparator. This implies the technologies that are most widely used in Ireland clinical practice. Therefore, like in the U.K, Ocrelizumab is compared with Interferon beta-1a (Eunethta, 2015) (NCPE, 2018).

Furthermore, Norway's preferable choice of comparator to be included is the one that the new treatment will most likely to replace if the currently used treatment is not cost effective. Therefore, Ocrelizumab, Rituximab, Alemtuzumab, Natalizumab, Fingolimod, Cladribine, Glatiramer Acetate, Dimethyl Fumerate and Teriflunomide are compared with Placebo. Comparison of Ocrelizumab to Rituximab, Cladribine and Alemtuzumab are later done.

As a result of Rituximab and Cladribine, Interferon beta-1a is excluded. More so, it is imperative to know that Cladribine is the only therapy that is authorized to treat RRMS. Meanwhile, even though other comparators that are included are authorized to treat other types of MS, Rituximab, an authorized cancer treatment is being used as an off label MS treatment (Eunethta, 2015) (NIPH, 2019).

Denmark situation is peculiar. The comparators are categorized into three groups. The first P1 are RRMS patients who have disease activities on first line therapy and who are John Cunningham Virus ''JCV'', including patients with a particularly high disease activity, who have not been previously treated but are JCV positive. Therefore, the comparator for P1 is Fingolimod.

P2 comprises of RMS patients who have disease activities on first line therapy and who is JCV negative. Including RMS patients with particularly high disease activity that had not been previously treated and which are JCV negative Therefore, the comparator for P2 is Natalizumab. P3 on the other hand are RMS patients who have disease activity on first line therapy and treatments with neither Natalizumab nor Fingolimod is possible, but with high disease activities that had not been treated before. Therefore, the comparator for P3 is Alemtuzumab (Medicinraadet, 2019).

3.2.2.3. Variation in Clinical Practice with Choice of Comparators as it affects the Clinical Effectiveness, Safety and Cost Effectiveness

This subchapter will elaborate on how the variation in clinical practice in regards to choice of comparators affects the clinical effectiveness, safety and cost effectiveness of the intervention.

3.2.2.3.1. Clinical Effectiveness

Annualized Relapse Rate ''ARR'', Confirmed Disability Progression ''CDP' 'and the MRI lesion/change in EDSS are the criteria to measure the clinical effectiveness of Ocrelizumab in comparison to its comparators.

Ireland VS the U.K.

Annualized Relapse rate ''ARR'' and Confirmed Disability Progression ''CDP''

To start, the primary end points are ARR and CDP. Meanwhile, for Ireland and the U.K., the ARR rate ''45%'' is the same, but the CDP rate of 33% for Ireland is less favorable by 3.0 percentage point compared to 35% for the U.K. The result shown for Ireland is only for 12 weeks. Therefore, the author assumes that the ARR might be the same if the 24 weeks' result is averaged with that of 12 weeks. Nonetheless, such variation can alter the cost effectiveness in both countries (NICE, 2018) (Medicinraadet, 2018).

Norway VS Denmark

Annualized Relapse rate ''ARR'' and Confirmed Disability Progression ''CDP''

For Norway and Denmark, the choice of comparators in both countries differ. This is because Denmark categorized the comparators into P1, P2 and P3 as described in the last two paragraphs of Chapter 3.2.2.2. As a result of the differences in the choice of comparators, the primary endpoints ARR and CDP for both countries are different, except for Natalizumab when compared to Placebo in P2 for Denmark that has the same ARR and CDP as Norway. Hence, they both have 68% RRR for annualized relapse rate, as well as 40% in approximation for CDP respectively.

It is important to know that in other categories where both countries choose a different comparator. The results for the respective endpoints vary. This variation will obviously impact the cost effectiveness result in both countries (NICE, 2018) (Medicinraadet, 2018).

Ireland & the U.K. VS Denmark

Expanded Disability Status Scale ''EDSS''

First, it is imperative to know that EDSS is a secondary endpoint for clinical effectiveness. Therefore, the RRR rates for T2 in Ireland and the U.K. when Ocrelizumab is compared to Interferon beta-1a are 64% and 36% respectively. However, it is 94% and 80% for both T1 and T2 in Denmark. The RRR rates of Fingolimod and Natalizumab of 82% and 86% in Denmark is better than in the U.K and Ireland.

So, the author assumes that the reason for the high effectiveness of Ocrelizumab in the EDSS state in Denmark is because grouping '' as described in the last two paragraphs of Chapter 3.2.2.2'' of patients according to their JCV status before they are enrolled into the study. Therefore, the patients are grouped based on the DMT that is suitable for them. As a result of JCV status patient eligibility criteria, the treatment of Ocrelizumab with 94% and 80% appears more effective in lowering the lesions for both GAL1 and GAL2 than for U.K. and Ireland of 36% and 64% for GAL2. Hence, the variation in the EDSS states with also cause variation in their respective cost effectiveness. (NICE, 2018) (NCPE, 2019) (Medicinraadet, 2018)

3.2.2.3.2. Safety

For safety, Serious Adverse Event ''SAE and treatment withdrawal as a result of adverse event will be used as the criteria for safety assessment of Ocrelizumab clinical effectiveness when compared to its comparators.

Denmark VS Norway

Serious Adverse Event ''SAE'' and Treatment Withdrawal due to SAE

To start, with the exception of Natalizumab in P2 which performs worse than placebo of 38% RRR in TWSAE in Denmark, Ocrelizumab performed best for both endpoints in Denmark with 21% for SAE and 44% for TWSAE. However, when it comes to Norway, Rituximab performed the best. It has the RRR rate of 60% and 81% for SAE and TWSAE when compared to Ocrelizumab with RRR rate of 26% and 16% in. Other standard therapies in Norway also perform better than Ocrelizumab (NIPH, 2019) (Medicinraadet, 2018).

As a result, the author of this report assumes that the reason may be that patients are already used to the existing treatment of Rituximab and other treatment in Norway. Especially, since Rituximab has been used as standard care. Therefore, the likelihood of a more adverse effects is expected with a new treatment or switching treatment. To corroborate this assumptions, in Denmark where Rituximab treatment is not in routine clinical practice, Ocrelizumab ranked the best in SAE and TWSAE (NIPH, 2019) (Medicinraadet, 2018).

3.2.3. Differences in Analytical Approach and Methodology requirements

This subchapter will elaborate the differences in Analytical Approach. The elements includes will range from Differences in types of Analysis, Choice of Perspectives, Choice of Discount Rate and Time Horizon, Differences in costing Methods, Differences in Utility Value Used and Differences in Willingness to Pay Threshold. (Drummond & pang, 2001) (Drummond et al, 2015)

3.2.3.1. Differences in Types of Analysis

Meanwhile, Denmark adopts a Cost Minimization Analysis ''CMA'', whereby all the therapies included in the analysis are considered to be equally effective, but are prioritized according to their respective serious side effects. As a result, SAE handling cost of NOK6,209 for Alemtuzumab is included only for Denmark. This also increase the total cost when compared to Norway where handling costs of SAE and TSAE are excluded because the economic model is driven by ARR and CDP. (Drummond et al., 2015) (NIPH, 2019).

It is also important to know that Denmark adoption of CMA means QALY calculation is excluded and the therapy with the most favorable incremental cost is cost effective as shown below;

Category P1: What clinical value does Ocrelizumab offer compared when compared with Fingolimod to patients with RRMS who are JCV positive?

For category P1, adopting Fingolimod leads to a cost savings of NOK67,372 when compared with Ocrelizumab. Therefore, Ocrelizumab is not cost effective. However, the CDP rate of 33% compared to 14% of Fingolimod and the fact that Ocrelizumab almost completely suppressed the gadolinium enhance lesions GAL per T1 of 94% and T2 by 80% compared with 82% and 67% for Fingolimod shows its efficacy over Fingolimod. In other words, Ocrelizumab is superior to Fingolimod ONLY in clinical value added, safety profile and efficacy (Medicinraadet, 2018).

Category P2: What clinical value does Ocrelizumab offer compared when compared with Natalizumab to patients with RRMS who are JCV negative?

For P2, adopting Natalizumab leads to a cost savings of NOK45,884 when compared with Ocrelizumab. More, the ARR of Natalizumab of 68% is favorable than 48% of Ocrelizumab. Their CDP are similar. However, Ocrelizumab 94% and 80% lower lesion of GAL1 and GAL2 compared with 86% and 67% for Natalizumab, as well as 21% compared to 9% of SAE makes Ocrelizumab a bit superior in efficacy and safety profile. In short, while Ocrelizumab has RRR rate of 44% in TWSAE, Placebo is more favorable than Natalizumab with 38% (Medicinraadet, 2018).

Category P3: What clinical value does Ocrelizumab offer to patients where Natalizumab and Fingolimod is not a possibility?

P3 is the only category where Ocrelizumab is cost effective. It has an incremental cost savings of NOK99,782 compared to Alemtuzumab. More so, the ARR of both are similar, while the CDP is not reported. However, Ocrelizumab EDSS of 94% and 80% compared to 69% and 43% for Natalizumab proves Ocrelizumab is better in terms of efficacy. Moreover, with SAE of 48% and 44% TWSAE for Ocrelizumab compared to 9% and 26% for Alemtuzumab shows that Ocrelizumab has a better safety profile (Medicinraadet, 2018).

3.2.3.2. Choice of Perspectives on Cost and Outcome

When it comes to perspective on costs and outcomes, Ireland, The U.K., and Norway adopt healthcare perspective whereby the costs and effects fall on healthcare budget. However, Denmark adopts societal perspective whereby all the relevant costs and effects are taken into consideration (Drummond et al, 2015).

In practice, this implies that Denmark includes all relevant costs including productivity cost. Therefore, the inclusion of cost as a result of ''Patient time'' by Demark increased the travel cost of Ocrelizumab and Alemtuzumab by 73% and 84% in Denmark compared to Norway i.e., NOK8,113 and NOK15,936 for Denmark and NOK2,160 and 2,592 respectively for Norway (Medicinraadet, 2018) (NIPH, 2019).

However, the difference in perspective between Norway and Denmark also implies that by choosing the healthcare perspective, Norway has underestimated the opportunity cost of life prolonging interventions. In doing so, Norway has factored in the effects, but excludes the corresponding costs. This leads to differences in cost effectiveness of Ocrelizumab in both countries (Drummond et al, 2015).

3.2.3.3. Choice of Discount Rate and Time Horizon

To enable compare the value of the future costs and its respective health effects that take place in different time, the annual health outcome and costs have to be converted to their present value. To be able to do this, both health effect and costs are discounted in accordance with the discount rate adopted in each of the country (Drummond et al., 2015). Having established that, Norway and Denmark adopt the same discount rate of 4%, while that of the U.K. is 3.5% and Ireland is 5%. It is important to know that the discount rate causes variation in cost effectiveness among the countries because the higher the discount rate, the lower the present value of cost and effect and vice versa. In other words, discount rate of the U.K. has the most impact on ICERs, while that of Norway and Denmark are the same. Ireland ICERs is the least impacted (ISPOR, 2012) (Drummond et al, 2015) (Arthur E et al., 2018)

Moreover, in economic evaluation, it is advised that the choice of time horizon between alternatives should be long enough to enable captures all the relevant differences of the expected future costs and its respective health effects. As a result, a lifetime horizon is usually advised (Drummond et al., 2015).

Having established that, the different time horizon also affects the cost effectiveness of Ocrelizumab. For example, Denmark uses 2-year time horizon, as a result, Ocrelizumab is cost effective against Alemtuzumab with NOK99,782 in P3. However, when four-year time horizon is chosen, Ocrelizumab is no longer cost effective against Alemtuzumab (Medicinraadet).

In the same vein, the list price of Alemtuzumab of NOK307,679 is higher than the list price of Ocrelizumab of NOK217,295 in Norway in the first year. However, in the third year, the list price of Ocrelizumab has dropped to NOK48,219, while that of Ocrelizumab remains the same. The respective 84% reduction in the list price will also affect the cost effectiveness of Ocrelizumab compared to Alemtuzumab with a longer time horizon (NIPH,2019) (Drummond et al, 2015).

3.2.3.4. Differences in Costing Method

The adoption of societal perspective by Denmark makes it the only country to include productivity (cost Drummond, et al). As a result, the Danish Medicine Agency revealed that productivity cost is described by Amgros as the average wage of salary by an employed person (Amgros, 2020). In other words, Denmark adopts a Human Capital Method that uses income as a proxy for the loss of production (Drummond et al., 2015).

Therefore, as a result of the fact that Ocrelizumab treatment is twice in a year, the productivity cost might be overestimated due to short term absence. On the other hand, as a result of issues with SAE when treated with a novel Ocrelizumab, lower productivity cost might also be estimated, which eventually also affects the cost effectiveness of Ocrelizumab in Denmark (Drummond et al., 2015).

3.2.3.5. Differences in Utility Value Used

When it comes to choice of utility use, Ireland prefers indirect methods using the generic measure of either EQ-5D or SF-6D. U.K. also prefers Indirect methods using EQ-5D using TTO. Norway also prefers indirect methods with EQ-5D, SF-6D and 15D, while Denmark prefers direct methods using TTO and SG. Note that if the relevant utility data from the generic instrument are not available, Ireland and U.K. allow mapping from disease specific quality of life measure. In addition, in the absence of utilities from generic instruments, Norway also allows mapping. However, in the absence of utility data from the direct instrument, Denmark do not prefer mapping (Eunethta, 2015)

It is imperative to know that the Ireland, the U.K. and Norway prefers the generic indirect method. Indirect method implies patients describing their health states, while the described health states is valued by the general public. Due to public veil of ignorance, the public might give a lower valuation compared to when the patients value themselves directly. This is adaptation and coping i.e., a patient who is already adapted to his/her condition over time might think he/she is healthy (Drummond et al., 2015).

More so, while the choice of direct method valuation by Denmark implies that patients might value the health state according to the reality of their health according to the disease severity and that might result in higher values than the generic instruments like the EQ-5D. It is also costly and time consuming. To further elaborate Denmark choice of TTO and SG implies that TTO is much in line with QALY, but it has no real utility. However, the presence of SG reflects real utility and clinical practice. More so, for TTO there is always a bias in the amount of years' individual is willing to trade off for a healthy year and the bias related to risk aversion with SG (Drummond et al., 2015).

More so, the fact that EQ-5D is prone to ceiling effect i.e., it is less sensitive in mild condition and SF-6D is also prone to bottom effect i.e., it less sensitive in the severe condition imply that these bias may compromise the predictive accuracy of the instruments. Hence, it might lead to variation in ICER (Drummond et al., 2015).

However, the fact that Denmark would not allow mapping by predicting the equivalent of SF-36 from a disease specific instrument might explains the reason why QALY is not calculated for the Danish HTA. Hence, focus is placed on only costs (Drummond et al., 2015) (Medicinraadet, 2018)

3.2.3.6. Differences of Willingness to Pay Threshold

When it comes to the uses of Willingness to Pay WTP, Ireland has a threshold of €45,000 per QALY or NOK475,895 and U.K. is between £20,000 - £30,000 or NOK233,607 to NOK350,411 per QALY. For Norway, the WTP is around NOK500,000 per QALY, but CBA is not recommended

due to ethical and technical challenges associated with monetary value on health improvements. For Denmark, WTP can be used as a complementary measure of outcome by asking a segment of the population to value the health outcome in monetary value. In doing so, contingent valuation is used (Eunethta, 2015) (James F. et al., 2015).

However, it was established that the Danish WTP is done using contingent valuation. The process is rooted in Cost Benefit Analysis whereby every individual WTPs for health improvement is added together; if benefits (B-C > 0), then society gains welfare and the new treatment is beneficial to the society without calculating the ICERs. It does not have no restrictions in the range of benefits valued. As a result, even though Ocrelizumab is not cost effective in category P1 and P2 in Denmark, the policy maker reimbursed the treatment (Medicinraadet, 2018). Finally, the only difference is while the policy maker of Ireland, Norway and the U.K. state the WTP for health gains on behalf of the society, Danish is not (Drummond et al., 2015) (Briggs et al., 2006)

3.2.7. In light of new evidence, would the decision to reimburse change or remain the same in Norway?

To start, the only therapy standing against Ocrelizumab reimbursement in Norway is Rituximab. Indeed, it is imperative to know that Rituximab has favorable incremental costs of NOK189,903 and NOK81,586 when compared to Ocrelizumab and Cladribine ''the two authorized RRMS therapy''.

In the same vein, Ocrelizumab generates the highest QALYs among other therapies when compared to 7,1 of Placebo of i.e., 8.29, 8.27, 8.15, 7.92 and 8.14 and 7.95 for Ocrelizumab, Alemtuzumab, Natalizumab, Cladribine, Rituximab and Fingolimod respectively. In other words, Ocrelizumab has incremental health effect of 0.15 than Rituximab and 0.37 than Cladribine ''the only authorized MS therapy beside Ocrelizumab''

Therefore, it is obvious that Rituximab is dominant against Cladribine because its less costly and more effective. Therefore, Cladribine is dominated. However, Rituximab is less effective and less costly than Ocrelizumab or Ocrelizumab is more costly and more effective than Rituximab (NIPH, 2019) (Fenwick E., 2004).

Meanwhile, as a result of parameters uncertainties, probability sensitivity analysis helps in estimating the probability that Ocrelizumab is cost effective with different WTP threshold. In doing so, it shows that Ocrelizumab has 54% chance that it generates more health gains in QALYs and 0% chance that its less costly than Rituximab. In other words, Ocrelizumab has 54% chance of being more effective and more costly than Rituximab and a 45% chance of being less effective and more costly than Rituximab. Nevertheless, the conclusion will still depend on the choice of assumed cost effectiveness threshold values and if Norway is willing to pay more for health gains. (NIPH, 2019).

Nonetheless, adoption of Rituximab due to being less costly may only be for a short term. This is because 0.15 QALY loss may translate to the therapy becoming more costly than Ocrelizumab over time (Gisela Kobelt, 2019).

Therefore, as shown in chapter 3.1., and its sub chapters, all of the reimbursement decision made in Denmark, the U.K. and Ireland are as a result of confidential agreement. Norway may also take a cue.

3.2.8. Can the cost effectiveness of any of the countries be adapted to be applied in Norwegian settings?

Also, Norway could start the grouping like Denmark. Knowing patients JCV status enrolment into the trials seems to have a correlation with lowering the damage to the brain with which Norway called one of the most risk associated with DMTs in chapter 2.3. Therefore, with 94% and 80% lower lesion for Ocrelizumab in GAL1 and GAL2 seems to have a correlation with lowering GAL 1 and GAL 2 lesion of EDSS.

In light of the above, Sweden digress from the value based reimbursement system that is rooted in cost effectiveness analysis as pointed out in chapter 2.5.5. However, Ocrelizumab is later reimbursed Ocrelizumab for PPMS patients citing ethical reason that comprises of the severity of the condition, effect size of the measure, rarity of the condition and the cost effectiveness of the measure. In doing so, PPMS patients below 55 years are eligible. Perhaps, Norway can also take a cue.

4. Result/Findings

This chapter will reveal the result and findings in this project, especially in chapter 3. Wallin, M. T. article is used to explain the patient population regarding the disease prevalence and severity as they impact the cost effectiveness of the MS therapy in Norway and its referenced countries. In addition, the result of the reimbursement decision made in the referenced countries as it deviates from the cost effectiveness recommendation will also be revealed. Moreover, the result of the differences in factors that cause variation in cost effectiveness among the countries will also be explained. Finally, the result of if the cost effectiveness of any of the referenced countries can be adapted to Norwegian settings, as well as the result of if the decision to reimburse Ocrelizumab in Norway should remain the same or not in light of new evidence will also be revealed.

4.1. What are the decision made on reimbursement or non-reimbursement of Ocrelizumab in Norway and the referenced countries?

First, as written in chapter 1.2.1.1., the author of this report reiterates an excerpts from Drummond which says; ''economic evaluation is a tool to inform decision about which of the therapies to recommend in comparison with the alternative''. Having stressed that, it is revealed that the cost effectiveness result is not enough for the reimbursement decision and there is a disconnect between the recommendation in the aftermath of economic evaluation and the decision for reimbursement.

For instance, in 2018 HTA from U.K. and Ireland, NICE and NCPE **DID NOT** recommended Ocrelizumab for the treatment of RRMS patients. For U.K., the committee were skeptical of the endpoints for ARR and CDP due to lack of direct comparison, even though it favors Ocrelizumab. Ireland also said the cost effectiveness of Ocrelizumab has to be improved against its comparators. However, with the same endpoints as it was in 2018, both country recommended the reimbursement of Ocrelizumab a year later, using the confidential pricing agreement.

Denmark also have a similar occurrence, where Ocrelizumab is cost effective for only P3 category, but Danish Medicine Agency recommended the therapy for reimbursement after entering into a confidential pricing agreement that Ocrelizumab can be used to treat the entire P1, P2 and P3 category.

Finally, the author reveals that the result of cost effectiveness study is not enough for reimbursement decision. This is because the reimbursement decision for the three countries are based on financial agreement from Ocrelizumab manufacturer. The specific financial agreement is not known because of its confidentiality. However, the author believes it may have been one of those elaborated in chapter 2.6., chapter 2.7., and chapter 2.8. (NICE, 2018) (NICE, 2018), (NCPE, 2018) (NCPE, 2019), (Medicinraadet, 2018).

4.2. What are the factors responsible for the variation in cost effectiveness of the therapy among these countries and Norway?

This chapter will reveal the results from chapter 3.1.2.

4.1. Differences in Burden of Disease, Disease Prevalence and Disease Severity

First, since there is no exact cost that indicates the burden of disease of each country, the overall productivity loss of DALYs i.e., may be quantified in monetary terms.

As pointed out in chapter 3.2.1. and Table 1, even though the U.K., Sweden and Norway have the highest mortality rates, it does not have effect on the cost effectiveness, because the aim of DMT therapies is to improve the quality of life of RRMS patients. In addition, it is established that intervention like vaccination that are delivered at the population level are most cost effective, unlike the entire patient population of MS who falls within the definition of a rare disease.

However, Sweden reimbursed Ocrelizumab for PPMS in addition to the cost effectiveness for patients younger than 45 years old, Sweden reimbursed the MS treatment ''PPMS'', which is 15% of the MS population, citing ethical reasons - whereby two out of the three elements are rarity and the disease prevalence. The U.K. also reimbursed the MS treatment citing the rarity of the disease (Wallin, M. T. et al., 2019) (NICE, 2018), (Janusinfo, 2019).

In addition to the fact that the third element of Swedish ethical reason for reimbursement is also the disease severity, reimbursement of pharmaceutical therapies in Norway as elaborated in chapter 2.5.7., depends on three criteria. They are the benefit of the therapy, the available resources and the disease severity – ''the severity disease according to Norway Norheim commission must fulfil both clinical and HTA level severity''. As revealed in chapter 3.1.4., Norway fulfils both severity criteria as its one of the countries with the highest severity rate expressed in DALYs, ''which might be equated to a patient having an EDSS between 3.5 and below 6.5''. in addition to that is a 32.1 expected loss of good health in QALYs ''assuming a 30-year-old receiving the treatment'' (NMHCS, 2017) (NIPH, 2019).

4.2. Differences in Health System Design and Variation in Clinical Practice

This chapter will reveal the result of how the differences in choice of comparators in its clinical effectiveness and safety impact the cost effectiveness. It will also show the result of how relative cost impact the total cost, which in turn affect the cost effectiveness.

4.2.1. Variation in Clinical Practice as it relates to Differences in Relative Prices and Costs

To start, the **differences in the relative prices and costs** as shown in Table 2 also lead to differences in the cost effectiveness across the countries. This is revealed in situation where the administration cost for Norway is about 35% higher than that of Denmark. This low cost for Denmark is attributable to the usage of DRGs system as opposed to Norway (Eunethta, 2015) (Medicinraadet, 2018)

Table 2. Significant Differences in Admin cost

	Norway	Denmark
Cost Category	Ocrelizumab	Ocre
Admin Cost	9.483	6.207
Number of Infusion		
NAB Analysis		
MRI	2.808	3.263
Eye Examination		
SAE Handling Cost		
Medical Consultation	7.938	6.550
Blood Tests	484	
Observation Start Up		6.538
Travel/Denmark Patient Time	2.160	8.113
List Price	217.295	258.073
Total	240.168	288.744

Sources; (Medicinraadet, 2018), (NIPH, 2019) Eunethta, 2015) (European health Summit, 2012).

More so, as a result of how the comparators of Denmark are categorized into three groups, start-up costs are included for all the comparators in Denmark as shown is Table 2, but not in Norway. This is necessary because the JCV test is initially mandatory in Denmark to enable determine which comparator is suitable for a category of patient. Moreover, Norway excluded the handling costs of SAE, but Denmark included The inclusion or exclusion of certain costs impact the total cost which affects the incremental cost. Invariably, it impacts ICERs and cost effectiveness result among the countries (Medicinraadet, 2019) (NIPH, 2019) (Drummond et al., 2015).

Finally, the fact that a non-authorized cancer therapy called Rituximab is used an off-label therapy for MS in Norway, it causes a huge variation in the cost effectiveness of Ocrelizumab. This is because the list price of Rituximab is 86% cheaper than Ocrelizumab as shown in Table 3 explains a huge variation of cost effectiveness in Norway compared to the referenced countries.

Table 3. Differences in the list price.

	List price Y1	Y1 Drug Cost	Total Y1
Ocrelizumab	217,295	22,872	240,167
Alemtuzumab	307,679	30,594	338,273
Natalizumab	169,636	60,478	230,114
Cladribine	119,707	12,143	131,850
Rituximab	29,559	20,705	50,264

Sources; (NIPH, 2019)

4.2.2. Variation in Clinical Practice as it relates to Choice of Comparators and its endpoints

In respect to Clinical Effectiveness, Safety, SAE and TWSAE, the choice of comparators also has one of the biggest impact in the factors that on cost effectiveness study of Ocrelizumab in

Norway and the reference countries. To derive the endpoints needed for the necessary comparison, all therapies are first compared to Placebo in the four countries (Eunethta, 2015).

Table 4. Choice of Comparators

Therapy	Ireland	U.K.	Norway	Denmark
Ocrelizumab	Intervention	Intervention	Intervention	Intervention
Alemtuzumab	Comparator	Comparator	Comparator	Comparator P3
Natalizumab	Comparator	Comparator	Comparator	Comparator P2
Rituximab	N/A	N/A	Comparator	N/A
Fingolimod	Comparator	Comparator	-	Comparator P1
Cladribine	N/A	N/A	Comparator	N/A

Sources; (NICE, 2018) (NCPE, 2019), (Medicinraadet, 2018), (NIPH, 2019)

In addition, the comparators for Ocrelizumab are categorized in three groups called P1, P2 and P3 as shown in Table 4. In P1, the comparator is Fingolimod – used for patients who tested positive to JCV virus. P2 is Natalizumab – for patients tested negative for JCV virus and P3 is Alemtuzumab – for patients treated with neither Fingolimod and Natalizumab (Medicinraadet, 2018).

Moreover, it is imperative to know that none of the comparators included are authorized RRMS therapy except Cladribine inclusion in Norway. Therefore, the U.K. and Ireland choose Interferon beta-1a as the main comparator with Ocrelizumab under the assumption that the two therapies are considered similar in terms of effectiveness. While, in Norway, Rituximab, is the main comparator for Ocrelizumab (NIPH, 2019) (NICE, 2018). Hence, the comparison of their clinical effectiveness, and safety is as follows;

Clinical Effectiveness

For clinical effectiveness, ARR and CDP are the primary endpoints, while EDSS states is the secondary endpoint.

To start, with the same ARR for both U.K. and Ireland as seen in Table 5. However, the CDP rate differ by an increase of 3.0 percentage point for Ireland as shown in Table 6.

Ireland VS the U.K.

Table 5; Annualized Relapse rate ''ARR''

	Ireland		U.K.	
	Ocr	IFN	Ocr	IFN
	0.16	0.29	0.16	0.29
RRR	45%		45%	

Source; (NICE, 2018) (NCPE, 2019)

The author believes the 3% variation might be as a result of the fact that the data for 24 weeks for Ireland is missing. However, such variation can also vary the cost effectiveness of Ocrelizumab in both countries.

Table 6; Confirmed Disability Progression ''CDP''

	Ireland		U.K.	
	Ocr	IFN	Ocr	IFN
	9.1	13.6	9.8	15.2
RRR	33%		36%	

Source; (NICE, 2018) (NCPE, 2019)

More so, as a result of the categorization of the comparators into their JCV status in Denmark, The ARR and CDP rates in Norway differ a lot between Norway and Denmark as shown in Table 7 and Table 8. In short, it shows in the ARR and the CDP that both countries have similar endpoints when similar comparators were used as seen in the 68% and 40% for Natalizumab for ARR and CDP in both countries. Hence, variation as a result of Denmark categorization of comparators will vary the cost effectiveness of Ocrelizumab in both countries.

Norway VS Denmark

Table 7; Annualized Relapse rate ''ARR'' II

	Norway				Denmark					
					P1		P2		P3	
	Ale/Pla	Nat/Pla	Ocr/Pla	Ritu/Pla	Ocr/IFN	Fin/Pla	Ocr/IFN	Nat/Pla	Ale/IFN	Ocr/IFN
	0.14/0.53	0.17/.53	0.15/0.29	0.23/0.53	0.16/029	0.19/.40	0.15/0.29	0.23/0.73	0.18/0.39	0.15/0.29
RRR	74%	68%	66%	57%	45%	51%	48%	68%	54%	48%

Source; (NICE, 2018) (Medicinraadet, 2018)

Table 8; Confirmed Disability Progression ''CDP'' II

	Norway				Denmark					
					P1		P2		P3	
	Ale/Pla	Nat/Pla	Ocr/Pla	Ritu/Pla	Ocr/IFN	Fin/Pla	Ocr/IFN	Nat/Pla	Ale/IFN	Ocr/IFN
	0.54	0.60	0.53	0.55	0.091/0.136	0.25/0.29	9.1/13.6	17.0/29.0	N/A	N/A
RRR	46%	40%	47%	45%	33%	14%	42%	41%	N/A	N/A

Source; (NICE, 2018) (Medicinraadet, 2018)

In addition to that, Ocrelizumab, as well as other comparators in Denmark generates a very remarkable EDSS scores of 94% GAL 1 and 80% GAL2 for Ocrelizumab compared to 64% and 36% for Ireland and Norway as seen in Table 9 and Table 10 respectively. The author of this report assumes that the remarkable effectiveness of Ocrelizumab, as well as other comparators in Denmark is due to the fact that Denmark tests every patient for JCV virus before they are enrolled in the program. Hence, that enables treatment compatibility for each JCV status. The variation will also impact the cost effectiveness of the therapy in both countries.

Ireland & the U.K. VS Denmark

Table 9; Expanded Disability Status Scale ''EDSS'' state

	Ireland		U.K.	
	Ocr	IFN	Ocr	IFN
T1	0.45	0.98	N/A	N/A
RRR	57%		N/A	
T2	0.45	1.26	0.16	0.29
RRR	64%		36%	

Source; (NICE, 2018) (NCPE, 2019)

Denmark

Table 10; Expanded Disability Status Scale ''EDSS'' state

	Norway			Denmark					
				P1		P2		P3	
	Ale/Pla	Nat/Pla	Ocr/Pla	Ocr/IFN	Fin/Pla	Ocr/IFN	Nat/Pla	Ale/IFN	Ocr/IFN
T1	Insignificant			5/718	N/A	5/718	97/718	N/A	5/718
RRR	Insignificant			94%	82%	94%	86%	69%	94%
T2	Insignificant			5/718	N/A	5/718	17.0/29.0	N/A	5/718
RRR	Insignificant			94%	67%	80%	67%	43%	80%

Source; (NICE, 2018) (NCPE, 2019)

Safety

Denmark VS Norway

Table 11; Serious Adverse Event ''SAE'' and Treatment Withdrawal due to SAE

	Norway				Denmark					
					P1		P2		P3	
	Ale/Pla	Nat/Pla	Ocr/Pla	Ritu/Pla	Ocr/IFN	Fin/Pla	Ocr/IFN	Nat/Pla	Ale/IFN	Ocr/IFN
SAE			0.74	0.40	6.9/6.7	12.55/1.32	6.9/8.7	19.2/24.0	20.0/22.0	3.0/7.0
RRR	N/A	N/A	26%	60%	21%	5%	21%	9%	9%	48%
TW/SAE	0.54	0.46	0.84	0.19	3.5/6.2	7.5/7.7	3.5/6.2	6.0/4.0	N/A	3.5/6.2
RRR	46%	54%	16%	81%	44%	3%	44%	33%	28%	44%

Source; (NIPH, 2019) (Medicinraadet, 2018)

The endpoints for safety are SAE and TWSAE. Table 11 shows that Rituximab performs the best for SAE and TWSAE with 60% and 81% respectively when compared to an RRR of 26% and 16% for Ocrelizumab in Norway (NIPH, 2019).

The author believes this woeful performance by Ocrelizumab in Norway is as a result of the fact that the patient's already adjusted to the standard treatments like Rituximab, Natalizumab and Alemtuzumab and that the novelty of Ocrelizumab triggers treatment reactions the patients are not used to. As a result, such variation across the countries will also impact their respective cost effectiveness. The author corroborates the assumption in the Denmark RRR rates for SAE and TWSAE whereby Ocrelizumab performs best because Rituximab is not allowed in the clinical routine. The variation as a result of that will also impact the handling cost associated. Hence, the cost effectiveness will also be varied (Medicinraadet, 2018)

4.3. Differences in Analytical Approach Methodological Requirements

This chapter sums up the results of differences in the analytical approach and methodological requirements as it relates to Analysis of Subgroups, Differences in types of Analysis, Choice of Perspectives, Choice of Discount Rate and Time Horizon, Differences in costing Methods, Differences in Utility Value Used, Differences in Willingness to Pay Threshold, Differences in choice of Currency Conversion and Differences in Uncertainty Description.

4.3.1. Differences in Types of Analysis

Moreover, the different **types of analysis** also play a huge role in the variation in the cost effectiveness among those countries.

Table 12: EDSS States Improvement

Country	Prefered Type of Analysis
Ireland	CUA
U.K.	CUA
Norway	CUA
Denmark	CMA

Sources; (NICE, 2018) (NCPE, 2019), (Medicinraadet, 2018), (NIPH, 2019)

As shown in Table 12, the only country that choose a different type of analysis is Denmark and the effect of that will be revealed Table 13.

Table 13: Treatment cost between Norway and Denmark

	Norway	Denmark		Norway	Denmark		Norway	Denmark
Cost Category	Ocre	Ocre		Alem	Alem		Nata	Nata
Admin Cost	9.483	6.207		15.804	12.451		41.092	37.246
Number of Infusion								
NAB Analysis							1.987	
MRI	2.808	3.263		2.808	3.263		2.808	3.263
Eye Examination								
SAE Handling Cost					6.209			
Medical Consultation	7.938	6.550		7.938	8.090		7.938	342
Blood Tests	484			1.452			605	
Observation Start Up		6.538			11.451			6.538
Travel/Denmark Patient Time	2.160	8.113		2.592	15.936		6.048	13.098
List Price	217.295	258.073		307.679	359.928		169.636	202.155
Total	240.168	288.744		338.273	417.328		230.114	262.642

Sources: (NIPH, 2019) (Medicineraadet, 2019)

Denmark adoption of Cost Minimization Analysis ''CMA'', whereby the effect of all the therapies included in the analysis are considered equal and the priorities are placed on their respective serious side effects, which is also expressed in their respective handling costs as shown in Table 13.

Due to that, the differences between them are reduced to their cost comparison. As a result, it contributes to the rise in the total costs of Alemtuzumab in Denmark compared to Norway as seen in Table 13. Hence, the incremental cost is also affected as will be revealed below (Drummond et al., 2015).

Category P1: What clinical value does Ocrelizumab offer compared when compared with Fingolimod to patients with RRMS who are JCV positive?

Table 14; Cost Effectiveness Analysis of P1

		Year1	Year2	Total
Ocrelizumab P1	Drug Cost	258.073	248.045	506.118
	Hospital Services	19.296	15.404	34.700
	Patient time and Transport	8.113	5.710	13.823
	Total	285.482	269.159	554.641
Fingolimod	Drug Cost	227.447	218.699	446.146
	Hospital Services	18.025	15.466	33.490
	Patient time and Transport	5.079	2.553	7.632
	Total	250.551	236.718	487.269
Incremental Cost		34.931	32.441	67.372

Source; (Medicinraadet, 2018)

Category P2: What clinical value does Ocrelizumab offer compared when compared with Natalizumab to patients with RRMS who are JCV negative?

Table 15; Cost Effectiveness Analysis of P2

	Cost Element	Year1	Year2	Total
Ocrelizumab P2	Drug Cost	258.073	248.045	506.118
	Hospital Services	19.296	15.404	34.700
	Patient time and Transport	8.113	5.710	13.823
	Total	285.482	269.159	554.641
Natalizumab	Drug Cost	202.155	194.380	396.535
	Hospital Services	44.127	42.265	86.392
	Patient time and Transport	13.098	12.732	25.830
	Total	259.380	249.377	508.757
Incremental Cost		26.102	19.782	45.884

Source; Medicinraadet, 2018)

Category P3: What clinical value does Ocrelizumab offer to patients where Natalizumab and Fingolimod is not a possibility?

Table 16; Cost Effectiveness Analysis of P3

	Cost Element	Year1	Year2	Total
Ocrelizumab P3	Drug Cost	258.073	248.045	506.118
	Hospital Services	19.296	15.404	34.700
	Patient time and Transport	8.113	5.710	13.823
	Total	285.482	269.159	554.641
Alemtuzumab	Drug Cost	359.928	208.430	568.358
	Hospital Services	38.166	19.870	58.036
	Patient time and Transport	15.936	12.093	28.029
	Total	414.031	240.392	654.423
Incremental Cost		-128.549	28.766	-99.782

Source; (Medicinraadet, 2018)

It is imperative to know that the adoption of CUA by Norway implied that ARR and CDP endpoints, as well as their respective reduction on the EDSS states in the clinical effectiveness drive the economic model. As result, SAE and TWSAE, as well as their respective handling costs are excluded in Norway. This also impact the incremental cost that has impact on cost effectiveness.

However, with Denmark adoption of CMA, ICER calculation is ignored and the cost effectiveness is determined by the incremental cost between therapies. Having said that, with incremental costs savings of NOK67,372 and 45,884 for Fingolimod and Natalizumab, it is revealed that Ocrelizumab is not cost effective in both P1 and P2 as shown in Table 14 and Table 15. However, in P3 as shown in Table 16, the handling cost of SAE add to the rise in the

total cost of Alemtuzumab. Hence, Ocrelizumab becomes cost effective with incremental costs of DKK128,549.

4.3.2. Differences in Choice of Perspectives on Cost and Outcome

Additionally, the **choice of perspectives on cost and outcome** also plays a huge role in the variation of cost effectiveness studies in Norway, whereby the U.K., Ireland and Norway adopt healthcare perspective – ''all costs are consequences are placed on healthcare budget''.

Table 17. Choice of Perspective as it affects the total cost between Norway and Denmark

	Norway	Denmark		Norway	Denmark
Cost Category	Ocrelizumab	Ocre		Alemtuzuma	Alem
Admin Cost	9.483	6.207		15.804	12.451
Number of Infusion					
NAB Analysis					
MRI	2.808	3.263		2.808	3.263
Eye Examination					
SAE Handling Cost					6.209
Medical Consultation	7.938	6.550		7.938	8.090
Blood Tests	484			1.452	
Observation Start Up		6.538			11.451
Travel/Denmark Patient Time	2.160	8.113		2.592	15.936
List Price	217.295	258.073		307.679	359.928
Total	240.168	288.744		338.273	417.328

Source; (Medicinraadet, 2018)

Moreover, unlike Demark that adopts a societal perspective whereby all the respective costs and consequences are contained in the regional budget. In doing so, informal care cost and estimation of loss of production by the patients is included in the travel time. As a result, Denmark travel cost of Ocrelizumab and Alemtuzumab as shown in Table 17, is 73% and 84% higher than that of Norway (Medicinraadet, 2019) (NIPH, 2019) (Drummond et al, 2015).

4.3.3. Choice of Discount Rate and Time Horizon

Moreover, since MS has no cure, the relevance of the DMTs is to slow down the disease progression. In doing so, the disability progression is also reduced. When it comes to the perspective of discount rate, disability progression also means that the time for a patient to transition to a more severe EDSS state as described in chapter 2.2. is postponed. Therefore, the cost is incurred at the present, but the benefit of health effect is in the future. As a result of the divergent time pattern, discount rates help bring both cost and health effect that take place in different time to a present value (Drummond et al., 2015).

Having established that, Norway and Denmark adopt the same discount rate of 4%, while that of the U.K. is 3.5% and Ireland is 5%. It shows that the incremental costs and incremental effects of U.K. will be bigger than that of Denmark and Norway. Hence, it also impacts the cost effectiveness (ISPOR, 2012).

Category P3: <u>What clinical value does Ocrelizumab offer to patients where Natalizumab and Fingolimod is not a possibility?</u>

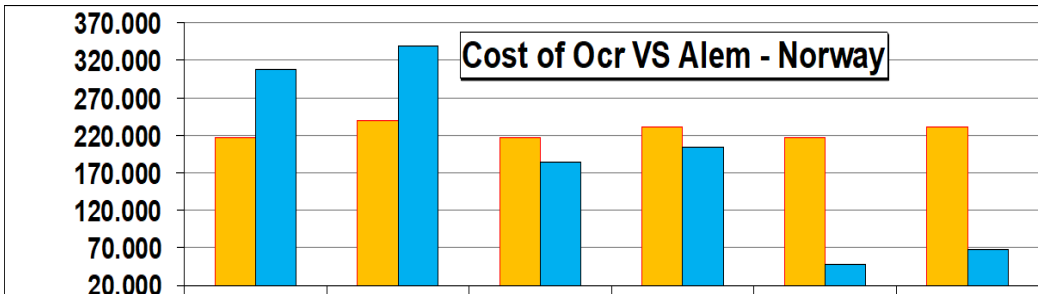
Table 18; Cost Effectiveness Analysis of P3

	Cost Element	Year1	Year2	Total
Ocrelizumab P3	Drug Cost	258.073	248.045	506.118
	Hospital Services	19.296	15.404	34.700
	Patient time and Transport	8.113	5.710	13.823
	Total	285.482	269.159	554.641
Alemtuzumab	Drug Cost	359.928	208.430	568.358
	Hospital Services	38.166	19.870	58.036
	Patient time and Transport	15.936	12.093	28.029
	Total	414.031	240.392	654.423
Incremental Cost		-128.549	28.766	-99.782

Source; (Medicinraadet, 2018)

In addition, Denmark opts for a 2-year time horizon which lead to incremental cost of NOK90,125 and NOK128,549 in favor of Ocrelizumab when compared to Alemtuzumab in P3 as shown in Table 18. However, in a four-year time horizon, Ocrelizumab is no longer cost effective. More importantly, the longer the time horizon, the cheaper the cost of all the therapies.

Table 19; List price of Ocrelizumab VS Alemtuzumab



	List Price Y1	Total cost Y1	List Price Y2	Total cost Y2	List Price Y3	Total cost Y3
Ocrelizumab	217.2950	240.1670	217.2950	231.500	217.2950	231.500
Alemtuzumab	307.6790	338.2730	184.6080	203.6150	48.2190	67.1660

Source; (NIPH, 2018)

Also, in Norway as seen in Table 19, Alemtuzumab is the most costly therapy among the comparators in the first year, but ranked the second in the third year as it has become 80% cheaper. These variations also impact the cost effectiveness of Ocrelizumab (NIPH, 2019).

4.3.4. Differences in Costing Method

As a result of the fact that only Denmark choose the societal perspective, it becomes the only country that allows the inclusion of an estimation of loss of patient's production time (Drummond et al., 2015)

More importantly, Danish Medicine Agency established that Amgros' used unit cost valuation guide to value patients' time. Therefore, chapter 2.6.3. of Amgros guidelines specified patient cost as the time spent by patients and patient caregivers. It is valued at the average hourly wage of a salaried employee in Denmark after taxes (Amgros, 2020).

This implies Human Capital Method ''HCM'' because Amgros uses the prognosis of income as a proxy to estimate production loss Time absent*rate in wages = Total productivity Cost (Drummond et al., 2015). However, as a result of the fact that Ocrelizumab therapy is administered twice a year, using HCM for short term absence might overestimate the cost of production lost because the patients can make up for the absence when back to work. Also, colleagues can as well take over or non-urgent work can also be cancelled (Drummond et al., 2015)

In the same vein, as a result of SAE associated with Ocrelizumab or other treatments, long term absence might also lead to lower productivity cost as a result of workers and jobs reallocation, replacement from the unemployment pool and labor can also be replaced by capital (Drummond et al., 2015). As a result of the short term and long term effect associated with the estimates of productivity costs, total cost might also be affected, which will affect incremental cost. Hence, the cost effectiveness is also impacted.

4.3.5. Differences Utility Value Used

In addition, the **differences in utility value used** contributes to the variation in the cost effectiveness. This is because Ireland, the U.K., and Norway adopt indirect method using either EQ-5D or SF-6D or SF-36. Doing so, indirect valuation entails the public might be undervaluing the patients' health description due to veil of ignorance (Eunethta, 2015).

EQ-5D is also prone to ceiling effect in mild condition, while SF-6D is prone to bottom effects in severe condition, which affect the estimate of the valuation and affect ICERs when value the mild condition using EQ-5D and severe condition using SF-6D. Also, Denmark opting for direct method TTO and SG entails the patients might over-value their own health as a result of adaptation and coping. That also impacts the valuation estimates and invariably impacts the cost effectiveness. Denmark adoption of SG reflect clinical practice and also corrects the weakness of TTO because it maximizes real utility (Drummond et al., 2015).

Meanwhile, Denmark uses SF-36, a generic instrument for the analysis in this report. However, there is an absence of utility data. Therefore, the author assumes that the fact that Denmark does not allow mapping as explained in chapter 3.2.3.6. by Eunethta, might be responsible for reasons why the utilities are not reported in the Danish HTA (Drummond et al., 2015)

As a result of the absence of EQ-5D and SF-6D valuation result in the HTA of the respective countries, it prevents the author of this project the opportunity to be able to assess the Reliability, Validity and Responsiveness of the instruments in response to their respective valuation. However, the author will like to enlighten the reader in the following way; take for instance an incremental cost of NOK10,000 and incremental effects of 0.15 for EQ-5D, .10 for SF-6D and 0.20 for SG. This implies that the ICER will vary between NOK50,000 to NOK100,000. This will also impact the cost effectiveness.

4.3.6. Differences in Willingness to Pay Threshold

With **willingness to pay threshold**, Ireland and the U.K. has a predefined threshold, which accounts for some of the reasons why Ocrelizumab become reimbursed in both countries. Norway also states a threshold of NOK500,00, but it is not recommended due to ethical and technical challenges associated with monetary value for health gains in CBA Eunethta, 2015). ICERs of Norway and Ireland are not given for Ocrelizumab (James F. et al., 2015).

Furthermore, Denmark uses WTP as a complementary measure of outcome with the help of contingent valuation. As a result, individual WTP is summed up instead of calculating QALYs. Therefore, the range of benefits to be valued is not restricted (Drummond et al., 2015).

However, according to chapter 3.2.3.6., it is established that the use of contingent valuation of WTP can be used as a complementary measure of outcome by asking a segment of the population to value the health outcome in monetary value. In doing so, there is no restrictions in the range of benefit valued because individual WTP are simply added together. From that point of view, could it be the reason why Ocrelizumab is reimbursed? Even though not cost effective in P1 and P2 as shown in Table 14 and Table 15, the therapy is reimbursed and should be adopted as a first line treatment for all categories. (Drummond et al., 2015) (Medicinraadet, 2018).

4.3.7. In light of new evidence, would the decision to reimburse change or remain the same in Norway?

To start, as shown in Table 20 and Table 21, Rituximab has a favorable incremental cost of NOK189,903 compared to Ocrelizumab. However, Ocrelizumab has a favorable incremental QALY of 0.15 than Rituximab. So, Ocrelizumab is more costly and more effective. Therefore, the question arises, how much more is Norway willing to pay for more health gains? Commercial agreement might be a tool to reduce the reduce the budget impact on the scarce resources. Other referenced countries use it for their reimbursement decision as seen in chapter 3.1 and the subchapters. Most importantly, Ocrelizumab if not reimbursed, the long term lost in QALY of 0.15 implies an increase in disease progression. Hence, the cost of treatment will also rise. Eventually, adopting Rituximab because its less costly may only be valid for a short term i.e., the loss of 0.15 QALYs may not lead to the cost savings in the long run.

Table 20; List price of Ocrelizumab VS Alemtuzumab

Therapy	Effect	Cost year 1
Ocrelizumab	8,29	240,167
Alemtuzumab	8,27	338,273
Natalizumab	8,15	230,114
Cladribine	7,92	131,850
Rituximab	8,14	50,264
Fingolimod	7,95	201,608
No Treatment	7,1	718,885

Source; (NIPH, 2018)

Table 21; List price of Ocrelizumab VS Alemtuzumab

Therapy	Incr QALY	Incr Cost
Ocre VS Ritu	0,15	189,903
Ocre VS Alemt	0,02	-98,106
Ocre VS Nata	0,14	10,053
Ocre VS Clad	0,37	108,317
Ocr VS Fingo	0,34	38,559

Source; (NIPH, 2018)

4.3.8. Can the cost effectiveness of any of the countries be adapted to be applied in Norwegian settings?

The author of this project has revealed in chapter 3.1. that cost effectiveness study is just a mean to an end i.e., a mean to a reimbursement decision. The author has also further revealed that irrespective of the result of cost effectiveness study, the aim of the payer is prudence when it comes to public spending for pharmaceuticals as a result benefits of the forgone alternative. Hence, various pricing, market access and reimbursement strategy as explained in chapter 2.6, chapter 2.7 and chapter 2.8 and as further demonstrated in chapter 3.1. can be applied.

In addition, Norway might adopt the grouping of RRMS patients into their JCV status. Analysis already revealed that there is a correlation between that and Ocrelizumab lowering the GAL1 and GAL2 lesion in the brain by 94% and 82% as revealed in Table 10 in chapter 4.2.2.

5. Conclusion and Discussion

5.1. Conclusion

To start, the title of this project ''Globalized the Evidence, Localize the Decision'' implies that while EMA grants a market authorization after accessing the Quality, Safety and Efficacy of a therapy, EMA has generalized that the evidence will hold true in another setting. However, due to some unique factors that vary the biological effects of a therapy among countries, access to such therapy is further subject to the reimbursement decision that is informed by an execution of an economic evaluation at the respective country's national, regional and local level.

As mentioned in chapter 1., this report objective is to test the idea of generalizability as to the reason why the therapy is not reimbursed in Norway. More importantly, the extent to which the result from cost effectiveness of Ocrelizumab in Denmark, U.K., Ireland and Sweden can hold true in Norway setting. To enable achieve this objective, those factors that cause variation in the cost effectiveness analysis among the countries are used. After some critical findings, the author also tests the idea of transferability i.e. such that if the result from any of those countries can be adapted to be applied in Norway. Hence, the reimbursement of Ocrelizumab in Norway. The concussion is expressed in the following two items;

5.1.1. Economic Evaluation; A Tool of Manipulation?

First, as shown in chapter 3.1., it is obvious that there is a disconnect in prior recommendation and the second recommendation that lead to reimbursement in the Ireland and the U.K. In addition to that is also the reimbursement of Ocrelizumab in Denmark in all three categories, even when category P1 and P2 are not cost effective as explained in chapter 3.2.3.1. Therefore, it is obvious that the countries where the therapy is reimbursed entered into a king of pricing agreement with the industry, as explained in chapter 2.6, chapter 2.7 and chapter 2.8.

As a result, it is safe to conclude that economic evaluation results is far from being a tool to inform reimbursement, but a tool by the payer to manipulate price of the therapy. Moreover, from all the results, it is obvious that all of the countries deviated from their respective healthcare architectural design for reimbursement pharmaceutical products as elaborated in chapter 2.5. In addition to that is a systematic way of exclusion or inclusion of some costs to enable a favorable incremental cost of the standard therapy and make the new intervention seem not cost effective – for instance, Norway left out the cost of SAE and TWSAE which would impact the estimated number of QALYs with 20-year horizon. Additional, the type of perspective is also used to enable an inclusion or exclusion of other costs or the choice of horizon of two years in Denmark to influence the incremental costs.

In other words, Economic Evaluation seems more like a tool to twist the hand of the therapy manufacturer into entering a form of commercial agreement that involves a huge price reduction of the therapy.

On the other hand, the author also concludes that the Pharma might also have accepted the challenges posed by Economic Evaluation Analysis and devised a way to also use the payers of a particular country to influence pricing in the other country. In other words, the pharmaceutical companies also use a differential pricing in the individual respective countries in other to influence the reimbursement of the therapy in another country. Otherwise, how would one explain the fact that Ocrelizumab is not cost effective in P1 and P2 in Denmark? Also, that the therapy becomes cost effective in P3 only for a two-year time horizon and when tested against a longer time horizon, the incremental cost in favor of Ocrelizumab came to a halt in the 4th year. How then should the Danish Medical Agency conclude that the therapy is cost effective in all categories? Sounds like quid pro quo (Medicinraadet, 2018).

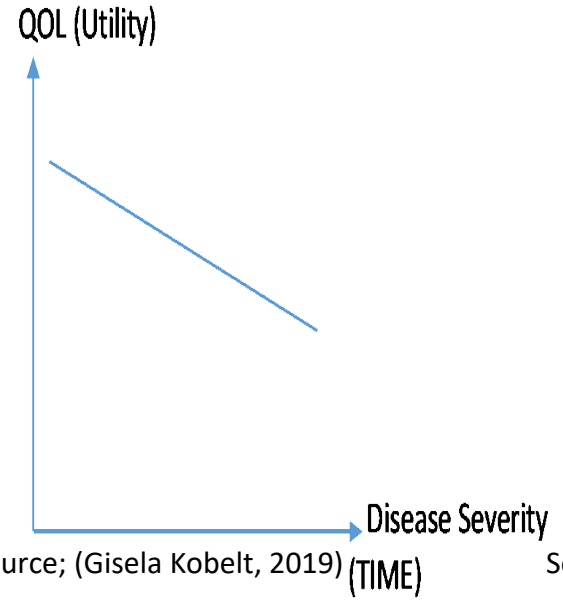
Furthermore, since there is no distinct or standard acceptance pathway of economic evaluation result, it cannot be generalized. Hence, the result from cost effectiveness of Ocrelizumab in Denmark, U.K., Ireland and Sweden cannot hold true in Norway setting.

5.1.2. Cost Effectiveness result does not always capture values

In chapter 3.2.7, the author reveals that Ocrelizumab is more costly and more effective with an incremental cost of NOK189,903 and incremental QALY of 0.15. Therefore, the question lies in if Norway will like to pay more for health gains. Eventually, Ocrelizumab is not reimbursed because of the cost savings of NOK189,903 in favor of Rituximab.

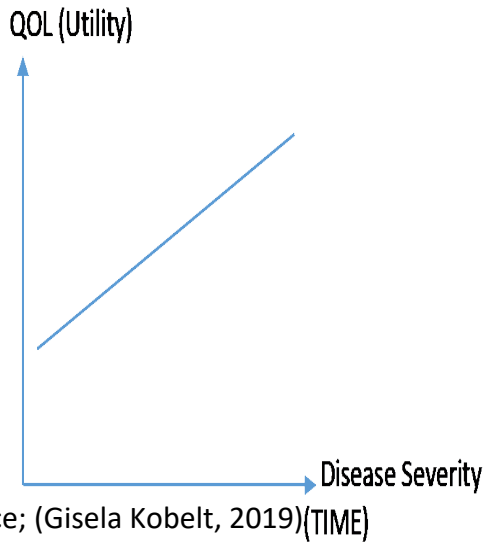
In addition, even though the choice of time horizon used in the Norway analysis is 20 years, the author of this report still assumes that Rituximab cost savings of NOK189,903 might be for a short time and in the long run, Ocrelizumab might become dominant ''less costly and more effective''. This is because of the special relationship between the disease progression and the EDSS states, as well as their respective cost and health gain/loss over time. Below depicts the authors assumption;

Figure 1; Increase in Disability VS Quality of Life



Source; (Gisela Kobelt, 2019)

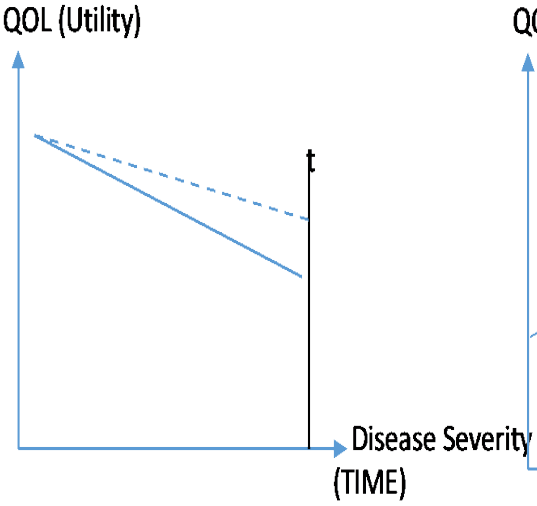
Figure 2; Increase in Disability VS Cost



Source; (Gisela Kobelt, 2019)

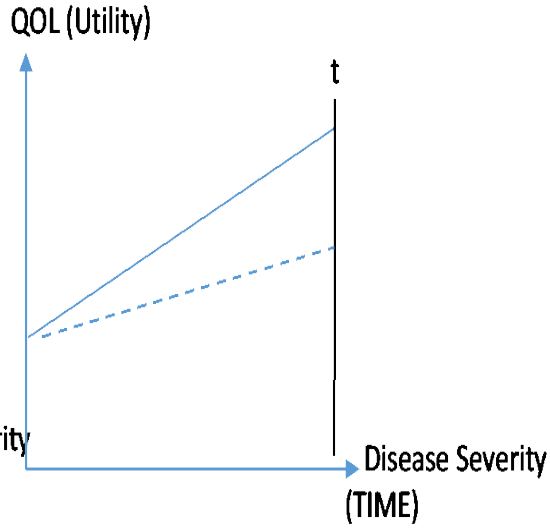
Figure 1 and Figure 2 above depict that as the disease progresses, the quality of life decreases over time and the cost of treatment and disability also increases.

Figure 3; Intervention VS QOL



Source; (Gisela Kobelt, 2019)

Figure 4; Intervention VS cost



Source; (Gisela Kobelt, 2019)

In addition, in Figure 3, timely intervention changes the slope of the disease over time, because the less steep the curve is, the longer it takes for the disease to progress into the severe EDSS state and the cost associated with treatment and the opportunity of being disabled will be saved. So, the cost decreases. However, the key element here is ''t'' time. The dotted line shows in figure 3 that the earlier the intervention, the more health is accrued and the more cost is saved.

This illustration, takes us back to relevance of Ocrelizumab 0.15 QALY gained against Rituximab at the expense of NOK189,903. So, the question to ask now is, how big is 0.15 QALY? NIPH asserts that the variation between therapies in terms of QALY gains might seem small ranging between 0.0127 and 0.3717. To contextualize the numbers, the average differences between QALY gained between alternatives when all published economics evaluation for one year is 0.07. The average in lifestyle intervention is 0.03, while the average for oncology and cardiovascular intervention is 0.07. Therefore, one can establish that 0.15 QALY gained for Ocrelizumab against Rituximab is substantial (NIPH, 2019).

In light of that, more research should be conducted by the Norwegian Medicine Agency by asking the question; what is the impact in the delay of 0.15 QALY on patient's progression on the EDSS scale to a more severe disease ''especially when SAE and TWSAE are included in a 20-year time horizon''? What is the short and long run of the delay on cost vis-à-vis cost savings of Ocrelizumab? This illustration help show further that cost effectiveness does not always capture value.

5.2. Discussion

This sub chapter discusses the Main Findings, the report Limitation, the Findings in Similar Studies and Future Research.

5.2.1. Main Findings

To start, one of the most significant findings is that cost effectiveness of therapy among countries will always vary as a result of factors ranging from disease prevalence to variation in clinical practice to mention a few. Therefore, the generalizability assumption by EMA cannot hold true in any of the countries compared. In addition to that, research also reveals that the entire cost effectiveness study cannot be transfer as a result of each country's autonomy on which types of analysis, perspective, time horizon to choose etc. For instance, as a result of Denmark choice of comparators that is driven by aftermath of JCV test and result, clinical data become difficult to transfer to Norway.

In the same vein, Denmark resource use and cost is also difficult to transfer as a result of the option of societal perspective whereby the opportunity cost of patient time is included. Also, Denmark adoption of CMA whereby all alternatives are presumed to have similar effect and their respective comparison are reduced to cost. Therefore, handling cost as a result of SAE and TWSAE will be difficult to transfer to the other three countries, especially Norway that excluded it. Furthermore, JCV test is compulsory for patients in Denmark, as a result, startup cost is mandatory for all the comparators in their respective groups P1, P2 P3 and such startup costs will be hard to transfer to other countries.

Additionally, the economic model in Norway is driven by the ARR and CDP, therefore the handling cost of SAE and TSAE are excluded. That will also be difficult to transfer to Denmark ''that focuses strictly on all of the costs'' and to other countries. In addition to that is the Norway inclusion of an off label therapy in the clinical routine. That is also not transferred to the other countries. In short, the U.K. specifically rejected the inclusion of Rituximab when suggested by one of the clinicians. While the U.K. and Norway choose a 20-year time horizon, Denmark choose two years with which the author assumes might be too short to factor in all the costs and the consequences relating to the intervention.

However, the research also finds that some elements of cost effectiveness of a certain country can indeed be adapted to be applied in other country. For instance, chapter 2.3. already reveals that Norwegian Institute of Public Health ''NIPH'' conducted a Health Technology Assessment ''HTA'' including a network meta-analysis on 11 different medicines for RRMS. In the study, it was established that one important acknowledged risk of DMT is progressive Multifocal Leukoencephalopathy ''PML''. PML is caused by the infection of the brain with John Cunningham Virus ''JCV'' which destroys the myelin sheaths of nerves in patients with decreased function of the immune system. Hence, approximately 25% of patients die within 6 months and the survivors have increased long-term disability (NIPH, 2019). Therefore, the initial JCV test in Denmark enables patients to be assigned the comparators that match their safety status. As a result, Ocrelizumab has an impressive performance lowering the lesion for GAL1 and GAL2 by about 94% and 80% as revealed in Table 10 of chapter 4.2.2.

5.2.2. Limitation

One of the limitation of this research is that most important documents are redacted. None of the countries actually reveal ICER for Ocrelizumab. As a result, the author of this report had to glean through all the published HTA from Norway to be able to calculate the incremental costs and effects for Norway. As a result, the author left out the ICER calculation in case the result might not reflect the true and fair value. In addition, the difficulties to translate some

of the content of HTA into English is a huge hurdle. More so, all the cost had to be converted to Norwegian NOK using the purchasing power parity to enable their comparability. More importantly, Norway defines severity in both clinical level and HTA level. The latter is measured as an 'absolute shortfall' that is defined as the expected loss of future health in QALYs (NIPH, 2019), while the clinical severity is measured on the EDSS scale as explained in chapter 2.2. However, the author is not able to link the severity expressed in DALYs mentioned in Wallin, M. T. et al. article to the patient's EDSS scores.

Moreover, as a result of lack of information on budget impact, the author is not able to assess the impact on the variation among the countries. Also, lack of CE plane, the CEAC and CEAF limit the author of this report to be able to compare the respective impacts and predicts the impact of some inclusion or exclusion of some uncertainty parameters could influence the probability of cost effectiveness.

Finally, due to the broad perspective of this report, it challenges the author to go back in time and revised the content of HTA learn in the previous semester. The complexity of the content of HTA studies took the author a while to be able to read through all the HTAs in about eight countries. That was time consuming and putting together the necessary information to build this report is a huge task. Irrespective of these limitations. The author is enthusiastic about the findings.

5.2.3. Finding in Similar Studies

The few similar studies the author is able to find are the following; first, ''Transferability of Economic Evaluation Results by Michael Drummond and Francis Pang''. Second, ''A decision chart for Assessing and Improving Transferability of Economics Evaluation Results Between Countries by Welte et al''. Third, ''The Transferability of Economic Evaluations; Testing the Model of Welte by Saskia et al''. Fourth, ''Transferability of Economic Evaluations Across Jurisdictions; ISPOR Good Research Practices Task Force Report''.

In light of that, the Drummond and Pang is the most similar to this project because some of the factors limiting transferability as expressed in this report is inspired by them. However, they took the research further to express the strategies to deal with the issues of transferability and proposed Modelling Approach, Multinational Clinical Trials, as well as their respective costing methods (Drummond & Pang, 2001)

Also, the second is also similar. However, they also include the method for improving Transferability and accessing the uncertainties of Transferability result using the Knock-out Criteria (Welte, R et al., 2004). Moreover, the third study from ISPOR is more of a paternalistic approach to transferability. It was conducted as a good research practice of transferability across national borders (Drummond, Barbieri et al., 2009) and fourth, is conducted to assess how the Welte's Knock-Out Model influence costs and effects estimates during transferability.

5.2.4. Future Research

To start, as pointed out in Chapter 5.1.2. It would be interesting to conduct more research on the impact in the delay of 0.15 QALY on patient's progression on the EDSS scale to a more severe disease. As well as the short and long term effect of the delay on cost vis-à-vis cost savings of Ocrelizumab?

In addition, it would also be interesting to conduct further research on the impact of costs and QALYs by transferring the Denmark Approach in Norway settings. Most importantly, it would be interesting using Welte's model to improve the probable uncertainties as stated in Chapter 5.2.4. on the findings (Knies, S., et al., 2009).

5.2. Declaration in Lieu of Oath

Declaration in lieu of oath

With this declaration, the student confirms having written the thesis him or herself without any outside help. Others' thoughts and ideas are clearly marked as such and the master thesis has not been handed in during the course of another program and has not yet been published. Each master's thesis needs to contain such a declaration and has to be signed by the student in person. An electronic signature cannot be accepted. Exact formulation of this declaration:

"DECLARATION IN LIEU OF OATH

I hereby declare, under oath, that this master thesis has been my independent work and has not been aided with any prohibited means. I declare, to the best of my knowledge and belief, that all passages taken from published and unpublished sources or documents have been reproduced whether as original, slightly changed or in thought, have been mentioned as such at the corresponding places of the thesis, by citation, where the extent of the original quotes is indicated.

The paper has not been submitted for evaluation to another examination authority or has been published in this form or another."

SIGNATURE	
27-07-2020	27 July 2020 Kurt R Wanjau
date and signature of student	date and signature of supervisor

Appendix 1 Conclusion of Denmark Cost Effectiveness Study

Konklusion per population

Tabel 1: Merværdi, meromkostninger og Amgros' anbefaling

Population	Komparator	Merværdi	Usikkerhed for klinisk merværdi	Amgros' konklusion om forhold mellem omkostninger og klinisk merværdi	Anbefaling som mulig standardbehandling
P1: Patienter med attakvis multipel sklerose, som er JCV positive	Fingolimod (Gilenya)	Ingen klinisk merværdi	Meget lav evidenskvalitet	Acceptabelt	Ja
P2: Patienter med attakvis multipel sklerose, som er JCV negative	Natalizumab (Tysabri)	Ingen klinisk merværdi	Meget lav evidenskvalitet	Acceptabelt	Ja
P3: Patienter med attakvis multipel sklerose, hvor behandling med natalizumab (Tysabri) og fingolimod (Gilenya) ikke er en mulighed	Alemtuzumab (Lemtrada)	Lille klinisk merværdi	Meget lav evidenskvalitet	Acceptabelt	Ja

Appendix 2; Breakdown of Costs in Denmark

	Average Drug Cost Per Year (Undiscounted)			
	Treatment Regimen	Year 1	Year 2	Total
	Ocrelizumab 150,59 KR/MG	257.752	257.752	515.505
	P1-Fingolimod 873,76 KR/M	227.447	227.447	454.894
	P2-Natalizumab 36,34/MG	202.155	202.155	404.310
	P3-Alemtuzumab 4.173,4 KR	357.161	214.296	571.457

	Hospital Cost (undiscounted)			
	Resource Use	Year1	Year2	Total
Ocrelizumab	Starting Cost	6.538	0	6.538
	Administration	6.207	6.207	12.415
	Control and Lab Test	6.550	6.550	13.100
	MRI Scan	0	3.263	3.263
	Total	19.296	16.021	35.316
Fingolimod	Starting Cost	6.538	0	6.538
	Administration	0	0	0
	Control and Lab Test	11.486	12.820	24.306
	MRI Scan	0	3.263	3.263
	Total	18.025	16.083	34.108
Natalizumab	Starting Cost	6.538	0	6.538
	Administration	37.246	40.350	77.596
	Control and Lab Test	342	342	685
	MRI Scan	0	3.263	3.263
	Total	44.127	43.956	88.082
Alemtuzumab	Starting Cost	11.451	0	11.451
	Administration	12.415	9.311	21.726
	Control and Lab Test	8.090	8.090	16.180
	MRI Scan	0	3.263	3.263
	SAE handling cost (outpatient)	6.209	0	6.209
	Total	38.165	20.665	58.829

		Year1	Year2	Total
Ocrelizumab P1	Drug Cost	258.073	248.045	506.118
	Hospital Services	19.296	15.404	34.700
	Patient time and Transport	8.113	5.710	13.823
	Total	285.482	269.159	554.641
Fingolimod	Drug Cost	227.447	218.699	446.146
	Hospital Services	18.025	15.466	33.490
	Patient time and Transport	5.079	2.553	7.632
	Total	250.551	236.718	487.269
Incremental Cost		34.931	32.441	67.372

	Cost Element	Year1	Year2	Total
Ocrelizumab P2	Drug Cost	258.073	248.045	506.118
	Hospital Services	19.296	15.404	34.700
	Patient time and Transport	8.113	5.710	13.823
	Total	285.482	269.159	554.641
Natalizumab	Drug Cost	202.155	194.380	396.535
	Hospital Services	44.127	42.265	86.392
	Patient time and Transport	13.098	12.732	25.830
	Total	259.380	249.377	508.757
Incremental Cost		26.102	19.782	45.884

	Cost Element	Year1	Year2	Total
Ocrelizumab P3	Drug Cost	258.073	248.045	506.118
	Hospital Services	19.296	15.404	34.700
	Patient time and Transport	8.113	5.710	13.823
	Total	285.482	269.159	554.641
Alemtuzumab	Drug Cost	359.928	208.430	568.358
	Hospital Services	38.166	19.870	58.036
	Patient time and Transport	15.936	12.093	28.029
	Total	414.031	240.392	654.423
Incremental Cost		-128.549	28.766	-99.782

Appendix 3; Initial write-up of Clinical Effectiveness and Safety of Norway, Denmark, the U.K. and Ireland

RRMS

3.3.1. Choice of Comparators

A crucial alternative should be an existing care, but it is important to consider whether the existing care itself is the best alternative. This is because any alternatives can look good when compared to a comparator that is sufficiently bad. This is one of the reasons why placebo is not usually a preferred option in HTA. However, since RRMS does not currently have any authorized therapy for its treatment, placebo might be a viable alternative. Therefore, the relevant alternatives are most efficient alternatives, Standard Treatments, Consideration of No Treatments and Placebo. Meanwhile, as a result of the devastating effect of MS, no treatment options will not be considered (Drummond, 2015).

More importantly, as discussed in chapter 2.6.4., it was established that all newly launched medicines in Germany are reimbursed by the sickness funds unless exclusion is stated by law like the OTC, lifestyle medicine and minor ailment. More so, such newly launch therapy is clustered in the groups of medicine with the same therapeutic value and subject to a maximum amount. However, the price is later renegotiated after 12 months. Therefore, Germany reimbursement criteria is automatic granted for every newly launch therapies. As a result, the comparison of the factors that cause variation in cost effectiveness analysis might not be comparable with other reference countries.

Except for a few DMTs that were withdrawn from some of the referenced countries including Norway were as a result of safety concern. Therefore, most DMTs included as the comparators for Ocrelizumab include; Placebo, Rituximab, Alemtuzumab, Interferon beta-1a (Avonex), Dimethyl fumarate, Fingolimod, Glatiramer acetate, Interferon beta-1a, Natalizumab, Peginterferon beta-1a, Interferon beta-1a SC and Teriflunomide. However, since interferon-beta 1a is the first line treatment for RRMS in most of these countries, the main comparative effectiveness was done between Ocrelizumab and interferon-beta 1a.

Furthermore, for Norway, the main comparator used are Placebo or Interferon beta-1a. The comparator used for both Ireland and the United Kingdom is also interferon beta-1a. In addition, the comparators used in Denmark HTA are categorised into three parts. The first P1 are RMS patients who have disease activities on first line therapy and who are John Cunningham Virus ''JCV'', including RMS patients with a particularly high disease activity, who have not been previously treated are JCV positive. Therefore, the comparator for P1 is Fingolimod. P2 comprises of RMS patients who have disease activities on first line therapy and who is JCV negative. Including RMS patients with particularly high disease activity that had not been previously treated and which are JCV negative Therefore, the comparator for P2 is Natalizumab. P3 on the other hand are RMS patients who have disease activity on first line therapy and treatments with neither Natalizumab nor Fingolimod is possible, but with high disease activities that had not been treated before. Therefore, the comparator for P3 is Alemtuzumab (Medicinradet, 2019).

Moreover, as a result of lack of publicized HTA for the Netherlands, the country will be excluded in the main analysis. Also, even though the comparator in the Swedish HTA is

Placebo, most useful contents in the published HTA are redacted. Therefore, some of the comparisons for Sweden will also be skipped (TLV, 2018).

Finally, the countries to be compared in this part are United Kingdom, Norway, Ireland and Denmark.

3.3.1.1. Clinical Effectiveness

Annualized Relapse Rate ''ARR'', Confirmed Disability Progression ''CPD' 'and the MRI lesion/change in EDSS are the criteria to measure the clinical effectiveness of Ocrelizumab in comparison to its comparators.

Ireland

To start, the primary end point is Annualized Relapse Rate. Therefore, with the intervention of intravenous 600mg dose of Ocrelizumab every 24 weeks and with 44µg dose of subcutaneous interferon beta-1a for 96 weeks for Ireland, the ARR was 0.16 for Ocrelizumab, while its 0.29 for Interferon beta-1a which represents about 44% relative risk reduction rate.

In addition, disability progression at 12 weeks was 9.1% in the ocrelizumab group, while that of interferon beta-1a group is 13.6%, representing a 40% lower risk with ocrelizumab. Moreover, the disability progression for Ocrelizumab group is 9.1% and 13.6% respectively for interferon beta-1a group. This leads to about 33% relative risk reduction. More importantly, in the intention to treat population, about 47.9% of patients in the ocrelizumab group had no evidence of disease activity by 96 weeks as compared to 29.2% interferon beta-1a group.

For MRI related case, secondary end point is the total mean of gadolinium enhancing lesions (GAL) per T1 weighted MRI scan, which is 0.42 and 0.45 for Ocrelizumab and 0.98 and 1.26 for interferon beta-1a group. This represents about 57% lower of lesions with Ocrelizumab groups (NCPE, 2018).

Conclusion

For Ireland, with ARR rate of 0,16 for Ocrelizumab and 0,29 for Interferon beta-1a, the absolute risk reduction of ARR is -0.13, which corresponds to a relative risk of 0.55 or a relative risk reduction of 0.45. **This implies that Ocrelizumab reduces the annual relapse rate by 45% when compared by interferon beta-1a.** In addition, in the CDP rate, with 9,1 for Orelizumab and 13,6 for Interferon beta-1a. T**his implies that Ocrelizumab reduces the risk of CPD by 33% in comparison with Interferon beta-1a**. Finally, **in the secondary endpoint, Ocrelizumab has a 57% lowers lesions than Interferon beta-1a in T1 and 64% for T2.**

Norway

Like Ireland, the primary endpoint for RRMS patients in Norway is the ARR. So, for Norway, Alemtuzumab, natalizumab and ocrelizumab were ranked as the best three treatments when it comes to the ARR with probabilities of 91%, 88% and 85% respectively. A patient treated with Alemtuzumab will experience 0.14 relapses per year in comparison with relapses per year with Placebo treatment. Natalizumab overlaps with those of Alemtuzumab with relapses of 0.17 relapses, while Ocrelizumab has relapses of .018. in addition, Rituximab has a relapse rate of 0.23 respectively.

Furthermore, for Norway, the disability progression rate is expressed in the log risk scale and presented as the number of patients per 1,000expected to experience disability progression during the trial. Having established that, Ocrelizumab, Alemtuzumab and Natalizumab are the best treatment when it comes to disability progression rate with probabilities of 77%, 77% and 71% respectively. Although, not statistically significant, 86 patients per 1,000 treated with Ocrelizumab and 88 patients treated with Rituximab are expected to experience a disability progression in comparison with 161 per 1,000 of patients treated with placebo.

In addition, for MRI, Natalizumab, Alemtuzumab and Rituximab are ranked the best treatment with 89% or 0,26, 82% or 0,18, and 76% or 0,25 respectively when compared with 0,10 for Placebo. Treatment with natalizumab would experience a change in EDSS of -0.26 steps during the course of the trial in comparison with 0.10 steps of Placebo treatment. However, a change in EDSS less than 0.5 steps may not be clinically significant. Therefore, these scores for MRI might be invalidated (NIPH, 2019).

Conclusion

For Norway, with Alemtuzumab ARR of 0.14, Natalizumab with 0.17 relapses, Ocrelizumab with 0.18 and Rituximab with 0.23 respectively compared to 0.53 ARR for Placebo. This corresponds to a relative risk of 0.26, 0,32, 0,34 and 0,43 or a relative risk reduction of 0.45. **This implies an ARR reduction rate by 73%, 68%, 66% and 57% for Alemtuzumab, Natalizumab, Ocrelizumab and Rituximab in comparison with Placebo.** In addition, in the CPD rate, Alemtuzumab comprises of 87 patients with confirmed disability progression, while Natalizumab comprises of 97 patients, Ocrelizumab with 86 and Rituximab with 88 patients respectively compared to 161 patients for Placebo. This translates to hazard ratio of 0,54 for Alemtuzumab, 0.60 for Natalizumab, 0,53 for Ocrelizumab and 0,55 for Rituximab. **This implies that Alemtuzumab, Natalizumab, Ocrelizumab and Rituximab reduce the risk of confirmed disability progression by 46%, 40%, 47%, 45% comparison with Placebo**. Finally, it is established that a change in EDSS less than 0.5 steps may not be clinically significant. Therefore, these scores for MRI might be invalidated (NIPH, 2019).

United Kingdom

For U.K. also, the primary endpoint of the ARR. Therefore, Ocrelizumab has the annualized relapse rate of 0.16, while Interferon beta-1a has 0,29.

More so, for Ocrelizumab, at 95% confidence interval, the CPD at 3 months is 9.8 in comparison to the CPD rate for Interferon beta-1a of 15.2. In the same vein, the CPD at 6 months for Ocrelizumab is 7.6 in comparison to 12.0 for Interferon beta-1a. This represents that few patients had confirmed disability progression at 3 months and 6 months respectively for Ocrelizumab in comparison with Interferon beta-1a. Therefore, Ocrelizumab reduces relapses and slows disability (NICE, 2019). In other words, Ocrelizumab slows down the disability progression when compared with Interferon beta-1a.

Furthermore, it is established that some benefits related to improvement in EDSS might not have been captured adequately in the modelling. However, it is noted that the economic model allows patients disability to improve at the same rate for Ocrelizumab and all the comparators. Moreover, the clinical experts stated that if not for the fact that the

improvement of EDSS is underestimated in the modelling, it might not be overemphasized that Ocrelizumab improve EDSS state more than other DMTs, especially in patients with severe relapses (NICE, 2019).

Conclusion

For U.K., the absolute risk reduction of ARR is the same as Ireland with -0.13, which corresponds to a relative risk of 0.55 or a relative risk reduction of 0.45. **This implies that Ocrelizumab reduces the annual relapse rate when compared by interferon beta-1a by 45%.** In addition, the U.K. differs in the CPD rate in comparison with Ireland. Ocrelizumab has an absolute reduction of -5.4 for 12 weeks and -4.4 for 24 weeks, which corresponds to a hazard ratio of 0.64 and 0,63 for both 12 weeks and 24 weeks respectively. **This implies that Ocrelizumab reduces the risk of confirmed disability progression by 36.5% in comparison with Interferon beta-1a**. It is further asserted that Ocrelizumab has a favorable CPD than most of its comparators. Finally, the total mean of gadolinium enhancing lesions (GAL) per T1 weighted MRI scan is not reported, however the clinical experts stated that if not for the fact that the improvement of EDSS is underestimated in the modelling, it might not be overemphasized that Ocrelizumab improve EDSS state more than other DMTs, especially in patients with severe relapses (NICE, 2019).

Denmark

Ocrelizumab VS Interferon beta-1a

The comparators of Ocrelizumab in Denmark are divided into three sub populations. The first one is Fingolimod for category P1. The second is Natalizumab for category P2 and the third is Alemtuzumab for category P3.

Category P1: What clinical value does Ocrelizumab offer compared when compared with Fingolimod to patients with RRMS who are JCV positive?

To start, Ocrelizumab has an ARR rate of 0,16 compared to Interferon beta-1a of 0,29. This leads to a relative risk of 0,55 and a relative risk reduction of 45% in favor of Ocrelizumab. In the same vein, Fingolimod has an ARR of 0,195 compared to 0,40 for Placebo. This implies a relative risk of 0,49 and relative risk reduction of 51% in favor of Fingolimod.

In addition, Ocrelizumab has a CPD of 0,091 when compared to 0,136 of Interferon beta-1a. This implies a relative risk of 0,67 or 33% relative reduction risk in favor of Ocrelizumab. points when compared to fingolimod. In the same vein, Fingolimod has a CPD rate of 0,25 compared to 0,29 for Placebo. This leads to a relative reduction of 0,86 or 14% relative risk reduction.

Moreover, with a relative reduction of 94% for Ocrelizumab compared to Interferon beta-1a and a relative reduction of 82% and 67% for Fingolimod when compared with Placebo. The good clinical effectiveness of Ocrelizumab is partly explained by its almost complete suppression of gadolinium enhancing lesions (GAL) per T1 lesion and new or enlarged T2 lesions.

Conclusion

Both Ocrelizumab and Fingolimod have a similar outcome with the ARR. However, with a relative risk reduction of 33% compared to 14% of Fingolimod, Ocrelizumab reduces the CPD better than Fingolimod. In addition, Ocrelizumab almost suppressed the gadolinium

enhancing lesions (GAL) per T1 and T2 in compared to Fingolimod. It is reflected in the fact that only 5 patients out of 718 had active lesions after 24 months. However, in respect to the two critical endpoints, Ocrelizumab for patients with RMS who are JCV positive provides better clinical added value compared to fingolimod (medicineraadet, 2018)

Category P2: <u>What clinical value does Ocrelizumab offer compared when compared with Natalizumab to patients with RRMS who are JCV negative?</u>

After 96 weeks, the ARR of patients treated with Ocrelizumab is 0,15, while that of Interferon beta-1a is 0,29. This leads to an absolute reduction of -0,14, which implies a relative risk of 0,52 and a relative risk reduction of 48% for Ocrelizumab when compared to Interferon beta-1a. In the same vein, patients treated with Natalizumab also has a low ARR of 0,23 in comparison with 0,73 for Placebo. This implies a relative risk of 0,31 and a relative risk reduction of 68% for Natalizumab when compared to Placebo.

In addition, patients treated with Ocrelizumab has a CPD of 9.1 compared to 13.6 for Interferon beta-1a. This leads to a hazard ratio of 0,58 and a relative risk reduction of 42% for Ocrelizumab when compared to Interferon beta-1a. In the same vein, Natalizumab has a CPD of 17,0 compared to 29,0 for Placebo. This leads to a hazard ratio of 0.59 and a relative risk reduction of 41% for Natalizumab compared to Placebo.

Moreover, as mentioned in the third paragraph of P1 category, Orelizumab has a relative reduction of 94% compared to Interferon beta-1a and a relative reduction of 91% for Natalizumab when compared with Placebo.

Conclusion

First, Ocrelizumab has a better ARR of 48% compared to Natalizumab. Also, considering that the CPD of Interferon beta-1a which is the comparator of Ocrelizumab is 13.6 and it is better that the CPD of 17.0 for Natalizumab. Therefore, the fact that Ocrelizumab CPD of 9.1 is better than Interferon beta-1a implies that Ocrelizumab reduces confirmed disability progression at a significant rate than Natalizumab. More so, for secondary endpoint, Ocrelizumab almost complete suppression of gadolinium enhancing lesions (GAL) per T1 lesion and new or enlarged T2 lesions is better explained in the fact that only 5 patients out of 718 who are treated with Ocrelizumab have active lesions after 2 years, compared to 97 of patients treated with Natalizumab. Conclusively, Ocrelizumab has a better outcome for the three critical endpoints when it comes to Category P2 clinical effectiveness.

Category P3: <u>What clinical value does Ocrelizumab offer to patients where Natalizumab and Fingolimod is not a possibility?</u>

In the event that Natalizumab and Fingolimod is not an option, Alemtuzumab can be compared to Ocrelizumab. In doing that, Interferon beta-1a can be a viable comparator for both Ocrelizumab and Almetuzumab.

Alemtuzumab VS Interferon beta-1a

RMS patients who have disease activity on first-line therapy and where neither treatment natalizumab or fingolimod is an option. Also including RMS patients with particularly high disease activity that has not previously been treated. To start, with intervention of Alemtuzumab, having Interferon beta-1a as a comparator, the annual relapse rate ARR is 0.18

compared to 0.39 Interferon beta-1a. This leads to an absolute reduction rate for ARR of -0.21, which implies 0,46 relative risk or 54% relative risk reduction.

Confirmed Disability Progression CDP after 12 weeks had not been reported. Meanwhile, the total mean number of gadolinium enhancing lesions (GAL) per T1 is 0.2 with alemtuzumab at 24 months in comparison with 0.3 with Interferon beta-1a. In the same vein, the average number of new or recent augmented hyper intense T2 lesions is 2.3 with alemtuzumab compared with 3.2 with Interferon beta-1a.

Comparative Analysis between Ocrelizumab and Alemtuzumab
It is imperative to know that Ocrelizumab has already been compared to Interferon beta-1a in the first paragraph of category P2. In addition, Alemtuzumab is also compared to Interferon beta -1a. In doing so, Alemtuzumab ARR has an absolute reduction rate of -0,21 compared to -0,14 for Ocrelizumab. In other words, a relative risk reduction of 54% for Alemtuzumab is favorable than 48% for Ocrelizumab.

The CDP after 12 weeks is not reported because comparative analysis is not performed for this endpoint. More so, when compared with Interferon beta 1-a, the total mean number of gadolinium enhancing lesions (GAL) per T1 was reduced by 33% with Alemtuzumab in two separate trials. Also, with total mean number of gadolinium enhancing lesions (GAL) per T2 is reduced by 28% with Alemtuzumab. In the same vein, gadolinium enhancing lesions (GAL) per T1 lesion and new or enlarged T2 lesions has a relative reduction of 94% with Ocrelizumab treatment when compared to Interferon beta-1a.

Conclusion
When Natalizumab and Fingolimod is not an option, Alemtuzumab can be compared to Ocrelizumab. To do that, Interferon beta-1a is a common comparator for both Ocrelizumab and Alemtuzumab. For ARR, Alemtuzumab has a favorable outcome in reducing the annualised relapse rate by 54% compared to 48% for Ocrelizumab. CPD is not reported, but Ocrelizumab reduces T1 lesion and new or enlarged T2 lesions with a relative reduction of 94% with Ocrelizumab treatment when compared to Interferon beta-1a.

3.3.2. Safety

For safety, Serious Adverse Event ''SAE and treatment withdrawal as a result of adverse event will be used as the criteria for safety assessment of Ocrelizumab clinical effectiveness when compared to its comparators. It is expressed in risk ratios of number of patients (per 1000) expected to experience one or more serious adverse event over a specified duration of a typical trial. In addition, treatment withdrawal as a result of SAE would also be used.

For Ireland, it is established that about 80% of patients in the trial reported an adverse event to Ocrelizumab, which might also be similar to the rate of adverse events in comparison with Interferon beta-1a. However, serious adverse events is the same with Ocrelizumab when compared to Interferon beta-1a.

For Norway, at 95% Confidence Interval, Rituximab has 0.40, Ocrelizumab has 0.74 and Fingolimod has 0.79 in SAE in compared to Placebo. These translate to 60%, 26% and 21% relative risk reduction rate.

In the same vein, when it comes to treatment withdrawal as a result of AE, Rituximab, Natalizumab and Alemtuzumab at 95% confidence interval and with probability of 92%, 80% and 74% respectively. The relative risks of the aforementioned treatments are 0.19, 0.46 and 0.54 respectively (NIPH, 2019).

Conclusion
Rituximab, Ocrelizumab and Fingolimod are ranked the best treatment with outcome probability of 94%, 69% and 65% respectively, which translates to 60%, 26% and 21% relative risk reduction rate. More so, Rituximab, Natalizumab and Alemtuzumab at 95% confidence interval are ranked the best treatments when it comes to treatment withdrawal due to AE with probability of 92%, 80% and 74% respectively. This implies 81% relative risk reduction for Rituximab, 54% for Natalizumab and 46% Alemtuzumab in comparison to Placebo (NIPH, 2019).

For U.K., it is established that PML is a possible adverse event with Ocrelizumab among other DMTs. Therefore, the PML for Ocrelizumab varies from 1.0% and 2.1%. In addition, even though the SAE of Natalizumab is not stated, it is established that the rate is lower than that of Ocrelizumab.

In the same vein, Natalizumab, Alemtuzumab and Ocrelizumab with discontinuation rate as a result of AE of 2.21, 3.0 and 6.19 in comparison with Interferon beta-1a of 9.34. This leads to a relative risk of 0.23, 0.32, 0.66 respectively (NICE, 2019).

Conclusion
For AE, the relative risk reductions are 76%, 68% and 34% for Natalizumab, Alemtuzumab and Ocrelizumab in comparison to Interferon Beta-1a. In addition, although the SAE rate of Interferon beta-1a is not stated, it is established that the adverse events were likely to be less frequent with ocrelizumab than with other similar therapies, including alemtuzumab. Also, one-third of patients having alemtuzumab experience autoimmune diseases such as thyroid diseases, so monitoring is needed for 48 months after stopping treatment. Additionally, the number of cases of breast cancer reported was higher for patients having ocrelizumab than for interferon beta-1a. However, the number of cases with ocrelizumab is low and there was no statistically significant difference between the rate of breast cancer for patients having ocrelizumab compared with the general population. Finally, adverse events such as fatigue and ability to concentrate experienced with other treatments, such as beta interferons, do not occur with ocrelizumab (NICE, 2019)

For Denmark, to enable compare the safety of Ocrelizumab in comparison to the respective comparative, the SAE and treatment withdrawals due to AE will be analyzed in the three categories as was done in chapter 3.3.1 above.

Category P1: What clinical value does Ocrelizumab offer compared when compared with Fingolimod to patients with RRMS who are JCV positive?

SAE is slightly lower with Fingolimod treatment with average of 12,55 when compared to 13,2 of Placebo in both study. In addition, 6.9 SAE is recorded for Ocrelizumab treatment in compared to 8,7 for Interferon beta-1a. This leads to a relative risk of 0,95 of Fingolimod in comparison to Place and 0,79 of Ocrelizumab compared to Interferon beta-1a. Hence, Fingolimod has a relative risk reduction of 5% when compared to Placebo, but Ocrelizumab has a relative risk reduction of 21% when compared with Interferon beta-1a.

Furthermore, Fingolimod has 7.5 rate of discontinuation of treatment as a result of SAE compared to 7.7 of Placebo, which leads to 0,97 relative risk or 3% relative risk reduction for Fingolimod in comparison with Placebo. In the same vein, Ocrelizumab rate is 3.5 compared to 6.2 of Interferon beta-1a. This leads to a relative risk of 0,56 or 43% relative risk reduction for Ocrelizumab in comparison to Interferon beta-1a (Medicineradet, 2018).

Conclusion

First, Ocrelizumab has a favorable SAE of 26% compared to Fingolimod. However, even though both Fingolimod and Ocrelizumab do not have the same comparator, the SAE of Interferon beta-1a of 8,7, which is a comparator for Ocrelizumab is much lower than the SAE of Fingolimod of 12,55. Therefore, the fact that the SAE of Ocrelizumab of 6,9 is lower than its comparator Interferon beta-1a of 8,7 implies that Ocrelizumab has a better safety profile than Fingolimod. In addition, Ocrelizumab has a favorable SAE of 43% when compared to Fingolimod and because they do not have the same comparator, rate of discontinuation due to SAE for Ocrelizumab comparator is favorable when compared to Fingolimod. More importantly, the fact that 3.5 rate of Ocrelizumab is favorable than 6,2 of its own direct comparator implies that Ocrelizumab reduced rate of discontinuation when compared to Fingolimod (Medicineradet, 2018).

Category P2: <u>What clinical value does Ocrelizumab offer compared when compared with Natalizumab to patients with RRMS who are JCV negative?</u>

To start, patients treated with Ocrelizumab have 6.9% Serious Adverse Effect in comparison to 8.7% of patients treated with Interferon beta-1a. This leads to an absolute difference of -1.8 and relative risk of 0.79 and a relative risk reduction of 21%. More so, Natalizumab safety profile is 19,0 of SAE in comparison to 24,0 Placebo. This leads to -5 absolute relative difference and a relative risk of 0.79., which implies a relative risk reduction of 21%.

For treatment withdrawal due to SAE, Ocrelizumab has 3,5 compared to 6,2 for Interferon beta-1a. This leads to 0,56 relative risk or 44% relative risk reduction in favor of Ocrelizumab. More so, Natalizumab has 6,0 when compared to Placebo of 4,0, which leads to 1,5 relative risk or relative risk increase of 50% in favor of Placebo (Medicineradet, 2018).

Conclusion

First, Ocrelizumab has a favorable SAE of 6,9% compared to Natalizumab. However, even though both Natalizumab and Ocrelizumab do not have the same comparator, the SAE of Interferon beta-1a of 8,7, which is a comparator for Ocrelizumab is much lower than the SAE of Natalizumab of 19,0. Therefore, the fact that the SAE of Ocrelizumab of 6,9 is lower than its

comparator Interferon beta-1a of 8,7 implies that Ocrelizumab has a better safety profile than Natalizumab. In addition, Ocrelizumab has a relative risk reduction of 44% when compared with Interferon beta-1a. Meanwhile, even when Natalizumab performs poorly than its own comparator, Ocrelizumab performs better than both Natalizumab and Placebo, its comparator. This implies that Ocrelizumab rate of withdrawal due to SAE is way lower than Natalizumab (Medicineradet, 2018).

Category P3: What clinical value does Ocrelizumab offer to patients where Natalizumab and Fingolimod is not a possibility?

As it was done in category P3 for in chapter 3.3.1 Clinical Effectiveness, in the event that neither Natalizumab nor Fingolimod is not an option, Alemtuzumab can be compared to Ocrelizumab. In doing that, Interferon beta-1a can be a viable comparator for both Ocrelizumab and Almetuzumab.

Alemtuzumab VS Interferon beta-1a

SAE for Alemtuzumab is 20,0 compared to 22.0 for Interferon beta-1a. This leads to relative risk of 0,91 and a relative risk reduction of 9% in favor of Alemtuzumab. In addition, for treatment discontinuation as a result of AE, Alemtuzumab scores a lower incidence rate of 3,0 when compared to 7,0 of Interferon beta-1a. This leads to a relative risk of 0,43 and a relative risk reduction of 57%. (Medicineradet, 2018).

Comparative Analysis between Ocrelizumab and Alemtuzumab

As analyzed in the above paragraph, Alemtuzumab has relative risk reduction rate for SAE of 9% when compared to Interferon beta-1a. Meanwhile, patients treated with Ocrelizumab have 6.9% Serious Adverse Effect in comparison to 8.7% of patients treated with Interferon beta-1a. This leads to an absolute difference of -1.8 and relative risk of 0.79 and a relative risk reduction of 21%.

In the same vein, Alemtuzumab scores a relative risk reduction of 57% on treatment discontinuation as a result of SAE when compared to Interferon beta-1a. Meanwhile, Ocrelizumab rate is 3.5 compared to 6.2 of Interferon beta-1a. This leads to a relative risk of 0,56 or 43% relative risk reduction for Ocrelizumab in comparison to Interferon beta-1a (Medicineradet, 2018).

Conclusion

Ocrelizumab with 21% relative risk reduction rate of SAE is more favorable when compared with 9% Alemtuzumab. Therefore, the safety profile of Ocrelizumab when it comes to SAE endpoint is more favorable than Alemtuzumab. In addition, with 57% rate of treatment discontinuation due to SAE in comparison with 43% for Ocrelizumab, it is obvious that Alemtuzumab has a better safety profile on treatment discontinuation as a result of SAE when compared to Ocrelizumab (Medicineradet, 2018).

3.3.3. Cost Effectiveness

So, for Ireland, the U.K. and Norway, the Cost Utility Analysis ''CUA'' of Ocrelizumab and its respective comparators is done and will be analyzed and compared. Therefore, the analysis compared will be expressed in Incremental Cost Effectiveness Ratio, which implies having

incremental costs of the new intervention and its comparators in the numerator and its corresponding incremental effects at the denominator. The cost will be expressed in monetary terms, while the effects will be expressed in QALY. Moreover, the outcome of that will be expressed in cost per health year gained or cost per quality Adjusted Life Year (QALY). In addition to that is that Denmark adopts Cost Minimization Analysis ''CMA'', where Ocrelizumab and its comparators are considered to be equally effective, but are prioritized according to their respective serious side effects. Meanwhile, the differences between them are reduced to their cost comparison (Drummond, 2015) (Medicinradet, 2019).

To start, for Ireland, most of the comparators included are all licensed DMTs currently reimbursed in Ireland. The list price for Ocrelizumab is €6,000 or NOK63,713.76 which results in annual cost per patients of €28,200 or NOK299,454.66 with 23% VAT included, but administrative costs are excluded. It is important to know that the cost effectiveness estimates are centered around the CPD and the time horizon, just like in the U.K. Therefore, In the Cost Effectiveness Acceptability Curve, Ocrelizumab is the dominant when compared with Fingolimod and Natalizumab. This implies that the therapy is the least costly and most effective. However, Natalizumab dominates Ocrelizumab, which implies that it is less costly and more effective. The ICER of Interferon beta-1a compared to Ocrelizumab is €42,433 or NOK452,199.75. This implies that Interferon beta-1a provides one extra QALY for €42,433 or NOK452,199.75 when compared with Ocrelizumab. Hence, Interferon beta-1a is cost effective at the threshold above €42,433 or NOK452,199.75 in comparison with Ocrelizumab. It is further established that the ICER value exceeds €100,000 per QALY against many of the comparators when the upper confidence interval of CDP values are used. Similarly, many of the ICERs for Ocrelizumab exceed €100,000 at the 10-year time horizon when compared to some of the comparators.

Conclusion

As established in the chapter 3.3.2., the Ocrelizumab has a relative risk reduction of 52% when compared to its comparator, but the data for the treatment withdrawal due to AE is not reported. More so, as reported in chapter 3.3.1, Ocrelizumab has a favorable clinical effectiveness data when compared to its comparator, with both primary endpoints ''a relative risk reduction of 47% when it comes to ARR and 34% for CPD'' and secondary endpoint of 57% lower lesions in GAL per T1 weighted MRI scan''. As a result, about 75% of the patients in the treated population has not received previous DMTs, so Ocrelizumab can be used as a first line treatment.

Furthermore, for Norway, with the exclusion of VAT, the list price for Ocrelizumab is NOK217,295, while that of Rituximab is NOK29,559 in year 1 and NOK19,706 in year 2. It is imperative to know that Rituximab is an unauthorized off-label therapy for MS patients. In addition, the list price of Alemtuzumab are NOK307,679 in year 1, NOK184,608 in year 2, NOK48,219 in year 3 and NOK22,504 in year 4. More so, the list price of Cladribine are NOK119,707 in year 1 and NOK119,721. For Natalizumab, the list price is NOK169,636. These costs amount to the total cost of NOK240,167 for Ocrelizumab, NOK338,273 for Alemtuzumab, NOK 230,114 for Natalizumab, NOK131,85 for Cladribine and NOK50,264 for Rituximab. In the same vein, the QALY for Ocrelizumab, Alemtuzumab, Natalizumab, Cladribine and Rituximab are 0,829, 0.827, 0,815, 0,792 and 0,814 respectively.

Moreover, as it is established for Norway that Placebo is not a relevant treatment options. This is because in instances where there is uncertainty as to whether a current practice reflects a cost effective alternative, Placebo would not be recommended. However, it represents a common comparator. Therefore, Alemtuzumab should have been the best comparator for both Ocrelizumab and Rituximab, but Alemtuzumab is currently with a restricted label i.e., its currently being investigated by EMA for ''immune mediated conditions and problem with heart and blood vessels, among other fatal cases. Also, JCV test is required before initiating Alemtuzumab treatment in Norway. As a result, Cladribine is considered to be most relevant comparator when it comes to both Ocrelizumab and Rituximab. Fingolimod is dominated i.e. its more costly and less effective, therefore excluded from the analysis.

Additionally, using Cladribine as comparator for both Ocrelizumab and Rituximab; Rituximab generates more health gains of 0,022 in terms of QALYs when compared to Cladribine. In addition, Rituximab is NOK81,586 cheaper than Cladribine in terms of cost saving. Therefore, one could conclude that Rituximab is a dominant therapy as its less costly and more effective than Cladribine. On the other hand, Ocrelizumab generates more health gains of 0,037 in terms of QALYs when compared to Cladribine. More so, Ocrelizumab is NOK108,317 more expensive than Cladribine. In other words, Ocrelizumab is more costly and more effective (NIPH, 2019).

In conclusion,
For both primary endpoints, Alemtuzumab has the best ranking with ARR, CDP and it should have been the best comparator for both Ocrelizumab and Rituximab, but it's excluded due to EMA investigation and JCV testing requirement. More so, according to CE place, Ocrelizumab is situated at the NE quadrant of more costly, more effective. Therefore, the question of whether or not Ocrelizumab can be considered as cost effective against Cladribine or **''more cost effective''** than Rituximab largely depends on the assumed estimate of threshold values for cost effectiveness. More holistically, head to head comparison of Ocrelizumab with Rituximab shows that Ocrelizumab has incremental QALY gained of 0.15, but Rituximab has a cost saving advantage of NOK189,903. So, does it worth it to reimburse more Ocrelizumab as a result of more QALY gained at the expense of cost saving of NOK189,903 for Rituximab and vice versa? The answer will depend on three factors;

First, the assume estimate of threshold values for cost effectiveness. Second, using the upper confidence level estimates of CPD and third, Only the ARR and the CPD are included in the analysis, **SAE and treatment withdrawal due to SAE are excluded, which can have an impact on differences in resource use when estimating monitoring costs associated with each of the treatment strategies. More importantly, treatment withdrawal can also be a proxy to show the efficacy of the therapies and Inclusion of it and their respective adverse events could also affect the estimated number of QALYs**.

However, in the Probability Sensitivity Analysis ''PSA'' result of Ocrelizumab compared to Rituximab, it shows that Ocrelizumab has 54% chance that it generates more health gains in QALYs and 0% chance that its less costly than Rituximab. In other words, Ocrelizumab has 54% chance of being more effective and more costly than Rituximab and a 45% chance of being less effective and more costly than Rituximab. Nevertheless, the conclusion will still depend

on the choice of assumed cost effectiveness threshold values i.e., if Norway is willing to pay more for more health gains. (NIPH, 2019).

Furthermore, for U.K., the list cost of Ocrelizumab is £4,790 or NOK56,189.98, which results to an annual cost of £19,000 or NOK201,748.76 excluding 20% VAT. NHS believes Ocrelizumab is a cost effective use of NHS resources for RRMS. This decision was made on the cost associated with CPD, SAE ''including the risk of PML'', treatment withdrawal as a result of SAE/reduction in efficacy over time and of course, the total mean of gadolinium enhancing lesions (GAL) per T1 and T2 weighted MRI scan as expressed in the EDSS scores (NICE, 2018).

Having established the above, the most ICERs are below £30,000 or NOK352,069.94 per QALY gained. Alemtuzumab and Pegylated Interferon beta-1a are dominated ''more costly and less effective'', perhaps will be excluded. More so, using confirmed CPD estimates, the average ICER is about £40,000 or NOK469,571.81 per QALY.

Conclusion

As a result of 45% relative risk reduction in ARR, 37% relative risk reduction in CPD and the fact the Ocrelizumab improves the EDSS states more than any other DMTs, Ocrelizumab can be considered cost effective for treating highly active and rapidly evolving severe RRMS patients. Such that, in the rapidly evolving severe group, Ocrelizumab was cheaper and less effective than Natalizumab and more cheap and more effective than Fingolimod. However, despite the uncertainties surrounding the clinical effectiveness data, it is established that Ocrelizumab has the potential to be more effective than the comparators. As a result, the committee concluded that Ocrelizumab could be considered a cost effective us of NHS resources for RRMS population, if Alemtuzumab is already dominated, as well as it's contra indicated and unsuitable. Finally, it is imperative to know that the ICERs that are used to reach a commercial agreement with the NHS remains confidential (NICE, 2018).

Denmark adopts a Cost Minimization Analysis ''CMA'', whereby all the therapies included in the analysis are considered to be equally effective, but are prioritized in accordance to their respective serious side effects. Meanwhile, the differences between them are reduced to their cost comparison. In the meantime, it is imperative to be reminded that RRMS treatment in Denmark is divided into three categories namely; P1, P2 and P3 as fully elaborated in the fourth paragraph of chapter 3.3.1. In other words, the difference in the Denmark analysis of each sub population is which comparator Ocrelizumab is compared with. Therefore, for P1 patients, it is Fingolimod, for P2, it is Natalizumab and for P3, it is Alemtuzumab (Medicineradet, 2018).

Having established that, the annual list cost price of Ocrelizumab is DKK180,709 or NOK258,657. While that of Fingolimod for P1, Natalizumab for P2 and Alemtuzumab for P3 are DKK159,462 or NOK228,191, DKK141,730 or NOK202,816 and DKK250,404 or NOK358,140. In addition, with other costs, the total cost of Ocrelizumab is DKK200,150 or NOK285,693. More so, the total cost for Fingolimod is DKK175,660 or NOK250,675. The incremental cost between Ocrelizumab and Fingolimod for P1 is DKK24,490 or NOK34,949 in favor of Fingolimod (Medicineradet, 2018).

Moreover, for P2, when compared with Ocrelizumab, the total cost of Natalizumab is DKK181,850 or NOK260,261 with incremental cost of DKK18,300 or NOK26,106 in favor of Natalizumab (Medicineradet, 2018).

Furthermore, for P3, the total cost for Alemtuzumab is DKK290,275 or NOK414,033 and incremental cost of DKK-90,125 or NOK128,552 in favor of Ocrelizumab (Medicineradet, 2018).

Conclusion

For P1, adopting Fingolimod leads to a cost savings of DKK24,490 or NOK34,949 when compared with Ocrelizumab. However, the primary endpoints of ARR for both are similar, but Ocrelizumab CPD rate if more favorable than Fingolimod. Moreover, Ocrelizumab efficacy to almost completely suppressed the gadolinium enhance lesions GAL per T1 and T2 by 94% shows its efficacy over Fingolimod. Moreover, in terms of SAE and treatment withdrawer due to SAE, Ocrelizumab also has a better profile in both critical endpoints as well. In other words, Ocrelizumab is superior to Fingolimod in clinical value added, safety profile and efficacy.

For P2, adopting Natalizumab leads to a cost savings of DKK18,300 or NOK26,106 when compared with Ocrelizumab. However, in all the outcomes of both primary and secondary endpoints in clinical effectiveness, Ocrelizumab has a superior ARR, CPD and suppresses the GAL per T1 and T2 lesions better than Natalizumab. For safety and treatment efficacy, it is established that Ocrelizumab has a better safety profile and higher efficacy as a result of treatment withdrawer due to SAE than Natalizumab.

For P3, adopting Ocrelizumab leads to a cost savings of DKK-90,125 or NOK128,552 when compared with Alemtuzumab. However, with lack of data on CPD, Alemtuzumab performs slightly better than Ocrelizumab with the primary endpoint ‘’ARR’’. Meanwhile, Ocrelizumab performs better in the secondary endpoint of GAL T1 and T1 lesions suppression. At the same time, while Ocrelizumab has a better SAE, Alemtuzumab is also superior in efficacy associated with treatment withdrawal due to SAE. Finally, although adopting Ocrelizumab might lead to a short term cost savings, but when match the four year cost of both therapies alongside with the 50/50 splitting of the clinical effectiveness, safety and efficacy between both therapies, adopting Alemtuzumab in the year 4 will be cost effective (Medicineradet, 2018).

List of References

Lasse Moe (2019, 08 December). Expect a new assessment of MS medicine. Access from; https://www.dagensmedisin.no/artikler/2019/08/12/forventer-ny-behandling-av-ms-medisin/?fbclid=IwAR1hzHwAt2WYYW2gys2C1ocqSXALd4WwdSfdSFqC74nJHuSvOEv43MmBCPA

Above MS (2020). Understanding Lesions. Accessed from; https://www.abovems.com/en_us/home/what-is-ms/ms-education/what-is-a-lesion.html

Allie Nawrat (2019, 13 September). Roche's Ocrevus slows disease progression in two types of MS. Accessed from; https://www.pharmaceutical-technology.com/news/roche-ocrevus-disease-progression-ms/

Amgros (2018, August). Guidelines for cost analyses of new medicines and indications in the hospital sector ''Patient cost pg7. Accessed from; https://amgros.dk/media/1773/guidelines-for-costanalyses.pdf

Arthur E. Attema, Werner B. F. Brouwer, and Karl Claxton (2018). ''Discounting costs and health effects pg2-14''. Accessed from; https://www.ncbi.nlm.nih.gov/pmc/articles/PMC5999124/#:~:text=If%20one%20uses%20an%20incremental,of%20health%2C%20whereas%20the%20discount

Barry, M., Tilson, L., & Ryan, M. (2004). Pricing and reimbursement of drugs in Ireland. *The European Journal of Health Economics, formerly: HEPAC*, *5*(2), 190-194.

Briggs, A., Sculpher, M., & Claxton, K. (2006). 'Alternative Paradigms for Economic Evaluation'' Accessed from; *Decision modelling for health economic evaluation*. Oup Oxford. 2-11.

County Council's Collaborative Model Pharmaceuticals (2018, 29 November). PPMS Reimbursement Recommendation citing Ethical Reasons in Sweden. Accessed from; https://janusinfo.se/download/18.5a3cbcf41675a5048c610f5d/1543503481144/Ocrevus%202018-11-29.pdf

Deborah Weatherspoon (2019, 4 february). The JC Virus and Risks for People with Multiple Sclerosis (MS). Accessed from; https://www.healthline.com/health/multiple-sclerosis/jc-virus-risks-for-ms-patients#1

Drummond, M. F., Sculpher, M. J., Claxton, K., Stoddart, G. L., & Torrance, G. W. (2015). ''Quantifying uncertainty in cost-effectiveness using patient-level data''. Accessed from; *Methods for the economic evaluation of health care programmes*. Oxford university press. 296-304

Drummond, M. F., Sculpher, M. J., Claxton, K., Stoddart, G. L., & Torrance, G. W. (2015). 'Measuring health Effect – ''patient's adaptation''. Accessed from; *Methods for the economic evaluation of health care programmes*. Oxford university press. 27-30

Drummond, M. F., Sculpher, M. J., Claxton, K., Stoddart, G. L., & Torrance, G. W. (2015). 'Stated preference Study – ''Contingent Valuation. Accessed from; *Methods for the economic evaluation of health care programmes*. Oxford university press. 184-209

Drummond, M. F., Sculpher, M. J., Claxton, K., Stoddart, G. L., & Torrance, G. W.

(2015). ‘Do all economic evaluation use the same thecniques? CUA and CMA’’. Accessed from; *Methods for the economic evaluation of health care programmes*. Oxford university press. 5-11

Drummond, M. F., Sculpher, M. J., Claxton, K., Stoddart, G. L., & Torrance, G. W. (2015). ‘Analysis of Observational studies’’. Accessed from; *Methods for the economic evaluation of health care programmes*. Oxford university press. 320-322

Drummond, M. F., Sculpher, M. J., Claxton, K., Stoddart, G. L., & Torrance, G. W. (2015). ‘Critical assessment of economic Evaluation’’. Accessed from; *Methods for the economic evaluation of health care programmes*. Oxford university press. 41-45

Drummond, M. F., Sculpher, M. J., Claxton, K., Stoddart, G. L., & Torrance, G. W. (2015). ‘Cost Analysis’’. Accessed from; *Methods for the economic evaluation of health care programmes*. Oxford university press. 219-240.

Drummond, M. F., Sculpher, M. J., Claxton, K., Stoddart, G. L., & Torrance, G. W. (2015). ‘’Quantifying uncertainty in cost-effectiveness using patient-level data’’. Accessed from; *Methods for the economic evaluation of health care programmes*. Oxford university press. 296-304

Drummond, M. F., Sculpher, M. J., Claxton, K., Stoddart, G. L., & Torrance, G. W. (2015). ‘Estimating the cost savings associated with reducing the length of stay’’. Accessed from; *Methods for the economic evaluation of health care programmes*. Oxford university press. 235-241.

Drummond, M. F., Sculpher, M. J., Claxton, K., Stoddart, G. L., & Torrance, G. W. (2015). ‘Choice of comparison therapy – Placebo and option?’’. Accessed from; *Methods for the economic evaluation of health care programmes*. Oxford university press. 270-273.

Drummond, M. F., Sculpher, M. J., Claxton, K., Stoddart, G. L., & Torrance, G. W. (2015). ‘Clinical assessment of Economic Evaluation ‘’Choice of Perspective’’. Accessed from; *Methods for the economic evaluation of health care programmes*. Oxford university press. 42-53

Drummond, M. F., Sculpher, M. J., Claxton, K., Stoddart, G. L., & Torrance, G. W. (2015). ‘Consumption benefits of healthcare ‘’Human Capital Method’’. Accessed from; *Methods for the economic evaluation of health care programmes*. Oxford university press. 183-187

Drummond, M. F., Sculpher, M. J., Claxton, K., Stoddart, G. L., & Torrance, G. W. (2015). ‘’Cost Analysis – choice of discount rate’’. Accessed from; *Methods for the economic evaluation of health care programmes*. Oxford university press. 244-259

Drummond, M. F., Sculpher, M. J., Claxton, K., Stoddart, G. L., & Torrance, G. W. (2015). ‘Measuring preferences for health states – choice of discount rate’’. Accessed from; *Methods for the economic evaluation of health care programmes*. Oxford university

press. 133-168.

Drummond, M. F., Sculpher, M. J., Claxton, K., Stoddart, G. L., & Torrance, G. W. (2015). 'Measuring preferences for health states – who should value health state?''. Accessed from; *Methods for the economic evaluation of health care programmes*. Oxford university press. 163-165.

Drummond, M. F., Sculpher, M. J., Claxton, K., Stoddart, G. L., & Torrance, G. W. (2015). 'Measuring preferences for health states – the purpose of mapping''. Accessed from; *Methods for the economic evaluation of health care programmes*. Oxford university press. 162.

(2015). ''Using decision analytic modelling'' – choice of Time Horizon''. Accessed from; *Methods for the economic evaluation of health care programmes*. Oxford university press. 334-413.

Drummond, M., & Pang, F. (2001). Transferability of Economic Evaluation results. *Economic evaluation in health care: merging theory with practice*, 257-259.
Drummond, M., & Pang, F. (2001). Basic Demographic and Epidemiology of Disease. *Economic evaluation in health care: merging theory with practice*, 257.

Drummond, M., & Pang, F. (2001). Relative prices and costs. *Economic evaluation in health care: merging theory with practice*, 258-261.
Drummond, M., Barbieri, M., Cook, J., Glick, H. A., Lis, J., Malik, F., ... & Severens, J. (2009). Transferability of economic evaluations across jurisdictions: ISPOR Good Research Practices Task Force report. *Value in health*, *12*(4), 409-418.
EMA (2020). Marketing authorisation. Accessed from; https://www.ema.europa.eu/en/human-regulatory/marketing-authorisation
EMSP (2015). Multiple sclerosis in Europe. Accessed from; http://www.emsp.org/wp-content/uploads/2015/08/MS-in-EU-access.pdf
EMSP (2019). MS Facts | MS Treatments. Accessed from; hhttp://www.emsp.org/about-ms/ms-treatments/
Eunethta (2015, May). '' Subgroup analyses in health economic evaluations ''. Accessed from; Methods for health economic evaluations - A guideline based on current practices in Europe
https://eunethta.eu/wpcontent/uploads/2018/03/Methods_for_health_economic_evaluations.pdf

Eunethta (2015, May). '' Sources for costs data''. Accessed from; Methods for health economic evaluations- A guideline based on current practices in Europe.
https://eunethta.eu/wpcontent/uploads/2018/03/Methods_for_health_economic_evaluations.pdf
Eunethta (2015, May). '' Willingness to Pat Threshold'' ''pg40&80''. Accessed from; Methods for health economic evaluations- A guideline based on current practices in Europe.
https://eunethta.eu/wpcontent/uploads/2018/03/Methods_for_health_economic_evaluations.pdf

Eunethta (2015, May). '' Preferred method to derive HRQoL weights for calculations of QALYs ''pg40-44''. Accessed from; Methods for health economic evaluations- A guideline based on current practices in Europe https://eunethta.eu/wpcontent/uploads/2018/03/Methods_for_health_economic_evaluations.pdf

Eunethta (2015, May). '' Choice of comparators pg 23-24''. Accessed from; Methods for health economic evaluations- A guideline based on current practices in Europe https://eunethta.eu/wpcontent/uploads/2018/03/Methods_for_health_economic_evaluations.pdf

European health Summit (2012, 24 January). Diagnosis Related Group in europe. Accessed from; https://www.mig.tu-berlin.de/fileadmin/a38331600/2012.lectures/Brussels.2012.01.24.rb_EuroHealthSummit-DRGs.pdf

F. Hoffmann (2019, 13, September). Roche presents new 6-year OCREVUS (ocrelizumab) data which showed that earlier initiation and continuation of treatment reduced disability progression in multiple sclerosis. Accessed from; https://www.globenewswire.com/news-release/2019/09/13/1915221/0/en/Roche-presents-new-6-year-OCREVUS-ocrelizumab-data-which-showed-that-earlier-initiation-and-continuation-of-treatment-reduced-disability-progression-in-multiple-sclerosis.html

Fenwick, E., O'Brien, B. J., & Briggs, A. (2004). Cost-effectiveness acceptability curves–facts, fallacies and frequently asked questions. *Health economics*, *13*(5), 405-415.

Fenwick, E., O'Brien, B. J., & Briggs, A. (2004). Cost Effectiveness Acceptability Curves – ''Dominance and Dominated''. *Health economics*, *13*(5), 407-412.

Foundation (Charcot, 2014). Multiple sclerosis: the disease. Accessed from; https://www.fondation-charcot.org/en/multiple-sclerosis-disease

G-ba (2018, 2 August). Medicinal Products Directive / Annex XII: Ocrelizumab. Accessed from; https://www.g-ba.de/bewertungsverfahren/nutzenbewertung/343/#beschluesse

Gisela Kobelt (2019). New Insights into the Burden and Costs of MS in Europe. Accessed from; https://onlinelibrary.ectrims-congress.eu/ectrims/2019/stockholm/279550/gisela.kobelt.burden.and.cost.of.multiple.sclerosis.html?f=menu%3D6*browseby%3D8*sortby%3D2*media%3D3*ce_id%3D1603*marker%3D616&fbclid=IwAR3Q_k75VSF3pWRZpuJOQ6HyJRjBoGE0oMhq-nOqjaSVqBIzIvV3VBrDdqQ

GLI (2019). Pricing and Reimbursement in the U.K. Accessed from; https://www.globallegalinsights.com/practice-areas/pricing-and-reimbursement-laws-and-regulations/united-kingdom#:~:text=In%20primary%20care%2C%20any%20medicinal,the%20dispensing%20pharmacist%2Fdoctor).

GLI (2019). Pricing and Reimbursement in Sweden. Accessed from; https://www.globallegalinsights.com/practice-areas/pricing-and-reimbursement-laws-and-

regulations/sweden#:~:text=In%20primary%20care%2C%20any%20medicinal,the%20dispensing%20pharmacist%2Fdoctor).

Gregson, N., Sparrowhawk, K., Mauskopf, J., & Paul, J. (2005). Pricing medicines: theory and practice, challenges and opportunities. *Nature Reviews Drug Discovery*, *4*(2), 121-130.

Hans Anderson (2019, 11 November). The MS medicine Ocrevus today received its third straight no in the Decision Forum. The reason is once again that the price is too high in relation to the effect. Accessed from; https://www.healthtalk.no/alle-artikler/alle-godeting-er-ikke-tre-ocrevus-fikk-nei-i-beslutningsforum/?fbclid=IwAR0mvHcPa7tP-FXHoiu61mTQBj0M-axwSwhSDGyYZus8WckonIARuVeXLTY

HIQA (2019). Guidelines for the Economic Evaluation of Health Technologies in Ireland. Accessed from; https://www.hiqa.ie/sites/default/files/2019-07/HTA-Economic-Guidelines-2019.pdf

Hollandzorg (2020). Insurance Condition and Regulations 2020. Accessed from; https://www.hollandzorg.com/dutch-healthcare-insurance/customer-services/conditions

INSPOR (2007, December). THE NETHERLANDS - REIMBURSEMENT PROCESS. Accessed from; https://tools.ispor.org/htaroadmaps/Netherlands.asp

INSPOR (2012). Guidelines on how to conduct pharmacoeconomic analyses. Accessed from; https://tools.ispor.org/PEguidelines/source/Norwegian_guidelines2012.pdf

INSPOR (2012). Present Value estimate and discounting ''pg20-21''. Accessed from; https://tools.ispor.org/PEguidelines/source/Norwegian_guidelines2012.pdf

INSPOR (2015, December). Denmark Pharmaceutical Reimbursement. Accessed from; https://tools.ispor.org/htaroadmaps/Denmark.asp#:~:text=143%20of%20the%20National%20Health,has%20granted%20reimbursement%20%5B7%5D.&text=Above%203280%20DKK%20the%20reimbursement%20rate%20is%2085%25

James F. O'Mahony & Diarmuid Coughlan (2015). The Irish Cost-Effectiveness Threshold: Does it Support Rational Rationing or Might it Lead to Unintended Harm to Ireland's Health System?. Accessed from; https://www.tcd.ie/Economics/assets/pdf/MScEPS/Economic%20Evaluation/nolan9.pdf

James F. ''The U.K., Ireland and Norway WTP threshold ''pgg2-5''. Accessed from; O'Mahony & Diarmuid Coughlan (2015). The Irish Cost-Effectiveness Threshold: Does it Support Rational Rationing or Might it Lead to Unintended Harm to Ireland's Health System? https://www.tcd.ie/Economics/assets/pdf/MScEPS/Economic%20Evaluation/nolan9.pdf

Jarosławski, S., & Toumi, M. (2011). Market access agreements for pharmaceuticals in Europe: diversity of approaches and underlying concepts. *BMC health services research*, *11*(1), 259.

Jolijn Kragt (2010). Measuring disease progression in MS: do patients' and physicians' perspectives match?. Accessed from; https://research.vumc.nl/ws/portalfiles/portal/701536/dissertation.pdf
Joseph R. Berger (2017). Classifying PML Risk with Disease Modifying Therapies. Accessed from; https://www.researchgate.net/publication/312255372_Classifying_PML_Risk_with_Disease_Modifying_Therapies
Kelly, S. B., Fogarty, E., Duggan, M., Buckley, L., Hutchinson, M., McGuigan, C., & Tubridy, N. (2014). Economic costs associated with an MS relapse. *Multiple Sclerosis and Related Disorders*, *3*(6), 678-683.
Knies, S., Ament, A. J., Evers, S. M., & Severens, J. L. (2009). ''Variability Impacts on Costs'' The transferability of economic evaluations: testing the model of Welte. *Value in Health*, *12*(5), 730-738.
Kolassa, E. M. (2009). *The strategic pricing of pharmaceuticals*. PondHouse Press.
Lasse Moe (2018, 29 November). MS medicine ''ocrelizumab'' is introduced at Swedish hospitals. Accessed from; https://www.dagensmedisin.no/artikler/2018/11/29/ms-medisin-innfores-ved-svenske-sykehus/

Maureen Rutten, (2018). Marketing Authorization is done by EMA, Market Access and Reimbursement is done nationally. Accessed from; Market Access and Reimbursement lecture.
Målfrid Bordvik (2018, 22 October). Norwegian patients do not receive new MS medicine. Accessed from; https://www.dagensmedisin.no/artikler/2018/10/22/norske-pasienter-far-ikke-ny-ms-medisin/
Medicinraadet (2018, 28 June). The Medical Council's recommendation regarding ocrelizumab as a possible standard treatment for recurrent multiple sclerosis. Accessed from; https://medicinraadet.dk/media/252hebhi/medicinraadets-anbefaling-vedr-ocrelizumab-til-recidiverende-multipel-sklerose-vers-10_adlegacy.pdf

Medicinraadet (2018, 28 June). Measuring hospital cost using DRGs ''page9''. Accessed from; The Medical Council's recommendation regarding ocrelizumab as a possible standard treatment for recurrent multiple sclerosis. https://medicinraadet.dk/media/252hebhi/medicinraadets-anbefaling-vedr-ocrelizumab-til-recidiverende-multipel-sklerose-vers-10_adlegacy.pdf

Medicinraadet (2018, 28 June). Cost effectiveness of Ocrelizumab in P1, P2 and P3 ''pg7-18; https://medicinraadet.dk/media/252hebhi/medicinraadets-anbefaling-vedr-ocrelizumab-til-recidiverende-multipel-sklerose-vers-10_adlegacy.pdf
Medicinraadet (2018, 30 May). The Danish Medicines Agency's assessment of clinical added value of ocrelizumab for recurrent multiple sclerosis. Accessed from; https://medicinraadet.dk/media/4drpqqfs/medicinr%C3%A5dets-vurdering-af-ocrelizumab-til-recidiverende-multipel-sklerose-1-1_adlegacy.pdf

Medicinraadet (2018, 30 May). Choice of comparators pg6-7. Accessed from; https://medicinraadet.dk/media/4drpqqfs/medicinr%C3%A5dets-vurdering-af-ocrelizumab-til-recidiverende-multipel-sklerose-1-1_adlegacy.pdf

Medicinraadet (2018, 30 May). Clinical Effectiveness ''ARR/CPD/EDSS'' and Safety ''SAE/TSAE'' for P1 pg11 of 41 – 17 of 41. Accessed from; https://medicinraadet.dk/media/4drpqqfs/medicinr%C3%A5dets-vurdering-af-ocrelizumab-til-recidiverende-multipel-sklerose-1-1_adlegacy.pdf

Medicinraadet (2018, 30 May). Clinical Effectiveness ''ARR/CPD/EDSS'' and Safety ''SAE/TSAE'' for P2 pg18 of 41 – 22 of 41. Accessed from; https://medicinraadet.dk/media/4drpqqfs/medicinr%C3%A5dets-vurdering-af-ocrelizumab-til-recidiverende-multipel-sklerose-1-1_adlegacy.pdf

Medicinraadet (2018, 30 May). Clinical Effectiveness ''ARR/CPD/EDSS'' and Safety ''SAE/TSAE'' for P3 pg19 of 41 – 29 of 41. Accessed from; https://medicinraadet.dk/media/4drpqqfs/medicinr%C3%A5dets-vurdering-af-ocrelizumab-til-recidiverende-multipel-sklerose-1-1_adlegacy.pdf

Michael Drummond, D Phil, Marco Barbieri et al. (2009, 4 November). Accessed from; https://www.valueinhealthjournal.com/article/S1098-3015(10)60782-6/pdf?_returnURL=https%3A%2F%2Flinkinghub.elsevier.com%2Fretrieve%2Fpii%2FS1098301510607826%3Fshowall%3Dtrue

MS Ireland (2020). DISEASE MODIFYING THERAPIES. Accessed from; https://www.ms-society.ie/about-ms/living-ms/treating-and-managing-ms/disease-modifying-therapies

MS Society (2020). Expanded Disability Status Scale (EDSS). Accessed from; https://www.mssociety.org.uk/about-ms/treatments-and-therapies/getting-treatment-for-ms/expanded-disability-status-scale

MS Society Ireland (2015). Societal Cost of Multiple Sclerosis in Ireland 2015. Accessed from; https://www.ms-society.ie/sites/default/files/2019-06/MS%20Ireland%20-%20Societal%20Cost%20of%20MS%20in%20Ireland%202015cc.pdf

Multiple Sclerosis Today (2020). Magnetic Resonance Imaging (MRI) and MS Diagnosis. Accessed from; https://multiplesclerosisnewstoday.com/multiple-sclerosis-diagnosis/mri-magnetic-resonance-imaging/

NCPE (2018). Cost-effectiveness of ocrelizumab (Ocrevus®) for the treatment of adult patients with relapsing-remitting multiple sclerosis (RRMS). Accesed from; http://www.ncpe.ie/wp-content/uploads/2018/08/Ocrelizumab-summary-FINAL-RMS.pdf

NICE (2013, 4 April). Guide to the methods of technology appraisal. Accessed from; https://www.nice.org.uk/process/pmg9/chapter/the-appraisal-of-the-evidence-and-structured-decision-making#decision-making

NHS (2018, 20 December). Multiple sclerosis Overview. Accessed from; https://www.nhs.uk/conditions/multiple-sclerosis/

NICE (2018, 25 July). Recommendation of Ocrelizumab for treating relapsing–remitting multiple sclerosis. Accessed from; https://www.nice.org.uk/guidance/ta533/chapter/1-Recommendations

NICE (2018, 25 July). Committee Discussion ''Comparators''. Accessed from; https://www.nice.org.uk/guidance/ta533/chapter/3-Committee-discussion

NICE (2018, 25 July). Committee Discussion ‘’Clinical Evidence’’. Accessed from; https://www.nice.org.uk/guidance/ta533/chapter/3-Committee-discussion

NICE (2018, 25 July). Committee Discussion ‘’Adverse Events in the Economic Model’’. Accessed from; https://www.nice.org.uk/guidance/ta533/chapter/3-Committee-discussion

NICE (2018, 25 July). Committee Discussion ‘’Treatment Withdrawal. Accessed from; https://www.nice.org.uk/guidance/ta533/chapter/3-Committee-discussion

Fullfact Organization (2018, 6 July). How is the NHS funded? Accessed from; https://fullfact.org/health/how-nhs-funded/

NICE (2018). Ocrelizumab for treating relapsing multiple sclerosis ''not recommended for reimbursement. Accessed from; https://www.nice.org.uk/guidance/ta533/documents/appraisal-consultation-document

NICE (2018, June). Ocrelizumab for treating primary progressive multiple sclerosis . Accessed from; https://www.nice.org.uk/guidance/ta585/documents/appraisal-consultation-document

NICE (2018, 25 July). Ocrelizumab for treating relapsing–remitting multiple sclerosis ''previous recommendation''. Accessed from; https://www.nice.org.uk/guidance/ta533

NIH (2020). Definition of Relative Risk. Accessed from; https://www.cancer.gov/publications/dictionaries/cancer-terms/def/relative-risk

Nina Grytten, Øivind Tolkidsen & Kjell-Morten Myhr (2015, July). Time trends in the incidence and prevalence of multiple sclerosis in Norway during eight decades. Accessed from; https://www.researchgate.net/publication/277777958_Time_trends_in_the_incidence_and_prevalence_of_multiple_sclerosis_in_Norway_during_eight_decades

NIPH (2019). Disease modifying treatments for relapsing remitting multiple sclerosis. A health economic evaluation. Accessed from; https://www.fhi.no/globalassets/dokumenterfiler/rapporter/2019/disease-modifying-treatments-for-relapsing-remitting-ms-rapport-2019-v2.pdf

NIPH (2019). Differences between health gains among therapy ‘’pg33’’. Accessed from; Disease modifying treatments for relapsing remitting multiple sclerosis. A health economic evaluation.https://www.fhi.no/globalassets/dokumenterfiler/rapporter/2019/disease-modifying-treatments-for-relapsing-remitting-ms-rapport-2019-v2.pdf

NIPH (2019). Disease severity calculation pg23. Accessed from; Disease modifying treatments for relapsing remitting multiple sclerosis. A health economic evaluation. https://www.fhi.no/globalassets/dokumenterfiler/rapporter/2019/disease-modifying-treatments-for-relapsing-remitting-ms-rapport-2019-v2.pdf

NIPH (2019). Probability Sensitivity Analysis of Ocrelizumab VS Rituximab ‘’pg31-32. Accessed from; A health economic evaluation

https://www.fhi.no/globalassets/dokumenterfiler/rapporter/2019/disease-modifying-treatments-for-relapsing-remitting-ms-rapport-2019-v2.pdf

NIPH (2019). ''Cost of intervention pg16-21''. A health economic evaluation. Accessed from; https://www.fhi.no/globalassets/dokumenterfiler/rapporter/2019/disease-modifying-treatments-for-relapsing-remitting-ms-rapport-2019-v2.pdf

NIPH (2019). Disease modifying treatments for relapsing remitting multiple sclerosis, including rituximab.
Accessed from; https://www.fhi.no/globalassets/dokumenterfiler/rapporter/2019/disease-modifying-treatments-for-relapsing-remitting-multiple-sclerosis-including-rituximab-hta-rapport-2019.pdf

NIPH (2019). Risk of DMT is progressive Multifocal Leukoencephalopathy ''PML''. PML is caused by the infection of the brain with John Cunningham Virus ''JCV'' pg 15-16.
Accessed from; https://www.fhi.no/globalassets/dokumenterfiler/rapporter/2019/disease-modifying-treatments-for-relapsing-remitting-multiple-sclerosis-including-rituximab-hta-rapport-2019.pdf

NIPH (2019). Risk of treatment withdrawal due to Adverse Events ''pg51-55''
Accessed from; https://www.fhi.no/globalassets/dokumenterfiler/rapporter/2019/disease-modifying-treatments-for-relapsing-remitting-multiple-sclerosis-including-rituximab-hta-rapport-2019.pdf

NIPH (2019). Risk of specific serious Adverse Events ''pg56-57''
Accessed from; https://www.fhi.no/globalassets/dokumenterfiler/rapporter/2019/disease-modifying-treatments-for-relapsing-remitting-multiple-sclerosis-including-rituximab-hta-rapport-2019.pdf

NOMA (2020). Accessed from; Guidelines for price setting in Norway. https://legemiddelverket.no/Documents/English/Public%20funding%20and%20pricing/Maximum%20Price/Price%20guidelines.docx.pdf

OECD (2018, June). PHARMACEUTICAL REIMBURSEMENT AND PRICING IN GERMANY. Accessed from; https://www.oecd.org/health/health-systems/Pharmaceutical-Reimbursement-and-Pricing-in-Germany.pdf

Patricia Silver (2017, 14 September). Ocrevus Less Expensive, More Efficient than Interferon, Analysis Reveals. Accessed from; https://multiplesclerosisnewstoday.com/2017/09/14/ocrevus-less-expensive-more-efficient-than-interferon-analysis/

Pharmacotherapeutic Compass (2020). Ocrelizumab Not Reimbursed. Access from; https://www.farmacotherapeutischkompas.nl/bladeren/preparaatteksten/o/ocrelizumab

Regjeringen (2017, January). Principle for priority Settings in Healthcare. Accessed from; https://www.regjeringen.no/contentassets/439a420e01914a18b21f351143ccc6af/en-gb/pdfs/stm201520160034000engpdfs.pdf
Regjeringen (2017, January). Main Criteria for Priority pg 16-25. Accessed from; https://www.regjeringen.no/contentassets/439a420e01914a18b21f351143ccc6af/en-gb/pdfs/stm201520160034000engpdfs.pdf
Roche (2018, 12 January). Roche's OCREVUS (ocrelizumab) approved in the European Union for relapsing forms of multiple sclerosis and primary progressive multiple sclerosis. Accessed from; roche.com/media/releases/med-cor-2018-01-12.htm
Seijgraaf Consultancy BV (2018). Dutch Healthcare Market. Accessed from; https://www.welfaretech.dk/media/6800/current-developments-in-the-dutch-healthcare-market.pdf
SPHweb (2018). Risk Ratios and Rate Ratios (Relative Risk. Accessed from; https://sphweb.bumc.bu.edu/otlt/MPHModules/EP/EP713_Association/EP713_Association3.html
Sussex, J., Towse, A., & Devlin, N. (2013). Operationalizing value-based pricing of medicines. *Pharmacoeconomics*, *31*(1), 1-10
Svendsen, B., Myhr, K. M., Nyland, H., & Aarseth, J. H. (2012). The cost of multiple sclerosis in Norway. *The European Journal of Health Economics*, *13*(1), 81-91.
The Commonwealth Fund (2020). INTERNATIONAL HEALTH CARE SYSTEM PROFILES ''Netherlands''. Accessed from; https://international.commonwealthfund.org/countries/netherlands/
TLV (2018, 12 September). Health economic assessment of Ocrevus in the treatment of multiple sclerosis. Accessed from; https://www.tlv.se/lakemedel/kliniklakemedelsuppdraget/avslutade-halsoekonomiska-bedomningar/arkiv/2018-09-12-halsoekonomisk-bedomning-av-ocrevus-vid-behandling-av-multipel-skleros.html
Wallin, M. T., Culpepper, W. J., Nichols, E., Bhutta, Z. A., Gebrehiwot, T. T., Hay, S. I., ... & Mokdad, A. H. (2019). Global, regional, and national burden of multiple sclerosis 1990–2016: a systematic analysis for the Global Burden of Disease Study 2016. *The Lancet Neurology*, *18*(3), 269-285

Wallin, M. T., Culpepper, W. J., Nichols, E., Bhutta, Z. A., Gebrehiwot, T. T., Hay, S. I., ... & Mokdad, A. H. (2019). Global, regional, and national burden of multiple sclerosis 1990–2016: a systematic analysis for the Global Burden of Disease Study 2016. *The Lancet Neurology*, *18*(3), 272-282
Welte, R., Feenstra, T., Jager, H., & Leidl, R. (2004). A decision chart for assessing and improving the transferability of economic evaluation results between countries. *Pharmacoeconomics*, *22*(13), 857-876.
WHO (2004) Burden of Disease. Accessed from; https://www.who.int/foodsafety/foodborne_disease/Q&A.pdf
Wiendl, H., & Meuth, S. G. (2015). Pharmacological approaches to delaying disability progression in patients with multiple sclerosis. *Drugs*, *75*(9), 947-977.
Zorginstituutnederland (2020). Reimbursement of extramural medicines (GVS). Accesed from; https://www.zorginstituutnederland.nl/over-ons/werkwijzen-en-procedures/adviseren-over-en-verduidelijken-van-het-basispakket-aan-zorg/beoordeling-van-geneesmiddelen/vergoeding-van-extramurale-geneesmiddelen-gvs

Zorginstituutnederland (2020). Reimbursement of outpatient medicines ''Summary of Appendix 1 and Appendix 2''. Accesed from; https://english.zorginstituutnederland.nl/about-us/tasks-of-the-national-health-care-institute/assessment-of-outpatient-medicines-for-the-benefit-of-the-medicine-reimbursement-system-gvs/reimbursement-of-outpatient-medicines