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Multiple Sclerosis in Ireland:

Costs, Health-related Quality of Life and

Cost Effectiveness of Disease-modifying Therapies

A thesis submitted to the University of Dublin, Trinity College, for the degree of Doctor in Philosophy

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April 2014

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&

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DECLARATION

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SUMMARY

This study aimed to evaluate the economic and health-related quality of life (HRQoL) burden of multiple sclerosis (MS) in Ireland, and to develop a framework for assessing the cost effectiveness of disease-modifying therapies (DMT). In achieving these aims, a cost-of-illness (CoI) study estimated the direct and indirect costs of MS from the Irish healthcare payer and societal perspectives; the relationship between MS disability and HRQoL was explored; and the relative efficacy of DMT was assessed by network meta-analysis (NMA). Each of these elements was integrated into a decision-analytic model which was developed to estimate the cost effectiveness of DMT in Ireland.

The CoI study established MS as a high cost therapeutic area with significant economic implications for the Irish healthcare system, individual patients and society as a whole. The mean annual direct (indirect) costs per person were approximately €10,000 (€9,500), €13,000 (€32,000) and €56,500 (€39,500) in mild, moderate and severe MS respectively. Progression from mild or moderate to severe disease was associated with the greatest economic consequences for the healthcare payer.

In its first reported use in an MS population, the five-level Euroqol-5D (EQ-5D-5L) displayed an inverse relationship with MS disability (measured on the EDSS scale). A linear decline in utility was observed as EDSS progresses from 0 to 6, followed by sharp declines in utility, falling below 0 at EDSS 8 and 9.

A systematic review identified twenty randomised, placebo-controlled and direct comparative trials of DMTs in relapsing-remitting MS, including interferon-beta, glatiramer-acetate, natalizumab, alemtuzumab, fingolimod, teriflunomide, laquinimod, and BG-12. An NMA was conducted to determine the relative efficacy of DMTs in reducing relapses and slowing short-term progression of disability. All DMTs were significantly superior to placebo in reducing relapse rates with many newer agents demonstrating significant improvements in efficacy compared with older DMTs. Significant benefits in reducing short-term disability progression compared with no treatment were limited to the newer DMTs. The analysis found little to distinguish the effects of different DMTs on short-term disability progression, with the exception of alemtuzumab which was superior to other comparators.

Health state costs and utility values estimated from the CoI and HRQoL studies, and treatment efficacy estimates from the NMA informed a decision-model of DMT for

relapsing-remitting multiple sclerosis (RRMS) in Ireland. Analysis revealed that from the healthcare payer perspective, the probability that fingolimod or natalizumab is cost-effective compared with current standard-of-care at a threshold of €45,000 per QALY is very low (10% and 27%, respectively). DMTs accounted for a substantial proportion of lifetime healthcare costs, while yielding less than one additional QALY. The primary economic benefit of DMT arose from delaying disability progression. A fully incremental analysis revealed best-supportive care (no treatment) as the appropriate comparator for new DMTs, as the existing standard-of-care (represented by a weighted average of interferon β and glatiramer acetate) is extendedly dominated. The price at which existing and new DMTs entering the market would be considered cost-effective compared with current standard-of-care, based on current evidence and model assumptions, was estimated. Price reductions of 12% and 27% were estimated for natalizumab and fingolimod respectively.

Limitations of the CoI and HRQoL study include the recruitment of patients from one specialist MS outpatient clinic. Extension of these studies to a wider population of patients with MS in Ireland would further enhance the reliability of the findings. The definition of disability progression was identified as a key determinant of relative efficacy in the NMA. The inclusion of trials which defined disability progression on the basis of a 6-month confirmation interval (as opposed to a 3-month interval used in the base case) had a substantial favourable impact on the efficacy versus placebo of the older agents and a slight negative impact on alemtuzumab. Key areas of uncertainty in the decision-model included lack of evidence on the long-term efficacy of various DMTs. The decision-model does not account for sequential use of DMTs which would more accurately reflect current practice and which necessitates evidence on the efficacy of second-line therapy following failure on first-line agents. Aggregated data on the natural history of MS was used in the model whereas patient-level data would have enhanced the reliability of individual estimates and allowed analysis in subgroups of interest.

The findings of this study present numerous issues for consideration by decision-makers. Based on the inputs and assumptions applied in the decision model, the prices at which DMTs are currently reimbursed are not cost-effective. It is essential that future therapies, which may not offer incremental benefits in terms of efficacy or other measure of innovation, are reimbursed at a price which represents value for money, at least over current "standard-of-care".

ACKNOWLEDGEMENTS

Sincere gratitude is extended to Professor Michael Barry, for providing me with the opportunity to conduct this research, and for the support and encouragement he provided throughout the process.

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Abbreviations

ACER	Average cost effectiveness ratio
AR DRG	Australian refined diagnostic related group
ARR	Annualised relapse rate
BSC	Best Supportive Care
CBA	Cost benefit analysis
CCA	Cost consequence analysis
CDS	Community drug schemes
CEA	Cost effectiveness analysis
CEAC	Cost effectiveness acceptability curve
CEAF	Cost effectiveness acceptability frontier
CHMP	Committee for medicinal products for human use
CI	Confidence interval
CIS	Clinically isolated syndrome
CMA	Cost minimisation analysis
CNS	Central nervous system
COI	Cost of illness
CSO	Central statistics office
CSRI	Client service receipt inventory
CUA	Cost utility analysis
DIC	Deviance information criterion
DMT	Disease modifying therapies
DP	Drug payments
DRG	Diagnostic related group
DSA	Deterministic sensitivity analysis
DSS	Disability status scale
EDSS	Expanded disability status scale
EQ-5D	Euroqol 5-domain
EQ-5D-3L	Three level EQ-5D
EQ-5D-5L	Five level EQ-5D
EU	European union
FCA	Friction cost approach
GA	Glatiramer acetate
GDP	Gross Domestic Product
GMS	General medical services
GP	General practitioner
HCA	Human capital approach
HR	Hazard ratio
HRQOL	Health related quality of life
HSE	Health service executive
HSE-PCRS	HSE primary care reimbursement service
HSUV	Health state utility value
HTA	Health technology assessment
HTD	High tech drugs

ICER	Incremental cost effectiveness ratio
IFN ß -1a	Interferon beta-1a
IFN ß -1b	Interferon beta-1b
IM	Intramuscular
IPHA	Irish pharmaceutical healthcare association
ITT	Intention to treat
JCV	John Cunningham virus
HUI3	Health utilities index mark 3
LO	London, Ontario
LTI	Long term illness
MRI	Magnetic resonance image
MS	Multiple sclerosis
NCPE	National centre for pharmacoeconomics
NICE	National institute for health and care excellence
NMA	Network meta-analysis
NMB	Net monetary benefit
OC	Opportunity cost
OR	Odds ratio
PAF	Population attributable fraction
PBAC	Pharmaceutical benefits advisory committee
PICOS	Population, intervention, comparator, outcome, study design
PIL	Patient information leaflet
PML	Progressive multifocal leucoencephalopathy
PPMS	Primary progressive multiple sclerosis
PRISMA	Preferred reporting items for systematic reviews and meta-analyses
PRMS	Progressive relapsing multiple sclerosis
PSA	Probabilistic sensitivity analysis
QALY	Quality adjusted life year
RCT	Randomised controlled trial
RES	Rapidly evolving severe
RRMS	Relapsing remitting multiple sclerosis
SA	Sensitivity analysis
SC	Subcutaneous
ScHARR	School of health and related research
SD	Standard deviation
SF6D	Short form 6-domain
SG	Standard gamble
SOT	Suboptimally treated
SPMS	Secondary progressive multiple sclerosis
SUCRA	Surface under the cumulative ranking curve
SVUH	St Vincent's university hospital
TPY	Total patient years
TTO	Time trade off
UK	United Kingdom

US	United States
VAS	Visual analogue scale
VOI	Value of information
WTD	Worse than death
WTP	Willingness to pay
21Y-LTF	21-year long term follow up

CHAPTER 1 - INTRODUCTION

CHAPTER 1 – INTRODUCTION

Multiple Sclerosis (MS) is a chronic, disabling disease of the central nervous system and is the leading cause of non-traumatic neurological disability in young adults. Functional impairment can severely impact physical activity, employment capabilities and opportunities for patients with MS. Physical limitations are compounded by psychological, social and psychiatric consequences giving rise to significant health related quality-of-life (HRQoL) burden. Healthcare resource utilisation in MS has significant financial consequences for the healthcare system, patients and their families. [1]

A growing number of biological and other innovative medicines offer the potential of therapeutic advances in disease areas such as MS, but come at a high cost, contributing significantly to the increase in drug expenditure in Ireland over the last decade. Disease-modifying therapies (DMTs) for MS have been shown to reduce the frequency of MS relapses and may delay disease progression in relapsing-remitting MS. Expenditure on pharmaceuticals in Ireland has been addressed by numerous policy initiatives over the last decade including the introduction of formal pharmacoeconomic assessment of new drugs seeking reimbursement by the Health Service Executive (HSE). Six DMTs are reimbursed in Ireland for the treatment of MS. However, only two of these products (natalizumab and fingolimod) have undergone pharmacoeconomic assessment by the National Centre for Pharmacoeconomics (NCPE). Cost of illness (CoI) and HRQoL research may be integrated into a decision-analytic model together with evidence on the natural history of the disease and the effects of treatment in order to assess the cost-effectiveness of DMTs. As the number of available DMTs increases, the development of robust methods for assessing the relative efficacy and cost effectiveness of these new DMTs is a priority for clinicians and health-policy decision-makers alike.

1.1 Aims and Objectives

The aims of this thesis are:

- to estimate direct and indirect costs of MS from the perspective of the healthcare payer and society

- to explore the relationship between MS disability and HRQoL and to derive health state utility values (HSUVs) for relevant MS health states
- to evaluate the relative efficacy of DMTs for MS
- to conduct an economic evaluation of DMTs in Ireland

The objectives identified and implemented in pursuit of this aim are to:

- review the international literature on the economic and HRQoL burden of MS, and the efficacy and cost effectiveness of DMTs.
- undertake a CoI in MS study to assess healthcare and wider societal resource utilisation in a cohort of patients with MS in Ireland
- to provide the economic framework for the assessment of cost effectiveness of DMTs
- derive HSUVs for MS through elicitation of health state description profiles from a cohort of MS patients with varying degrees of disability in Ireland
- synthesise the evidence on comparative efficacy of DMTs by network meta-analysis (NMA) methods
- develop a decision-analytic model for the synthesis of evidence on MS natural history, health state costs and utilities and DMT efficacy.

1.2 Overview of Thesis Chapters 2 to 8

Chapter 2 provides background information on economic evaluation in healthcare and MS. The first part of the chapter describes trends in pharmaceutical expenditure and health technology assessment (HTA) processes in Ireland. The main concepts involved in economic evaluation of pharmaceuticals are also introduced. The second part of this chapter describes the disease area on which this thesis is focused, MS.

Chapter 3 reviews the existing research which is relevant to the aims of this thesis. The approaches and findings of individual studies are compared, focussing on the economic burden of MS, HRQoL in MS, and the relative efficacy and cost effectiveness of disease-modifying therapies for MS.

Chapter 4 provides a methodological review and discussion of the various procedures and techniques relevant to the subsequent original research chapters,

including the collection and analysis of primary data, and decision-analytic modelling for the purposes of informing resource allocation decisions in healthcare.

Chapters 5, 6, 7 and 8 concentrate on the original research of this thesis, drawing on methods described in Chapter 4 and incorporating comparisons with existing research reviewed in Chapter 3. Chapters 5 and 6 describe CoI and HRQoL studies which provide the economic and HRQoL evidence for a decision analytic model for DMT in MS. Chapter 7 describes the process by which evidence on the relative efficacy of all relevant DMTs was identified and synthesised using systematic review and network meta-analysis methods. Chapter 8 describes the economic evaluation conducted to assess the cost effectiveness of DMT in Ireland. The economic evaluation integrates various aspects of other chapters in the thesis including costs, HRQoL, and DMT efficacy.

CHAPTER 2 – BACKGROUND

CHAPTER 2 – BACKGROUND

This chapter provides background information to economic evaluation in healthcare and MS. The first part of the chapter describes the mechanisms for the funding of pharmaceuticals in Ireland, trends in pharmaceutical expenditure, and national health technology assessment (HTA) processes. The main concepts involved in economic evaluation of pharmaceuticals are introduced – the decision analytic model outlined in Chapter 8 is based on these concepts. The second part of this background chapter describes the clinical features, epidemiology and treatment of MS.

2.1 Pharmaceutical Expenditure and Economic Evaluation in Ireland

2.1.1 Introduction

In publicly funded healthcare systems, decision-makers must make difficult choices in the allocation of limited resources in order to maximise health gain. Since 1991 when the requirement for economic analyses in submissions to the Pharmaceutical Benefits Advisory Committee (PBAC) was formalised in Australia, the use of economic evaluation in the drug-reimbursement decision-making process has become widespread throughout the EU and elsewhere. In Ireland, the NCPE performs the economic evaluation of new medicines within the framework of HTA. Against a backdrop of sustained budget cuts and rising pharmaceutical expenditure, economic evaluation has become a core component of the national decision-making process.

2.1.2 Funding of Pharmaceuticals in Ireland

Funding of pharmaceuticals in primary care in Ireland occurs through the demand-led, publicly-funded Community Drug Schemes (CDS). These schemes account for approximately 85% of pharmaceutical expenditure in the state. [2] The General Medical Services (GMS) scheme provides free prescription medicines to those earning an income below a specific threshold (approx. 40% of the population at the time of writing). Those who are not eligible for the GMS scheme are covered by one of the

three CDS which include the Drug Payment (DP), Long Term Illness (LTI) and High Tech Drugs (HTD) schemes. Under the DP scheme, the cost of prescriptions above a monthly threshold of €144 is reimbursed by the state. The cost of prescription medicines for fifteen chronic diseases, including MS, is covered under the LTI scheme and the HTD scheme covers the cost of very expensive medicines generally initiated in the hospital setting e.g. chemotherapy, immunomodulators etc. The largest increase in expenditure among the CDS has been seen in the HTD Scheme, and despite the reduction in total expenditure achieved in 2010, spending on the HTD scheme continues to rise. Total expenditure under this scheme was over €360 million in 2010, increasing by 65% over the previous five years. [3] The HTD scheme was introduced in 1996 to facilitate the supply by community pharmacies of certain high cost medicines e.g. those used in conjunction with chemotherapy, which had previously been supplied primarily in the hospital setting. Since its inception, the scheme has grown to include over 100 different drugs, including disease-modifying therapies for MS. This expansion reflects the growing number of biological and other innovative medicines which offer the potential of therapeutic advances but come at a high cost.

2.1.3 Pharmaceutical Expenditure in Ireland

Total healthcare expenditure in Ireland increased rapidly between 2000 and 2009 at a rate of 8.4% per year, exceeding €15 billion at its peak (9.5% of gross domestic product (GDP)). [4] Pharmaceutical expenditure increased in line with overall health expenditure, influenced by a number of factors including the increased utilisation of new high cost medicine, the largest population growth rates in Europe, an ageing population with more chronic illness, and medicines being used in preference to invasive surgery. [3] Budgetary cuts sparked by an economic recession led to a sharp reduction in overall health spending in 2010, and a drop in expenditure on pharmaceuticals, reversing the trend of year on year increases over the previous decade (Figure 2.1). Despite cuts in resource allocation, health spending per capita in Ireland is among the highest in the OECD ($3718 US Dollars in 2010, adjusted for purchasing power parity), second only to the United States and Canada. [5] Total expenditure on pharmaceuticals in Ireland was €1.9 billion in 2010. [3]

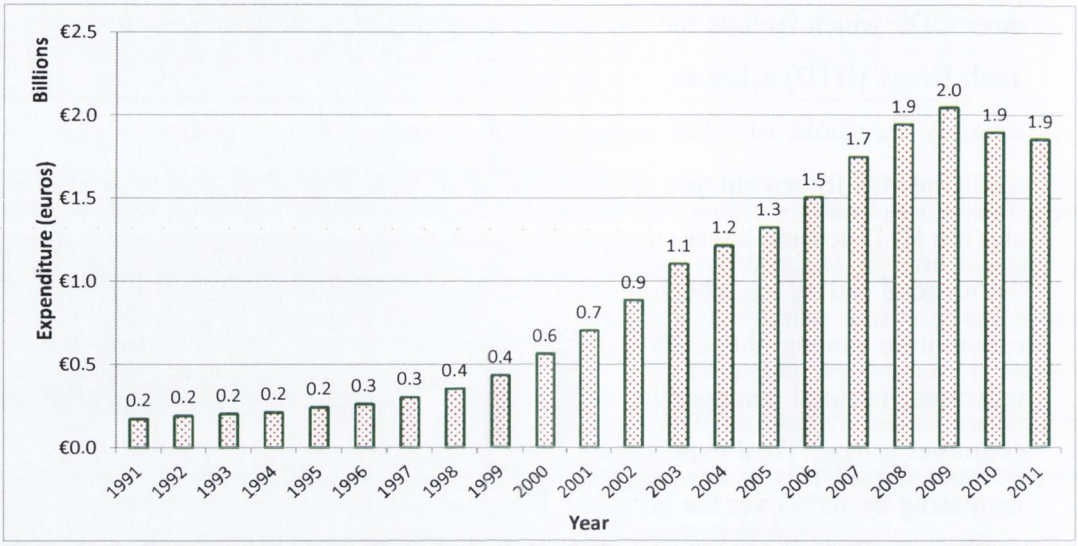


Figure 2.1: Expenditure on medicines in Ireland (Community Drugs Schemes 1991 - 2012)
Extracted from HSE-PCRS annual financial reports [3]

2.1.3.1 Expenditure on disease-modifying therapies for MS

DMTs for MS are among the most expensive drugs reimbursed in Ireland, ranging from €11,000 to €24,000 per patient per year. Five products are currently reimbursed under the HTD scheme, Betaferon® (Interferon β-1b), Avonex ® (Interferon β-1a 30mcg), Rebif® (Interferon β-1a 22mcg or 44mcg), Copaxone® (Glatiramer acetate) and Gilenya® (fingolimod). A sixth product, Natalizumab (Tysabri®) is restricted to hospital-only use. In line with other agents on the HTD scheme, expenditure on DMTs for MS has increased from less than €10 million in 2000 to €31.5 million in 2011, accounting for almost 2% of total expenditure on pharmaceuticals under the CDS (Figure 2.2). Expenditure on these products in the community appears to have stabilised since 2009. However, it is estimated that treatment with natalizumab in hospitals has increased year on year, bringing the total cost of all DMTs up to an estimated €49 million in 2012.

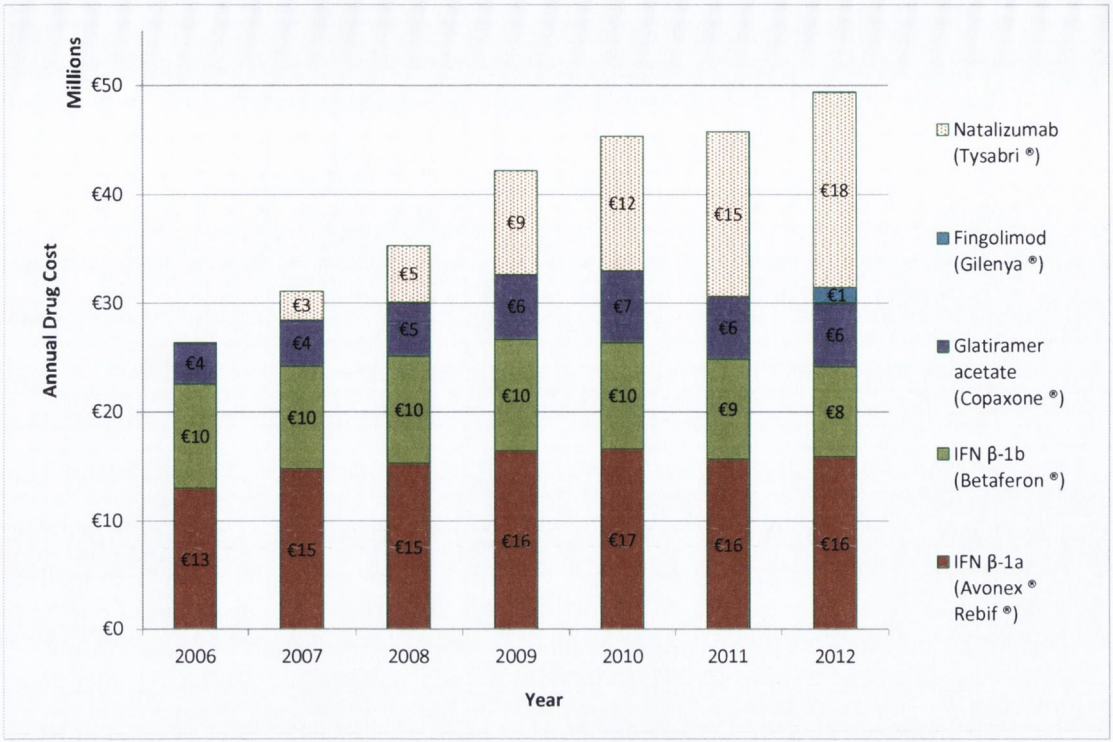


Figure 2.2: National Annual Cost of DMTs for MS 2006-2012

Drug costs from 2010 to 2012 were calculated from HTD prescribing data. Natalizumab costs were estimated from Dee *et al*, 2011 [6] All other drug costs obtained from HSE-PCRS annual financial reports. [3]
IFN ß=interferon beta

2.1.4 Health Technology Assessment in Ireland

HTA is a multidisciplinary process that summarises information about the medical, social, economic and ethical issues related to the use of a health technology in a systematic, transparent, unbiased and robust manner. Its aim is to inform the formulation of safe, effective health policies that are patient-focused and seek to achieve best value. [7] HTA is conducted by interdisciplinary groups using explicit analytical frameworks drawing from a variety of methods. The role of economic evaluation, as part of the HTA process, has been embedded in Irish legislation under the terms of the Health (Pricing and Supply of Medical Goods) Act 2013 which allows the Health Service Executive (HSE) to attach conditions to the supply or reimbursement of listed items in the interests of cost effectiveness, among other relevant factors. [8] The NCPE conducts the economic evaluation of pharmaceuticals in Ireland within the agreed framework of HTA.

2.1.5 Economic Evaluation in Ireland

Economic evaluation refers to the comparison of alternative options in terms of their costs and effects. [9] A formal requirement to demonstrate cost effectiveness prior to reimbursement of new health technologies was introduced in Ireland in 2006 under the terms of an agreement between the Irish Pharmaceutical Healthcare Association (IPHA) and the HSE. [10] Under this agreement, the HSE reserves the right to assess new and existing technologies (pharmaceuticals, diagnostics and devices) that may be high cost or have a significant budget impact on the Irish healthcare system. This strategy was one of a number of measures introduced in the last decade to ensure greater value for money from pharmaceutical expenditure and to ensure continued provision of innovative and affordable medicines. In 2009, the requirement to demonstrate cost effectiveness was extended to *all* new medicines following an application for reimbursement in Ireland. The new IPHA/HSE agreement, reached in October 2012, reaffirmed the role of pharmacoeconomic assessment in the Irish drug reimbursement process. [10] Guidelines for the Economic Evaluation of Health Technologies in Ireland were updated in 2010, and outline the methodology for the conduct of economic evaluation in order to provide the decision-maker with assessments that are timely, reliable, consistent and relevant to their needs. [7]

2.1.5.1 Types of Economic Evaluation

Cost-consequence analysis (CCA), cost-benefit analysis (CBA), cost-minimisation analysis (CMA), cost effectiveness analysis (CEA) and cost-utility analysis (CUA) are the major analytic techniques used in health economic evaluation. These analysis-types may be distinguished largely on the basis of how consequences are identified, measured and valued. In cost-consequence analysis, costs and outcomes are disaggregated and reported separately leaving the decision-maker to decide on the relative importance of each and interpret results accordingly. CBA places a monetary value on both costs and consequences (benefits). CMA assumes that health outcomes are equivalent and compares alternatives only in terms of their costs. The aforementioned techniques are not widely used in health policy decision-making. In CEA, consequences are measured in the same common unit of health outcome, clinically related to the programme of interest (e.g. life years gained, relapses prevented in MS). CUA is a specific type of CEA which measures outcomes in units of utility or preference, usually as the quality

adjusted life year (QALY). In CEA and CUA alternatives (e.g. treatment A and treatment B) can be compared by calculating the differences in mean costs (C) and mean effects (E), presented in the form of a ratio i.e the incremental cost effectiveness ratio (ICER).

$$ICER = \frac{C_B - C_A}{E_B - E_A} = \frac{\theta_C}{\theta_E}$$

CUA has become the preferred method for evaluating the cost effectiveness of healthcare choices.

2.1.5.2 The Quality Adjusted Life Year (QALY)

A QALY is a life year adjusted by a preference-based weighting or utility, corresponding to the HRQoL during that year. In this way the QALY captures disparate outcomes including mortality, morbidity and adverse effects into a single measure. While the results of CEAs using an outcome such as relapses avoided can be compared with each other, they cannot be compared with analyses reporting cost per life year gained. In contrast, a QALY is a universal health outcome measure applicable to all individuals and all diseases, thereby enabling comparisons across diseases and across programs. [11] HRQoL weightings or utilities are measured on a cardinal scale anchored between 1 (perfect health) and 0 (absence of life or dead). Weightings less than zero reflecting health states worse than death (WTD) can exist. Utilities represent the preferences of individuals for relevant health states and, for the purposes of CUA which inform healthcare resource allocation decisions, preferences from the informed general public are generally regarded as most relevant. Further discussion on the QALY and its application in decision analytic models is provided in Chapter 4.

2.1.5.3 The Cost effectiveness Threshold

When comparing across different alternatives and analyses, ICERs may be compared to a critical threshold value (λ), the maximum cost per QALY specified by the decision-maker, below which the intervention is classed as value for money ($\theta_C/\theta_E < \lambda$), and above which the intervention would not represent an efficient use of limited resources ($\theta_C/\theta_E > \lambda$).

Use of a threshold promotes optimum allocation of a fixed budget, where the threshold value represents the highest cost per QALY of currently funded treatment, and any additional intervention must be more efficient (i.e have a lower cost per QALY) in order to displace this treatment and add to health. In Ireland, the upper threshold limit is determined by the decision-maker's maximum willingness to pay (WTP) for an additional QALY and is set at €45,000. [10] Ireland is one of the few countries which operate an explicit single threshold rather than a threshold range (such as the National Institute for Health and Clinical Excellence in the UK, which uses a range of £20,000-£30,000). The empirical basis of the €45,000 cost effectiveness threshold is limited, and was likely originally based on the £30,000 per QALY threshold implicit in NICE decision-making. In the past, NCPE assessments have assessed cost–effectiveness at a €20,000 per QALY threshold level in addition to the €45,000 threshold, reflecting the decision makers' interest in how threshold level influences the cost–effectiveness of new technologies.[12] Since October 2012, following negotiations between the IPHA and HSE, a single threshold of €45,000 has been agreed. [10]

2.1.5.4 The Incremental Cost effectiveness Plane

Plotting ICERs on a incremental cost effectiveness plane is a useful way of visualising and interpreting CEA results (Figure 2.3). [13] In many cases, the new therapeutic intervention B represents an advance over the current treatment A in terms of health outcomes, but may be more costly. ICERs for such treatments may be found in the top-right (north-eastern) quadrant. The slope of the dotted line represents the threshold ICER. In the north-eastern quadrant interventions with ICERs falling to the left of this line may be regarded as "not cost-effective". ICERs to the right of the line may be regarded as "cost-effective". If treatment B is more effective and less costly than treatment A, the ICER will feature in the bottom-right (south-eastern) quadrant and treatment B is said to dominate treatment A. The opposite is true in the case of ICERs in the top-left (north-western) quadrant. In the latter two examples, while the interpretation is clear when visually aided by the incremental cost effectiveness plane, ICERs will be negative and therefore cannot be easily interpreted. Interpretation and presentation of results may be particularly problematic in probabilistic analysis when ICERs may span more than one quadrant. A further issue arises when ICERs feature in

the bottom-left (south-western) quadrant. ICERs in this quadrant indicate the savings which may be gained for a one-unit loss in effect. In contrast to ICERs in the north-east quadrant where lower ICERs are preferable and treatments below a threshold are considered cost-effective, higher ICERs are preferable in the south-west quadrant and only those with an ICER above a certain threshold are accepted. A further issue with technologies in the south-west quadrant is the validity of WTP threshold in this context. Empirical evidence suggests that the minimum acceptable savings per QALY lost in the southwest quadrant probably exceeds the maximum that people are willing to pay per QALY gained in the northeast quadrant. "Decrementally cost-effective" technologies are very rarely described in the medical literature. [14] The net benefit approach overcomes the problems in interpreting ICERs from different quadrants. Further discussion on the generation and interpretation of ICERs is provided in the CEA methodology section of Chapter 4.

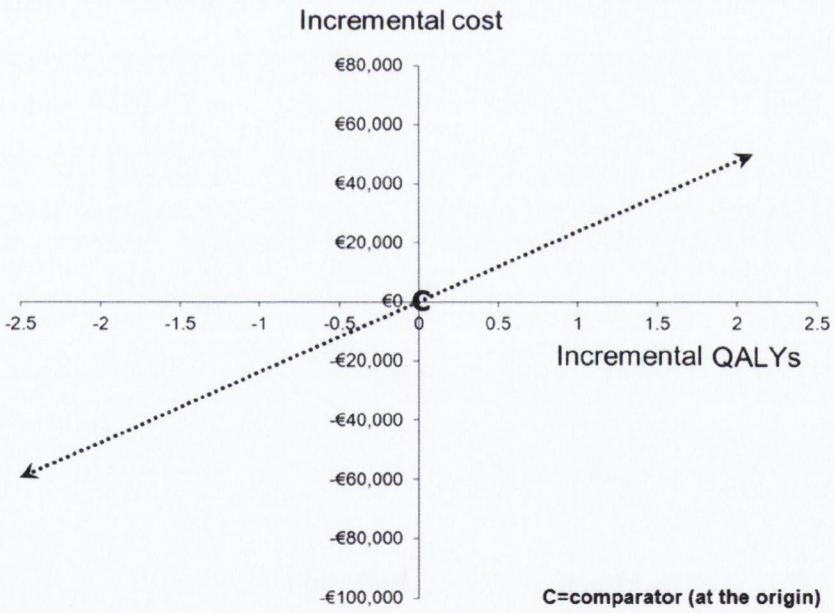


Figure 2.3: Incremental Cost effectiveness Plane

QALY=quality adjusted life year

2.1.5.5 Net-Benefit Approach

The net monetary benefit (NMB) of the intervention is the increase in effectiveness (θE) multiplied by the WTP for one unit increase in effectiveness (λ). An intervention is deemed cost-effective if the NMB is positive.

$$NMB = \lambda.\theta E - \theta C > 0$$

The problems with interpretation of ICERs discussed above can be avoided using the net-benefit approach. The intervention with the highest NMB is the obvious choice.

2.1.6 Handling Uncertainty in Economic Evaluation

Uncertainty is inherent in all economic evaluations. In order for decision-makers to have confidence in applying CUA results to a particular decision problem, it is imperative that uncertainty is systematically examined and reported. Briggs *et al* distinguish variability (the differences that occur between patients by chance) and heterogeneity (the differences that occur between patients that can be explained) from decision uncertainty. [15] The various types of uncertainty can be dealt with through deterministic sensitivity analysis (DSA), scenario analysis, and probabilistic sensitivity analysis (PSA) which are discussed further in Chapter 4. The results of PSA can be presented using cost effectiveness acceptability curves (CEACs), cost effectiveness acceptability frontier (CEAFs), and also with an accompanying value of information which estimates the opportunity cost of an incorrect decision. [16] Further discussion on the presentation of CEA results is provided in the CEA methodology section of Chapter 4.

2.1.7 Other Considerations in the Decision-making Process

Notwithstanding the importance of the ICER and its relationship to the threshold in the decision-making process, the reimbursement decision will be further influenced by the degree of uncertainty in calculating the ICER, the innovative nature of the technology, particular features of the condition and population receiving the technology, and wider societal costs and benefits. [12] For example, despite the explicit WTP threshold of €45,000 per QALY in Ireland, a number of drugs for cancer and other rare orphan diseases have been reimbursed with ICERs well in excess of this value reflecting a

higher WTP in these situations. Empirical research on the true value of the threshold i.e. the opportunity cost (health gain forgone) of implementing new treatments, is ongoing in the UK. [17]

The critical influence of affordability was illustrated in the case of human papilloma virus (HPV) vaccination. [18] Vaccination of 12-year old girls against the HPV was recommended by the NCPE in 2008, however as a result of the "serious and rapid decline of the economic situation in Ireland later that year" the vaccination programme was delayed. This case highlights that while the incremental cost effectiveness of a technology is an important consideration, budget impact may have a greater influence over reimbursement decisions.

2.2 Multiple Sclerosis

In this section, a general background to MS is provided in addition to a more detailed description of the aspects of the disease which are most relevant to the assessment of treatment efficacy and cost-effectiveness. These aspects include the main clinical features of MS, natural history and epidemiology, disease management and treatment.

2.2.1 Pathogenesis

MS is a chronic, disabling disease, characterised by inflammation and multifocal demyelination in the central nervous system (CNS). The exact pathogenesis of MS is not fully understood but it is widely considered to be an autoimmune demyelinating disease, involving both environmental exposure and genetic susceptibility. A failure of local regulatory mechanisms in the brain of susceptible individuals allows the passage of autoreactive lymphocytes across the blood-brain barrier in response to environmental factors.[19] Subsequent production of effector cytokines and chemokines in the CNS attracts immune cells like granulocytes and macrophages into the CNS mediating tissue inflammation and demyelination. [20] Demyelination causes an abnormal proliferation of sodium channels within the cell membrane that can slow or block axonal conduction causing the neurological symptoms associated with MS. The hallmark of the disease is the formation of lesions, or sclerotic plaques, within the white matter of the CNS, caused by demyelination, visible on MRI. [19] CNS lesions can be identified on MRI even before clinical dissemination has occurred, although a definite diagnosis requires a clinical presentation of neurological disturbance in addition to objective MRI evidence of lesions disseminated in time and space.[21] The anatomical site and size of the lesion and the integrity of the neuronal pathway involved determines whether or not a lesion results in clinical signs or symptoms. [22]Persistent demyelination leads to a gradual loss of axons, and the development of progressive neurological impairment.

2.2.2 Clinical Features of MS

The clinical hallmarks of the disease are relapses and disability progression. Relapses are characterised by episodic recurrence of acute neurological symptoms which can

evolve over days to weeks and are followed by complete or partial recovery over weeks to months. The wide distribution of lesions throughout the CNS results in a variety of clinical features such as pain and loss of sensation, fatigue, impaired muscle control, balance and postural problems, visual loss, cognitive impairments, and bowel and bladder disturbance.[23] Progression refers to the steady and irreversible worsening of symptoms and signs over ≥6 months, independent of the occurrence of relapses. [24 25] Different biological mechanisms are thought to be responsible for relapses and progression (Figure 2.4).

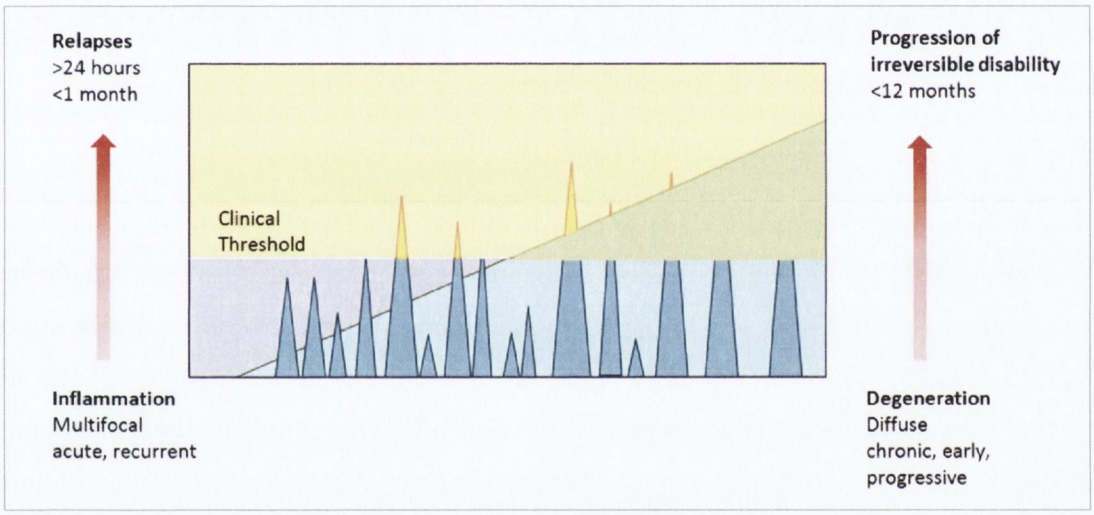


Figure 2.4: Interplay between relapses and progression, and focal inflammation and diffuse degeneration in MS

Adapted with permission from McAlpine's Multiple Sclerosis 4th Edition, Compston A (Ed). [26] With permission from Elsevier ©2006.

Relapses represent focal, acute, recurrent inflammation, while progression is the result of diffuse, early, chronic, progressive neurodegeneration.[24] The contribution of relapses to disability accumulation is unclear, but appears to diminish with time. [27 28] Lublin *et al* determined the percentage of patients with residual deficits following MS relapses in a database of patients assigned to the placebo group in several RCTs. The authors estimated that 42% and 28% of patients have residual deficit of ≥0.5 and ≥1.0 EDSS (Expanded Disability Status Scale, discussed below) units respectively, at an average of 64 days following a relapse. [25] In a population-based series of 806 patients with relapsing-remitting MS (RRMS) from the London Ontario (LO) database, frequent

relapses in the first two years and shorter first inter-attack intervals were found to predict shorter times to reach hard disability endpoints. [29] However Confavreux *et al* have shown that the predictive effect of early relapse rate of disease progression disappears at fixed higher disability milestones and once the progressive course predominates.[30] This has implications for the use of disease-modifying therapies (DMT) which have traditionally targeted the inflammatory component of MS and have not been proven to substantially impact on long term progression.

The association between relapses and disability, and HRQoL and economic outcomes, is of key importance in the assessment of DMT cost-effectiveness. This association will be further explored in Chapters 5, 6 and 8 of this thesis.

2.2.3 Clinical Outcome Measures

2.2.3.1 Disability Progression

The Expanded Disability Status Scale (EDSS) is the most widely used validated measure of disability in MS.[31] The Disability Status Scale (DSS) was first published by Kurtzke in the 1950s and subsequently modified several times until publication of the EDSS in 1983, where half points were added to the original ten-point DSS. The EDSS quantifies disability in a number of functional systems, including vision, brainstem, pyramidal, cerebellar, sensory, bowel and bladder, mental (cerebral) and ambulation (500 metre walk). The scale ranges from from 0 (normal neurological examination) to 10 (death from MS) (Figure 2.5). Studies have sometimes grouped individual levels together so that EDSS 0 to 3.5 refers to fully ambulatory with at most moderate disability in at least one functional system, 4.0 to 6.5 refers to fully ambulatory, although relatively severe disability, eventually constant bilateral assistance needed to walk 20 metre, and 7.0 to 9.5 refers to patients restricted to wheelchairs, confined to bed and totally dependent. [32]

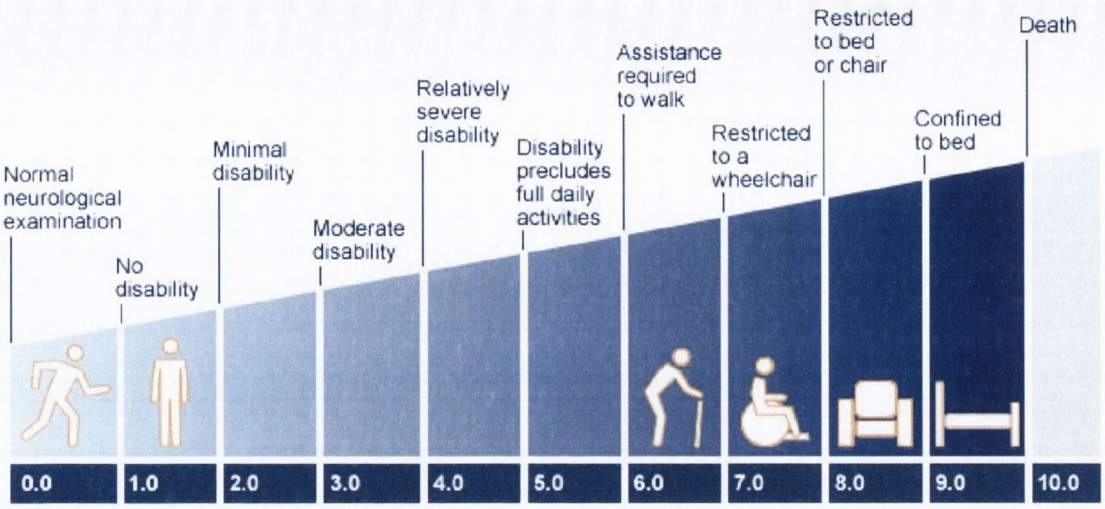


Figure 2.5: Kurtzke's Expanded Disability Status Scale

Adapted with permission from Wolters Kluwer Health: Neurology, Kurtzke, © 1983 [31] Scale has been simplified for illustrative purposes displaying just integer points on the EDSS scale i.e. 0.0, 1.0, 2.0 etc. and not half-points i.e. 0.5, 1.5, 2.5 etc. From EDSS 0 to 3.5, the EDSS score is based on modest-to-moderate changes in one or more functional system. Above 4.0, scoring is primarily based on gait dysfunction. Above EDSS 6.0, disability is almost exclusively dependent on walking function and a score of 8.0 marks loss of ambulation.
EDSS=expanded disability status scale

Change in EDSS score is the standard definition for disability progression in MS clinical trials, often defined as a 1.0 step increase for individuals with an overall EDSS $\leq$6.0 confirmed at three months or six months. [33] Other disability-related endpoints include time to sustained accumulation of disability and mean EDSS score at a defined endpoint. Despite its extensive use and acceptance in MS research, the EDSS scale has been criticised as differences between EDSS scores are not comparable in terms of disease progression, the probability of progressing from one level to the next or the time spent at each level.[34] The scale has been described by Confavreux *et al* as "ordinal and categorical but neither quantitative nor continuous". [26] Goldman *et al* provide a detailed discussion of possible alternative clinical outcome measures in MS including the Multiple Sclerosis Functional Composite, the Timed 25-foot Walk, and the Six-minute Walk, concluding that the optimal MS disease progression measure is still not clearly defined. [35] MRI endpoints are now routinely included in MS RCTs and include percentage change in T2-hyperintense lesion volume and brain volume. However these endpoints are still unvalidated surrogates for unremitting disability and the EDSS remains the "gold standard" for grading clinical impairment and MS-related

disabilty. [36] The administration of the EDSS is often too complex and time-consuming for long-term follow up and DSS is often used in such settings as a result. [26 29 30 37-39]

2.2.3.2 Relapse

Clinical relapses represent the most reliable marker of disease activity and in most cases relapse is used as a primary or secondary efficacy outcome measure. [40]The definition of 'relapse' is subject to slight variation across trials but it is commonly defined as new or worsening symptoms that last 24 hours and occur in the absence of fever or infection. [41] Relapse outcomes include relapse rate over the study period, annualised relapse rate (ARR, defined as the mean number of confirmed relapses per patient adjusting for the duration of follow-up to annualise it), average number of relapses per patient, time to first and second relapse, proportion of relapse-free patients and relapses requiring corticosteroid therapy or hospital admission. The ARR is the most common summary measure of relapses. [42]

2.2.4 Clinical Subtypes of MS

The natural course of MS is highly variable ranging from asymptomatic to an aggressive course with rapidly accumulating disability. [23] A consensus by an international survey of MS clinicians considers the disease spectrum to comprise four distinct categories, relapsing remitting MS (RRMS), secondary progressive MS (SPMS), primary progressive MS (PPMS) and progressive relapsing MS (PRMS). The interplay between relapses and progression in each of these sub-types is illustrated in Figure 2.6. [25]

85% of patients experience an initial RR course that lasts approximately 20 years.[43] The majority of people with initial RRMS will develop secondary progressive MS (SPMS) at some stage.[43] A smaller subset of patients (about 10%-15%) present with primary progressive MS (PPMS) from onset. Progressive-relapsing MS refers to progressive disease from onset with superimposed relapses. A disease course with minimal or no disability many years after disease onset is often referred to as benign MS. Clinically isolated syndrome (CIS) is a term that describes a first clinical episode with features suggestive of MS, excluding an explanation other than that of suspected MS. Confavreux and Vukusic suggest that MS might be considered as one disease with different clinical phenotypes and that RRMS "can be regarded as MS in which

insufficient time has elapsed for the conversion to secondary progression", that SPMS is a form of RRMS "that has 'grown older'", and that PPMS is MS which has been "'amputated' from the usual preceding RR phase". [24]

The focus of Chapter 7 and 8 will be on patients with RRMS as DMTs have not demonstrated efficacy in either primary or secondary progressive MS. In modelling a chronic disease such as MS, however, incorporation of the SPMS phase is necessary, given that the majority of patients with RRMS will eventually progress to SPMS.

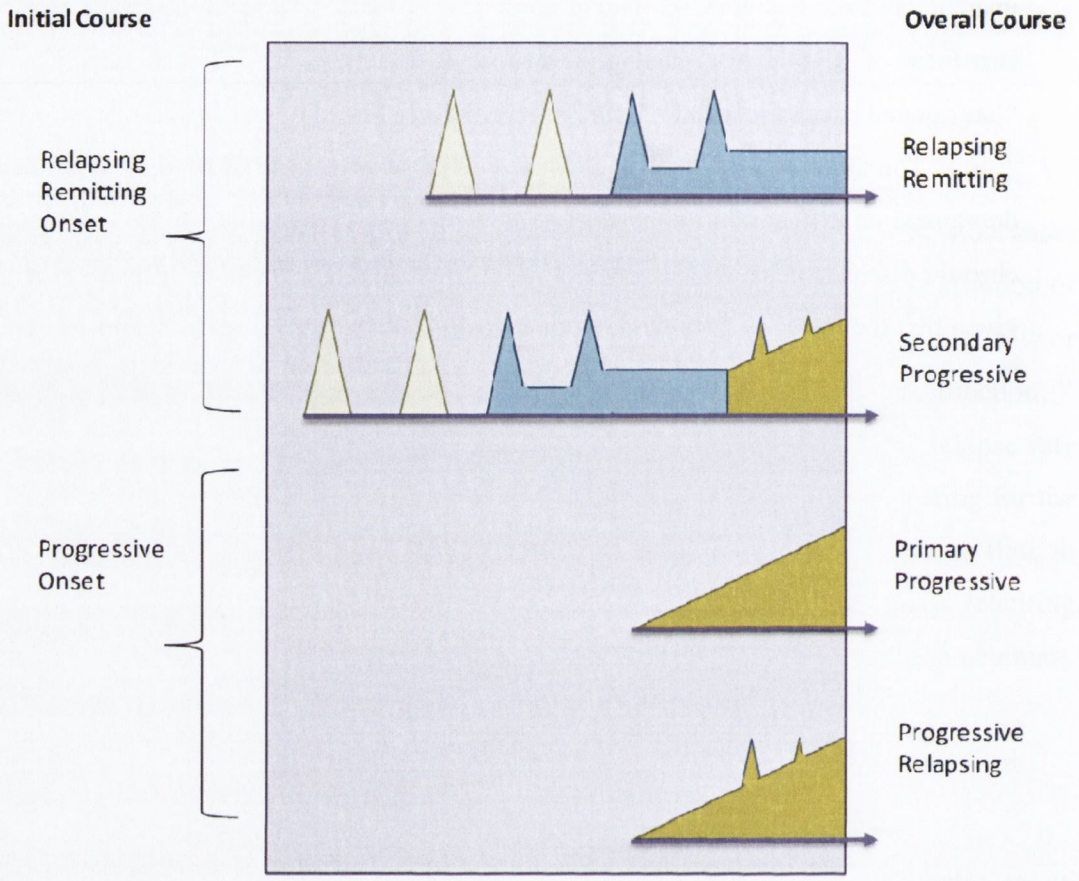


Figure 2.6: Classification of the course of multiple sclerosis

Adapted with permission from Wolters Kluwer Health: Neurology, Lublin and Reingold, ©1996. [25]
Relapsing-remitting MS: "clearly defined relapses with full recovery or with sequelae and residual deficit upon recovery; periods between disease relapses characterised by a lack of disease progression"
Secondary progressive MS: "intitial relapsing-remitting disease course followed by progression with or without occasional relapses, minor remissions, and plateaus"
Primary progressive MS: "disease progression from onset with occasional plateaus and temporary minor improvements allowed"
Progressive-relapsing MS: "progressive disease from onset, with clear acute relapses, with or without full recovery; periods between relapses characterised by continuing progression"

2.2.5 Natural History of MS

An understanding of the untreated disease course, or natural history, is of particular importance in the case of a chronic, progressive disease like MS, where the impact of long-term treatment is often compared with best-supportive care (BSC), or a "do-nothing" approach. The natural history of both disability progression and relapses is of interest, as these are the two main clinical features of the disease.

The widespread use of DMTs restricts the possibility of conducting ethically designed, current population-based natural history studies. As a result, the majority of evidence on the natural history of MS is based on retrospective studies of patient

cohorts, some of which began recruitment in the 1970s. Nevertheless as the duration of follow-up increases, data continues to emerge from some longitudinal cohorts on the natural history of both MS disease progression and relapses.

2.2.5.1 Disability Progression

Wide variation in the MS disease trajectory has been demonstrated within and between natural history studies. Longitudinal studies have variously found that the RR phase lasts around two decades. [43] Scalfari *et al* reported a median time to SPMS of 15 years among 806 relapsing-remitting onset patients in the LO study cohort (>80% of the cohort had reached the secondary progressive phase). [29] The median time to SPMS among the 1562 patients in the Lyon database was 19.1 years, and this figure has been approximated by other studies. [30 44-46] Skoog *et al* recently reported on follow-up of the Gothenberg MS cohort of 202 patients with RRMS. [47] 80% of the cohort developed SPMS. The median time to secondary progression was 12 years (SE 1.11). [47] The rate of change from a relapsing-remitting to a progressive course is accepted as being fairly constant over time, with a gradual rise in the total percentage of progressive cases as the disease advances. [26] Age at onset has been shown to be a strong predictor of the conversion to SPMS: the older the age at onset, the shorter the time to the onset of progression. [46]

In a recent study of 806 patients from the LO database with relapsing-remitting disease onset patients, median times to DSS 3 (10 years), DSS 6 (18 years), DSS 8 (28 years) and DSS 10 (63 years) were reported, based on 81.5%, 67.4%, 48.4% and 16.4% having reached those disability endpoints, respectively. [29] Confavreux *et al* reported slightly longer times from a cohort of 1562 patients with RRMS from onset in the Lyons MS database. Kaplan-Meier estimates of the median time (95% CI) from onset of RRMS to assignment of DSS 4, 6 and 7 were 11.4 (10.5 to 12.3), 23.1 (20.1 to 26.1) and 33.1 (29.2 to 37.0), respectively. [27] Table 2.1 summarises the findings from long-term follow-up of the main natural history cohorts from LO, Canada, Lyon, France, Gothenburg, Sweden and British Colombia, Canada, which have estimated median time from disease onset to the ascertainment of selected levels of disability. In general, recent natural history studies have shown that disability progression in MS is slower than was previously reported. Tremlett *et al* suggest that this may represent a change in the type of patient with MS being seen in MS clinic, driven perhaps by an increased

recognition of the disease, advances in diagnostic techniques and treatment options, and better health care and disease management. [43]

The Tremlett review found that most studies agree that complete or near complete recovery from the first attack is indicative of a slower progression to disability milestone or secondary progression. Also, once a certain disability level or the progressive phase was reached, progression to higher fixed disability milestones thereafter appeared similar for most subgroups examined in most studies. [43] Scalfari *et al* also investigated the role of early relapses on long-term disability progression in the LO RRMS cohort. [29] Frequent relapses in the first two years and shorter first inter-attack intervals were related to a higher probability of conversion to SPMS and predicted shorter times to reach DSS 6, 8 and 10. Relapse frequency beyond year two did not maintain this association. Relapses appear to have little long-term effect once SPMS is reached.

Studies investigating the association between age and disability have generally shown that patients with a RR disease course from onset are older when reaching most disability milestones compared to those with primary-progressive MS. [43] Most studies show that men and those who are older at MS onset progress more rapidly to EDSS milestones, however the latter group are also, on average, older when reaching fixed disability milestones. [43]

In CEAs using historical cohorts to model the natural history of MS disability progression, the LO cohort has been the most frequently used data-source. [48-56] Patient outcomes from this cohort have been analysed and reported on since 1989 and studies continue to be published in 2012 and 2013[39 57].

Table 2.1: Natural history cohorts median time from onset of MS to reach selected levels of disability

Setting	LO, Canada	LO, Canada	British Colombia, Canada	Lyon, France	Gothenberg, Sweden	LO, Canada
Population	Total Population (n=1099)	Seen from Onset (n=197)	RRMS (n=2020)	RRMS (n=1562)	RRMS (n-255)	RRMS (n=806)
Author, year	Weinshenker, 1989[39]	Weinshenker, 1989[39]	Tremlett, 2006[38]	Confavreux, 2003[30]	Runmarker, 1993[37]	Scalfari, 2010[29]
DSS 3	7.69 (0.42)	6.28 (0.34)	NR	NR	NR	10 [18.5%]
DSS 4	NR	NR	NR	11.4 (10.5-12.3)	NR	NR
DSS 6	14.97 (0.31)	9.42 (0.44)	30.3 (28.6–32.0)	23.1 (20.1-26.1)	NR	18 [32.6%]
DSS 7	NR	NR	NR	33.1 (29.2-37.0)	NR	NR
DSS 8	46.39 (0.14)	NR	44.2 [25%]	NR	18	28 [51.6%]
DSS 10	NR	NR	NR	NR	NR	63 [83.6%]

Median time expressed as years (SD) or years (95% confidence interval). % of cohort not reaching endpoint, where available, expressed in square brackets [%]

Abbreviations: LO= London, Ontario; DSS= Disability Status Score; RRMS= Relapsing Remitting MS; SPMS= Secondary Progressive MS; NR= not reported

2.2.5.2 Relapses

Relapses are characterised by a gradual onset of symptoms which stabilise over days or weeks and resolve gradually, either completely or partially. [58] A number of "triggers" have been associated with precipitating MS relapses including infection, stress, post-pregnancy, cranial irradiation and tumour necrosis factor inhibitors. [59] The average time between exposure to a trigger factor and the onset of a relapse ranges from two to six weeks. [59] Substantial variability exists in studies reporting the frequency of MS relapses. [26] In general, prospective studies yield higher figures than retrospective studies. [60 61] Prospective studies involve more frequent assessment which is impractical for a large cohort with longitudinal follow-up. Classification of subtle or transitory symptoms may be problematic in the setting of frequent assessments, while it has been suggested that longitudinal natural history studies will probably underestimate the true relapse rate.[26 62] A longitudinal study by Patzold *et al*, published in 1982, reported relapse rates over 19 years for 102 patients with MS. [61] The average number of relapses was 1.1 per year but as outlined in Table 2.2, there was an obvious decrease in relapse rate over time, from 1.85 relapses in the first year to 0.2 relapses after 19 years. Relapse rates from this study have been widely used in CEAs of DMTs in RRMS to reflect the natural history of the disease. [48-51]

Table 2.2: Natural History of MS Relapses

Years from onset	Estimated ARR relapse rate
1	1.85
2	1.10
3	1.00
4	0.85
5	0.65
7	0.75
9	0.25
11	0.60
13	0.28
15	0.30
19	0.20

Data extracted from Patzold *et al* [61]
ARR=annualised relapse rate

Confavreux *et al* and others consider relapse rate to be stable, at 0.5 or slightly more per year, when calculations are restricted to the relapsing-remitting phase. [63 64] In a recent retrospective cohort study by Tremlett and colleagues, 2477 patients with RRMS in British Colombia were followed up for a mean time of 20.6 years from onset. [62] The main finding of this study relates to the relative pattern of relapse rates over time, demonstrating a decrease in relapse rate by 17% every five years between years five to 30 post-onset. This decline increased in magnitude with increasing onset age. 16.8% of patients started a DMT at some stage during the study. When "DMT contaminated" data was removed the mean follow-up time decreased slightly from 20.6 years (SD 9.79) to 19.9 years (9.83) and findings differed little.

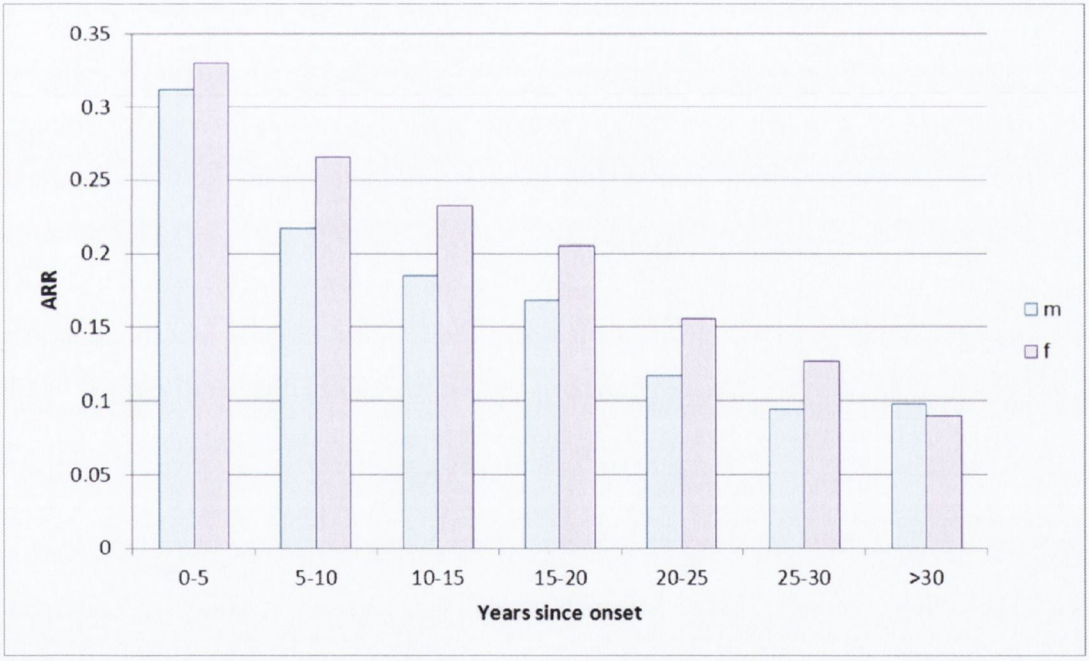


Figure 2.7: ARR for males and females every five years from MS onset

The values of the ARRs for males and female in this figure were derived from figure 2a of the report by Tremlett *et al* using an electronic ruler
ARR=annualised relapse rate; m=males; f=females.

Nicholas *et al* identified a similar trend of decreasing ARR during clinical trials in RRMS. [65] Among 52 randomised, placebo-controlled trials identified through a systematic review, the ARR was 25% and 40% higher in the first year compared to the second year for placebo and active treatments respectively. [65] In addition to this natural

decrease in relapse rate over time, a reduction in ARRs between RCTs is evident when comparing trials conducted over the last two decades. ARRs in the placebo arms of pivotal trials for interferon-beta and glatiramer acetate (recruited between 1988 and 1995) ranged from 0.82-1.27. [66-69] These are significantly higher than ARRs recruited to the two most recent placebo-controlled RCTs for MS DMTs, oral BG-12 and laquinimod, where ARR in the placebo arms were 0.36 and 0.39 respectively. [70 71]

Nicholas *et al* have conducted a systematic review of RRMS RCTs and identified a negative association between ARR and year of publication, with ARR in the placebo arm decreasing by 6.2% per year. [72] A similar association was identified in a separate systematic review by Inusah *et al.* [42] The authors suggest that the fall in ARR is a result of changing definition of MS, selection of patients for trials (earlier trials may have selected more active patients as alternative treatments were not widely available while in later trials active patients may not have been recruited by clinicians due to acceptance of the need to initiate treatment), and selective removal of patients from trials once relapse occurs in order to provide adequate care for their active disease. The trend of decreasing ARR both within and between trials has implications for the design and analysis of clinical trials. Also, Nicholas *et al* question whether placebo groups in early studies are comparable with placebo groups in later studies, where the ARR can be threefold lower. [72] Such differences have implications for the conduct and interpretation of between-trial comparisons, which will be further discussed in Chapter 7.

2.2.6 Epidemiology of MS

The number of people with MS in Ireland is not known. A study by Lonergan *et al* from St.Vincent's University Hospital in Dublin estimated MS prevalence in Ireland based on a cross-sectional study incorporating patients from three locations throughout Ireland. [73] Prevalence ranged from 127.8 per 100,000 (95% CI, 111.3 to 148.2) in South Dublin (East), to 290.3 per 100,000 (95% CI, 262.3 to 321.7) in Donegal (Northwest). It is estimated that between 7000 and 8000 people in Ireland have MS. The female to male ratio in the Lonergan *et al* study was 2.0:1. This female predominance is representative of other population studies.

Various environmental factors have been implicated including infectious agents (e.g. Epstein-Barr virus), sunlight, vitamin D deficiency, diet, geomagnetism, air

pollutants, radioactive rocks, cigarettes, and toxins.[74 75] There is a distinct geographical distribution of MS with the greatest incidences at high latitudes, both north and south of the equator. [76]

The average age at onset of disease is approximately 30 years. [77] Ireland is among the exceptions as regards disease prevalence by age, with higher prevalence in the age group of 50-64 years compared to other European countries which report highest prevalence estimates for age group of 35-49. [32] For many years it was thought that MS did not significantly impact on mortality, however several long-term population-based studies have confirmed that MS diagnosis does confer a survival disadvantage. Three cohort-studies from Norway, the UK and Denmark found a three-fold risk of death in MS compared to the general population and findings of a Danish Registry suggest life expectancy in MS is approximately 10 years shorter than that of the age-matched general population. [78-80] An epidemiological study by Pokorski *et al*, assessed the long-term survival of 6727 MS patients based on the Danish MS Registry and reported standard mortality rate (SMR) multipliers by level of disability: mild (EDSS 0-3) 1.60, moderate (EDSS 4-6) 1.84, severe (EDSS 7-9) 4.44. [81]MS itself is not fatal, rather MS-disability in the advanced stages of the disease can predispose patients to other conditions or complications which can be fatal, particularly aspiration pneumonia, sepsis arising from pressure sores or urinary tract infections, thromboembolism and suicide. [82] MS is three times as common in women as in men and this ratio has been increasing over the last century. [83]

2.2.7 Management and Treatment of MS

No curative treatment is available for MS. During the RR phase of the disease, pharmacological and non-pharmacological interventions are used to treat relapses, manage symptoms, and attempt to delay disease progression. As the disease progresses, symptom management predominates with the aim of maintaining independence and functioning both at work and at home. This often requires a complex multidisciplinary approach including inpatient, ambulatory, and home-based rehabilitation interventions under medical supervision.[84] No treatments have shown convincing evidence of altering the course of progressive MS in the absence of relapses once the progressive stage of the disease has been reached and treatment is not recommended in non-relapsing SPMS. No DMT is indicated in PPMS. [85]

2.2.7.1 Relapse Treatment

MS relapses can be treated in a number of ways depending on the severity of symptoms. Acute relapses are generally managed with high-dose intravenous corticosteroids administered in the outpatient setting e.g. 500mg to 1g methylprednisolone daily for three to five days. Some relapses require more intensive management, if severe neurological deficit is present for example, and require admission to hospital. [86] Corticosteroids reduce the duration of a relapse but do not effect the disability which may be accrued as a result of the relapse and have no impact on the subsequent disease course. [58] Plasmapheresis is indicated for patients with severe relapses who have not responded to intravenous corticosteroids. [22]

2.2.7.2 Symptom Management

The clinical presentation of MS is highly variable and symptoms can include pain and loss of sensation, fatigue, impaired muscle control, balance and postural problems, visual loss, cognitive impairments, and bowel and bladder disturbance. Symptom management is the cornerstone of long-term management of MS, as symptomatic therapies have the potential to significantly improve quality of life. [22] A multidisciplinary approach to symptom management includes both pharmacological and non-pharmacological therapies such physiotherapy, occupational therapy, counselling and rehabilitation. Pharmacological treatments include baclofen, benzodiazepines and tizanidine for stiffness and spasms (present in more than 60% of patients), oral antimuscarinic drugs, alpha-blockers, intranasal desmopressin spray and intravesical botulinum toxin A for bladder problems, phosphodiesterase-5 inhibitors for sexual dysfunction, amantadine and modafinil for fatigue, amitriptyline, pregabalin and lamotrigine for neuropathic pain, among many others. [87] Very few symptomatic medications are specifically licensed for use in MS. Cannabis extract is licensed for use in some European countries in the form of a nasal spray for the treatment of moderate to severe spasticity in patients who have not adequately responded to other medication. [87] In Ireland the use of cannabis in any form is prohibited under the Misuse of Drugs Act 1977. Fampridine is licensed for improvement of walking in adult patients with MS with walking difficulty (EDSS 4-7) although it is not reimbursed in Ireland as the manufacturer failed to demonstrate cost effectiveness. [88] Lifestyle interventions are also

encouraged such as exercise to reduce fatigue and offset muscle weakness, diet control and measures to improve sleep hygiene. [89 90] At different stages of the disease, various non-neurology specialities become involved in MS care including urologists, gastroenterologists, psychiatrists, ophthalmologists, physiotherapists, occupational therapists, clinical psychologists, speech and language therapists and rehabilitation physicians. [58] As MS disability increases the overall management approach changes from acute inpatient and outpatient intervention to more supportive home-based management strategies, long-term multidisciplinary management and rehabilitation, in order to achieve the highest possible independence and HRQoL for patients. Multidisciplinary rehabilitation aims to maximise activity and social integration to achieve the highest possible independence and the best quality of life. [84] Rehabilitation can be delivered in an inpatient or outpatient setting or in the patient's own home or community. [84]

2.2.7.3 Disease-modifying Therapies

DMT aims to reduce MS relapses and delay or prevent disease progression. The advent of DMT for MS in the 1990s transformed the perspectives of neurologists and patients on what was previously a relentless cycle of relapses and inexorable disability progression. A number of DMTs are licensed for use in RRMS including Interferon beta-1b (IFN β-1b), interferon beta-1a (IFN β-1a) and glatiramer acetate (GA), currently considered as first-line agents; natalizumab and fingolimod which are licensed for use in patients who are suboptimally treated with first-line agents or who have rapidly evolving severe MS; and new and emerging agents alemtuzumab, laquinimod, teriflunomide and BG-12 which have yet be approved in the EU but which are expected to be introduced as first-line agents.

2.2.7.3.1 Interferon-beta and Glatiramer acetate

IFN β-1b, IFN β-1a and GA were the first DMTs shown in RCTs to reduce the frequency of relapses and reduce MRI activity in RRMS.[66-69 91] The mechanism of action of IFN β and GA in MS is complex and not fully understood. It is thought that IFN β binds to a cell-surface receptor on target cells, such as T cells, and induces the transcription of several genes involved in the promotion of an anti-inflammatory response within the immune system, preventing access to the CNS of pro-inflammatory

T cells. [92] GA induces proliferation of anti-inflammatory Th2 cells in the periphery which enter the CNS and exert a bystander suppression effect locally. [93]

Meta-analyses suggest that these agents reduce the risk of relapse by about one third in the first year of treatment but the effect is diminished beyond the first year. [85 94 95] It has not been definitively established whether long-term treatment reduces the accumulation of disability or prevents or delays conversion to SPMS. In CIS, IFN β and GA have been shown to delay time to development of MS. In placebo-controlled RCTs, treatment with DMT was associated with a 35% to 37% conversion to MS after two years compared with ~50% conversion in patients who received placebo. [96-98] The Association of British Neurologists recommends IFN β or GA for RRMS with active disease (two clinically significant relapses in the previous two years). [85] Treatment may also be considered in patients within 12 months of a CIS when MRI evidence predicts a high likelihood of developing MS. In patients with only a single major relapse in the preceding two years, but combined with MRI evidence of continuing disease activity, treatment may also be considered. [85]

IFN β and GA products are all formulated for regular, frequent self-injection given daily, every other day, three times weekly or weekly depending on the formulation. The most common side effects of IFN β therapy are flu-like symptoms (usually subside within two to three months of initiating therapy and are minimised by gradual dose escalation and co-administration of paracetamol and non-steroidal anti-inflammatories) and injection site reactions (e.g. redness, swelling, tenderness and rarely skin necrosis). Liver function test abnormalities and mild lymphopaenia necessitate regular blood monitoring. GA causes mild, transient skin reactions and rarely a systemic reaction with tightness of the chest and facial flushing. IFN β can induce an immune response and neutralising antibodies can develop, reducing efficacy. Neutralising antibody testing (12-monthly if negative, more frequently if positive) is therefore recommended as part of clinical management to guide treatment decisions. [99]

2.2.7.3.2 Natalizumab

Natalizumab is a monoclonal antibody effective against the alpha-4 integrin molecule on the cell surface of leucocytes. It inhibits migration of inflammatory cells into the CNS by preventing adherence of activated leucocytes to inflamed endothelium. [100] A 68% reduction in relapse rate was observed with natalizumab compared to placebo in

the pivotal placebo-controlled trial. [101] The risk of disability progression was reduced by 42% to 54% and there was an 80% to 90% reduction in MRI markers of disease activity. Natalizumab is approved for use in patients with highly active RRMS who have failed on first-line therapy or who have rapidly evolving severe RRMS. The restricted license for natalizumab is largely due to its association with progressive multifocal leukoencephalopathy (PML), a rare, potentially fatal opportunistic brain infection caused by the JC virus. The risk of PML is lowest amongst patients who are negative for anti–JC virus antibodies (0.09 cases or less per 1000 patients (95% CI, 0 to 0.48)). [102] Patients with the highest established risk of PML include those who were positive for anti–JC virus antibodies, had previously taken immunosuppressants before starting natalizumab therapy, and had received 25 to 48 months of natalizumab treatment (11.1 cases per 1000 patients (95% CI, 8.3 to 14.5). [102] Because of the association between duration of use and risk of PML it is recommended that following two years of continued therapy, further therapy should be considered following a reassessment of the potential for benefit and risk. [103] Natalizumab is administered once monthly by intravenous infusion in an outpatient setting.

2.2.7.3.3 Fingolimod

Fingolimod, the first orally-administered DMT, is a sphingosine 1-phosphate receptor modulator which blocks the capacity of lymphocytes to egress from lymph nodes, leading to reduced infiltration of potentially autoaggressive lymphocytes into the CNS. [104] The pivotal RCT of fingolimod demonstrated a 60% reduction in relapse rate compared with placebo and a 40% reduction compared with IFN β-1a. [104 105] The risk of short-term disability progression was also reduced compared with placebo. Similar to natalizumab, the use of fingolimod is restricted to RRMS patients with high disease-activity in Europe but in the US, Australia and Switzerland its use is not restricted. It is expected that fingolimod will be a welcome alternative to natalizumab given its accessibility in the community, ease of administration and more favourable safety profile. Fingolimod is generally well tolerated, however initiation of treatment can cause a transient reduction in heart rate and a decrease in atrioventricular conduction including the occurrence of heart block. All patients should be monitored before, during, and immediately after the first six hours of treatment. Monitoring should also be

extended at least overnight if significant atrioventricular block, bradycardia, or QTc prolongation occurs. [106]

2.2.7.3.4 Alemtuzumab

Alemtuzumab is a humanised monoclonal anti-CD52 antibody that induces a pronounced and long-lasting depletion of T cells. [107] Alemtuzumab has been used for many years in the treatment of various leukaemias and has been in development as a potential treatment for RRMS for some years also. One phase II and two Phase III single-blind RCTs have compared alemtuzumab with IFN β-1a 44mcg. [108-110] In the phase II CAMS223 trial alemtuzumab reduced the risk of sustained disability (confirmed at three months) by 71% and the relapse rate by 74%, compared to IFN β-1a. In the phase III CAREMS1 trial, in patients who had not previously been treated with a DMT, alemtuzumab significantly reduced the relapse rate by 54%, however the difference in the accumulation of disability (confirmed at six months) compared to IFN β-1a. was not statistically significant. [109] In CAREMS2, in patients with refractory disease activity despite treatment with first-line DMT, alemtuzumab significantly reduced the relapse rate by 50% and also the risk of progression (confirmed at 6 months) by 40%. This study also showed that patients disability level on alemtuzumab was more likely to improve from baseline than worsen (progress) or remain stable, an outcome which heretofore had not been considered a target for DMT.[111] Alemtuzumab is administered by IV infusion once daily for five days at baseline and once daily for three days at 12 months. The phase II study was originally designed to comprise of three infusions, including a third at 24 months. [110] The trial was suspended early in 2005 due to three incidences of immune thrombocytopenic purpura, one of which was fatal. At the time of suspension, 99% and 28% had received their second and third cycles of alemtuzumab, respectively. In 2008, the dose suspension was lifted and a five-year follow-up study reported that a number of patients were retreated. [112] In subsequent trials treatment has been limited to two infusions (24 months). In June 2013, alemtuzumab received a positive opinion from the Committee for Medicinal Products for Human Use (CHMP) recommending the granting of a marketing authorisation. The approved indication is: "treatment of adult patients with RRMS with active disease defined by clinical or imaging features". [113]

The most common side effects of alemtuzumab are infusion associated reactions (headache, flushing, nausea, urticaria, rash, pruritus, pyrexia and fatigue), upper respiratory tract infection, urinary tract infection, lymphopenia and leukopenia. Side effects pertaining to the thyroid gland (including over-active or under-active thyroid gland, or goitre and auto-immune conditions) were observed in 17%-18% of patients treated with alemtuzumab in phase III RCTs.[113] Alemtuzumab was rejected by the FDA for the treatment of RRMS on the grounds that the risks of treatment outweighted the benefits.

Alemtuzumab has been used off-label for MS for a number of years. The license-holder of alemtuzumab surrendered the license for all licensed preparations of alemtuzumab in 2012 as part of plans to promote alemtuzumab as a drug for MS. It is expected that the new formulation of alemtuzumab will be significantly more expensive than the old formulation.

2.2.7.3.5 Teriflunomide

Teriflunomide is an oral DMT, the active metabolite of the pro-drug leflunomide. It reversibly inhibits dihydroorotate dehydrogenase to reduce T- and B-cell activation, proliferation, and function in response to autoantigens. [114] In the pivotal placebo-controlled RCT of teriflunomide, both the 7mg and 14mg daily doses reduced the risk of relapse by 31%. The risk of sustained short-term disability progression was significantly reduced by 29.8% with the higher of two teriflunomide doses. [114] In June 2013, teriflunomide 14mg daily received a positive opinion from the CHMP recommending the granting of a marketing authorisation. [115] The indication for teriflunomide is: "treatment of adult patients with RRMS" and it is approved for use in the United States. The most common side effects of teriflunomide in RCTs were upper respiratory tract infections, urinary tract infections, diarrhoea, nausea, paraesthesia (pins and needles), alopecia (loss of hair) and increase in the liver enzyme alanine aminotransferase. [115]

2.2.7.3.6 Laquinimod

Laquinimod is a second-generation oral quinolone-3-carboxamide. It is thought to induce a shift from the proinflammatory Th1 profile to the anti-inflammatory Th2 profile, decreasing CNS leukocyte infiltration. [116] Laquinimod may additionally provide

neuroprotection by increasing production of neurotrophic factor, and by exerting other potential neuroprotective effects. [117] A modest reduction in ARR versus placebo (23%) and a more impressive reduction in the risk of short-term disability progression confirmed at three months (hazard ratio 0.64 (95% CI 0.61 to 0.86)) was observed in the pivotal placebo-controlled trial of laquinimod. [71] It was also associated with a 33% reduction in progression of brain atrophy. Preliminary results from a second placebo-controlled study reveal that laquinimod failed to reach its primary endpoint, showing no different in ARR compared with placebo. [118] Laquinimod has a favourable safety and tolerability profile however animal studies showed a higher occurrence of cancers after long-term exposure to the medicine. A possible risk of effects on the unborn baby was also noted in animal studies suggesting that effects may be delayed and only seen later on in a child's life. Some patients experienced dose dependent increases in liver enzymes in RCTs. [71] Laquinimod received a negative recommendation by the CHMP in January 2014 on the grounds that the modest effects on relapse may not outweigh the risks. The CHMPs decision is being appealed by the manufacturer of Laquinimod.

2.2.7.3.7 BG-12

BG-12 is an oral formulation of dimethyl fumarate, a derivative of fumaric acid. BG12's beneficial effects in MS are primarily mediated through activation of the nuclear 1 factor (erythroid-derived 2)–like 2 antioxidant response pathway, the primary cellular defence against the cytotoxic effects of oxidative stress. [70] It may also play a number of other roles in modulating immune cell responses. [70] Two randomised phase III RCTs investigated the efficacy of two BG-12 doses versus placebo and versus placebo or GA. [70 119] Significant relapse reductions with BG-12 versus placebo ranged from 44% to 51%. The relapse reduction versus placebo with GA was 29%. Reductions in the relative risk of confirmed short-term progression of disability ranged from 34% to 38% with BG-12 versus placebo in one RCT whereas the reductions in the second RCT (24% to 24%) were not significant. The relapse reduction versus placebo with GA was 7%, also non-significant. No direct comparisons were made between BG-12 and GA. Fumaric acid has been used in psoriasis since the 1950s and the long-term safety profile is favourable. [120] The most common side effects in RCTs were flushing and gastrointestinal events (e.g. diarrhoea, nausea and abdominal pain). In March 2013, BG-12 received a positive opinion from the CHMP recommending the granting of a

marketing authorisation. The indication for BG-12 is: "treatment of adult patients with RRMS", and it is approved for use in the United States at a maintenance dose of 240mg daily.[121]

2.2.7.3.8 Other Agents

Other agents such as mitoxantrone and azathioprine are occasionally used for severe, rapidly worsening MS but are not licensed for use in RRMS.

2.2.7.3.9 Long-term efficacy of DMT

The maximum duration of all pivotal RCTs was two years. As a chronic, progressive disease, RRMS may require treatment with DMT for many years, but there is little evidence on the long-term efficacy of these agents. Results from the US Glatiramer Acetate Trial suggest maintained efficacy on relapse rate over extended periods of ongoing use of GA.[122] Conflicting results have been reported for the long-term efficacy of first-line DMT on reducing disability progression.[123] [124] Longer-term studies are required to provide evidence that efficacy on short-term progression translates into meaningful, long-term effects on disability progression and the development of secondary-progressive disease.

2.2.7.3.10 Impact of DMT on survival

The short duration of RCTs limits the potential for identifying any benefit of treatment on mortality rates. Long-term follow up of the pivotal IFN β-1b trial included 98.4% (366/372) of the original patient cohort and identified a significant reduction in the hazard-rate for all-cause mortality in patients originally assigned to receive IFN β-1b compared with those originally randomised to placebo (hazard ratio 0.532, 95% CI 0.314–0.902). [82] It is difficult to draw definitive conclusions based on these results as patient experiences in the intervening period is not characterised, and the degree to which the trial population are representative of the general MS population may also be questioned. [29]

2.2.7.3.11 DMT Utilisation and cost effectiveness in Ireland

In 2012, 3351 patients received DMT under the HTD scheme at a cost of €31.5 million, approximately 45% of the estimated MS population in Ireland. [125] Seventy per cent of those on DMTs were female and the average age was 46 years. In 2012, 669 new patients were initiated on DMT on the HTD scheme. Since fingolimod was introduced onto the scheme in September 2012 until the end of the first quarter of 2013, 344 patients were initiated on treatment. One hundred and thirty (38%) of these patients had not received a DMT previously (based on prescribing records from 2010) indicating a high level of rapidly evolving severe MS among new patients or substantial off-label utilisation of this agent. While the introduction of fingolimod should promote cost-offsets, through the displacement of other DMTs, it is expected to increase DMT expenditure further as it is 60%-110% more expensive than these first-line agents

Natalizumab was found to be borderline cost-effective from the HSE perspective when assessed by the NCPE in 2006 but a follow-up assessment was recommended. Fingolimod was also recommended by the NCPE for reimbursement following a price reduction. The cost effectiveness of IFN β and GA in the Irish healthcare setting has not been assessed to date, however their place in therapy is well established since their introduction into practice in the 1990s at a time when there were few barriers to reimbursement in Ireland. Expenditure on DMT is significant and continues to rise with the introduction of the newer agents natalizumab and fingolimod. Further cost increases may be expected with the introduction of additional oral agents and alemtuzumab, highlighting the need for robust pharmacoeconomic assessment of all available DMTs.

CHAPTER 3 – METHODOLOGY

CHAPTER 3 – METHODOLOGY

This chapter provides a methodological review and discussion of the various procedures and techniques involved in the conduct of CoI research, the derivation of HSUVs, the synthesis of data on relative efficacy and the economic evaluation of pharmaceuticals. The application of these methods in the context of this thesis is described in subsequent original research chapters.

3.1 Cost of illness Research

CoI research aims to determine the total cost of a disease to the healthcare service, patients and society in general. The financial consequences of ill-health can arise from changes in the frequency of healthcare service use, the duration and intensity of healthcare consultations, the ability of patients to work in the short-term (absenteeism and sick leave) and long-term (early retirement from the workforce), and the use of other non-medical but related resources such as living aids, transport, home and car modifications. Drummond suggested that CoI studies are a useful means of highlighting the relative importance of particular diseases, in addition to usual epidemiological estimates of morbility and mortality. [126] In addition, they can help determine medical research priorities and provide a baseline from which new interventions can be assessed. The World Health Organisation asserts that the primary purpose of CoI studies should be to inform decision makers by providing descriptive indicators of the magnitude of a disease or a health problem as a complement to methods of deciding how scarce resources should be used to improve health.

The three stages of cost analysis include identifying resources consumed in the delivery of a particular health programme, quantifying that resource consumption and multiplying resources by their relevant valuations. [9] The general approach to costing may be described as "top-down" or "bottom-up".

3.1.1 Top-Down or Bottom-Up Approach

Top-down is a population-based approach where aggregated data is first used to calculate either overall expenditure or expenditure by cost-component. Total costs are then disaggregated and portions assigned to specific diseases, departments, services etc. Data sources are generally large databanks such as national statistics, national insurance claims databases etc. Costs may be attributed to specific cost centres based on number of patients treated or number of bed-days etc., or to specific diseases based on population-attributable fractions (PAF).

The "bottom-up" approach uses actual resource-use data from individual patients to identify and quantify resource utilisation in order to calculate the cost of a specific service. This approach can be retrospective or prospective using surveys, questionnaires, patient diaries, medical records etc. [9]

A "top-down" approach can often be less costly and quicker to implement than a bottom-up approach and may be useful where detailed resource-use data is not available. [127] It can be more comprehensive than bottom-up costing, including all relevant costs, but is less detailed and may be less accurate. The accuracy and reliability of the top down method depends on the quality of the secondary data used, and how accurately costs are allocated to diseases. [128] Furthermore, the top-down approach assumes negligible practice variation and due to the reliance on secondary data, the approach is retrospective in practice.[129] The bottom-up approach is more detailed and can be more accurate than the top-down approach, and can be prospective or retrospective. [127] Patient-level data can be interrogated for variability and allows stratification by disease subgroups or patient characteristics. The bottom-up approach relies on the availability of accurate unit cost of resources. If unit costs are obtained separately to the resource quanitification exercise, an average cost per unit may be applied instead of the actual cost which could over or underestimate the real cost of the resource. The approach can be costly and time-consuming to implement, and may suffer from limited generalisability from the study sample to the population of interest. [130]

In practice, the costing approach taken will depend on the aim of the analysis, the level of precision required and the availability of data. For health economic evaluations, the requirement to separately identify, measure and value resource utilisation is more closely represented by the bottom-up approach. A mixed approach is

often applied whereby detailed patient-level data may be used for certain costs where precise estimates are required (e.g. cost drivers, or those costs which are likely to form the largest components of overall cost) and a top-down costing approach may be used, for example, to assign costs to rare or infrequent hospitalisations (e.g. Diagnostic Related Group (DRG) costs). [7] [131]

3.1.2 Resource identification and Perspective

A wide range of resources may be considered depending on the perspective of the analysis (Figure 3.1). Most economic evaluations in Ireland are conducted from the perspective of the healthcare payer. Guidelines for economic evaluation of health technologies in Ireland specify that the costs perspective should be that of the publicly-funded health and social care system. This approach maximises health gain for the population and represents the most efficient use of the finite resources available to the HSE including direct medical costs such as drug, medical devices, medical services including procedures, hospital services and emergency visits, and primary care visits. [7] Other resources reimbursable by non-health governmental departments may fall under a wider governmental perspective e.g. disability payments, housing etc. The societal perspective is the most comprehensive approach that can be taken, incorporating the broadest range of costs regardless of the payer, including costs to patients, family and friends, employers in the form of productivity losses, in addition to healthcare costs. Welfare economic theory dictates that a societal perspective should be adopted as the welfare of the whole society is of concern. The narrower perspective of the healthcare payer may maximise efficiency within the healthcare budget but not necessarily maximise the welfare of society as a whole. Luce *et al* recommend that even if productivity costs are not formally considered in a CEA, they should be at least pointed out to the decision maker. [130] Drummond *et al* recommend that both healthcare and non healthcare costs and benefits should be presented in order to clearly identify the opportunity cost of the healthcare budget. [9] For the reference case in Ireland (i.e. the preferred set of methodological principles that should be used for the 'base case' analysis, as defined by Gold *et al*)[132], the healthcare payer perspective is recommended. [7] Additional societal costs may be presented separately if expected to impact on the results of the analysis significantly. [7]

Cost components inevitably vary in order of magnitude. The time taken to consider small costs, which are unlikely to make any difference to study results, may not be worthwhile. [9] Luce *et al* recommend that all resource use that is both germane to the analysis and nontrivial in magnitude should be included. [130] Justification for all costs included and excluded should be provided.

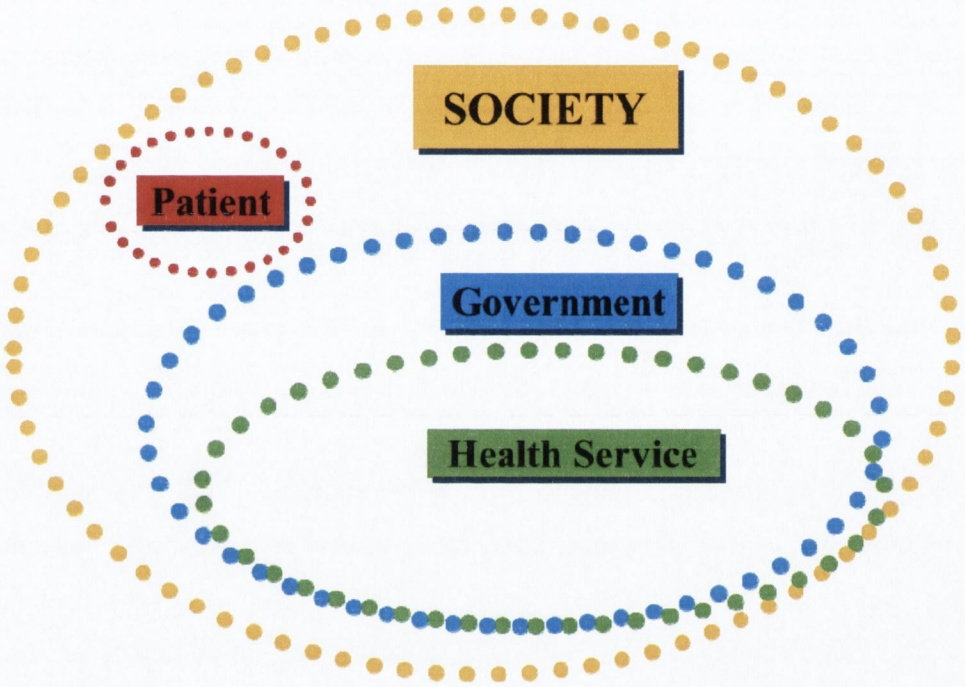


Figure 3.1: Study Perspective

3.1.3 Resource quantification

Identification of resources is the first stage of cost analysis. These resources must then be quantified and valued in order to estimate total costs. The quantity of resources used in a specific setting may be measured alongside a clinical trial e.g. routine collection of type and quantity of resources using case report forms, or as part of a separate costing study. The latter approach involves the estimation of resource quantities from various sources e.g. patient medical records, patient diaries, service-use questionnaires and interviews, time and motion studies.

3.1.3.1 Economic Evaluation Alongside Clinical Trials

The various problems and pitfalls inherent in economic evaluation alongside clinical trials are summarised, together with associated solutions by O'Sullivan *et al.* [133] The collection of costs can be a convenient addition to safety and efficacy data as part of a clinical trial and has the advantage of randomisation, blinding and other clinical trial design elements which reduce bias in the comparison of treatments. However, the highly controlled protocol-driven RCT environment may not always be compatible with the objectives of an economic evaluation which aims to examine resource use and costs in a pragmatic setting, involving real patients in actual clinical practice.

3.1.3.2 Observational Costing Studies

In the case of stand-alone observational costing studies, collection from charts or provider databases can be more accurate than self-reported questionnaires, which are subject to recall bias, but all relevant data may not be available from just one source, and resource-use capture may not be comprehensive e.g. unlikely to cover over the counter medication, informal care etc. Patient resource-use questionnaires are particularly useful where a broad range of relevant resources over a prolonged period have been identified. Structured questionnaires may be administered by interview, either face-to-face or over the phone. Alternatively self-reported questionnaires may be completed by patients themselves, often following a postal survey, or more recently through an electronic web-based platform. [1 134] Self-report methods can be quicker and cheaper than interviews. They can be used to target a large sample size but can result in low response rates in addition to selection bias. [135] Self-administration methods impose a greater cognitive burden on respondents compared with face-to-face interviews, in terms of literacy, visual function and manual dexterity. In general, postal surveys report higher item non-response than face-to-face interviews. [135 136] Interview based surveys can increase motivation of respondents to respond through clarification, pausing and encouragement, and can ensure that questions are not missed [135] However interviewer and social desirability bias can also be a feature of face-to-face interviews. [137] Interview-based studies have the potential to encompass a more complete range of resources compared with self-report questionnaires which may need to use exhaustive lists of named resources in order to standardise responses e.g. lists of named medications or healthcare professional types etc. [138]

3.1.3.3 Recall Bias in Retrospective Observational Costing Studies

Recall bias can be a particular problem in retrospective resource-utilisation studies. Longer recall periods e.g. 12 months, provide more information but are associated with recall error i.e. forgetting or incorrectly remembering resources. [139] As a result, shorter recall periods are often used and resource use is annualised under the assumption that resource use during a particular recall period is representative of other periods of similar duration throughout the year. However, shorter recall periods have a greater risk of missing relevant information rendering any extrapolation misleading. Clark *et al* acknowledge that there is no clear optimal recall period and a trade-off must be made, ultimately depending on the objective of the study. MS CoI studies have typically used different recall periods for different types of resources e.g longer recall periods (12 months) for less frequent events such as inpatient admissions, six months for outpatient and primary healthcare, tests and investigations, and one month for medication. [1 134 138 140 141]

3.1.4 Resource valuation

Once resource utilisation data have been collected they are generally combined with unit cost data for each resource to generate an overall cost dataset which may be used to estimate total cost per patient, per cost-component, per cost type and various other subgroups of interest.

3.1.4.1 Opportunity Cost versus Market Price

The theoretical price for a resource is its opportunity cost (OC) i.e. the value of the foregone benefits because the resource is not available for its next best alternative use [9] In practice market prices, healthcare tariffs or charges are assumed to reasonably approximate the OC, as most healthcare organisations are not-for-profit or public organisations, and prices are widely available for many resources. The price used should reflect the prevailing prices in the location where the intervention in question will be implemented. [130] There are occasions where market prices are not an appropriate reflection of OC to society e.g. where prices include a component of profit which exceeds a fair rate of return on investment, where significant geographical

variation exists (between the setting of the CEA and the origin of the price), where prices come from different time periods. [130] In these cases the market price is often still used, with appropriate adjustment e.g. application of a cost-to-charge ratio to deflate market prices to account for profits, converting costs from other countries using purchasing power parities, inflating past prices to current prices using the consumer price index.

Within the "mixed approach" to costing i.e. both bottom-up and top-down, gross-costing of specific health services, interventions or events may be used as an estimate of its "typical" cost. This is often the case with acute care hospitalisations, nursing home care etc. In Ireland, the DRG system is used to fix payment for services provided by public hospitals. The DRG system groups hospital cases together based on similar clinical attributes and levels of resource consumption in order to establish baseline reimbursement for that type of patient. The Irish system uses the Australian Refined DRG system (AR DRGs) which currently comprises 698 groups. [142] DRG costs represent the average across a number of seemingly similar clinically related episodes/procedures, but the extent to which an individual episode/procedure of interest may be expected to differ from the average must be considered when utilising DRG cost data for CEA purposes.

3.1.4.2 Valuing Indirect Costs

Informal care costs and productivity losses are not typically included in CEA. This is due to debate over their valuation, the predominance of the healthcare perspective over the societal perspective, equity concerns and the potential for double-counting. Equity concerns arise where the value of an intervention might depend on the productive capacity of the target population rendering treatments for those who are not working, on low wages, elderly or disabled, less valuable. [143] It has been argued that questionnaires used to measure HRQoL changes will implicitly take account of changes in income and effects on consumption and double-counting may therefore occur when benefits are measured in QALYs. [130] However a more recent study by Tillings *et al*, investigating whether responses to HRQoL questionnaires consider income effects, found that the QALY does not represent the effects of lost productivity. [144] The approach to valuation discussed thus far cannot be applied to non-market items such as volunteer/family time

employed in providing informal care to patients, and productivity losses associated with illness-related absenteeism and early withdrawal from the workforce.

3.1.4.3 Productivity Losses

The two main approaches to valuing productivity losses are the human capital approach (HCA) and the friction cost approach (FCA). The HCA essentially values productivity losses as the expected or potential earnings lost due to illness by multiplying the total period off work by the gross wage of the absent worker. It is argued that HCA valuations overestimate actual economic losses. For short-term absences, production losses could be compensated on return to work or by colleagues, and it is likely that the less important tasks of a job will be foregone during this time making the value of productivity at the margin lower than the average wage. [9] For long-term absences a replacement worker will likely be hired. The FCA limits productivity losses to the time (friction period) it takes to replace the absent worker, which varies by profession, industry etc. [145] Estimation of relevant friction periods is one of the biggest challenges with the FCA which gives much lower estimates of lost productivity compared with the HCA.[146] The HCA is the most widely used approach in CEA. [147] Productivity losses can also result from impaired ability at work (presenteeism).

3.1.4.4 Informal Care

Informal care provided by family or friends can include personal care, cooking, cleaning etc. For some illnesses, particularly chronic progressive illnesses such as MS or dementia, informal care costs may account for a substantial proportion of total costs. The two most widely used methods to value informal care time in monetary terms are the opportunity cost approach (OCA) and the replacement cost approach. The OCA values care on the paid/unpaid work it displaces, measured by the wage the carer would earn in paid employment (or using average mean annual earnings, age- and gender-stratified as appropriate). The replacement cost approach values the care at the market price, usually that of a paid carer or a cleaner. [148] A recent review by Goodrich *et al* found that the OCA is used more often. [148]

3.1.5 Summary

The choice of CoI methodology largely depends on the purpose of the research and the application of the results. Among the aims of this thesis are the assessment of healthcare and wider societal resource utilisation in a cohort of patients with MS in Ireland. Both direct and indirect costs of MS are of interest, from the perspective of both the healthcare payer and society in general. In addition to highlighting the economic burden of the illness in Ireland, it is intended to generate economic evidence for inclusion in a decision analytic model for DMT in MS. A bottom-up, prevalence-based approach will be taken whereby healthcare and non-healthcare MS-related resource use will be measured from data collected from Irish patients using an interview-based approach. Nationally applicable unit costs will be applied to each resource component in order to estimate total direct medical and non-medical costs related to MS. Productivity losses due to absenteeism, early retirement and informal care will be valued using the HCA, assuming the labour earnings reflect productive capacity. Individual patients' clinical status will also be assessed in order to relate costs to MS-disability. Further details on the application of these methods is provided in Chapter 5.

3.2 Health Related Quality of Life (HRQoL)

Chapter 2 introduced the concept of the quality adjusted life year (QALY), a key component of cost-utility analysis (CUA). National guidelines on the conduct of economic evaluation of health technologies in Ireland recommend that health effects should be valued in QALYs, with changes in quantity and quality of life reported separately. [7] A QALY is a life year adjusted by a preference-based weighting or utility, corresponding to the HRQoL during that year. Key issues in the use of QALYs in CUA are the measurement of HRQoL utilities and the identification of HRQoL data for use in decision analytic models.

3.2.1 HRQoL Utility Measurement

HRQoL utilities represent the preferences of individuals for relevant health states by means of a quantitative score. These utilities are measured on a cardinal scale anchored between 1 (perfect health) and 0 (absence of life or dead). Values of less than zero, reflecting health states that are worse than dead (WTD) can exist. For a patient with a life expectancy of five years, during which time HRQoL is expected to deteriorate from a high of 0.8 for the first three years, by 50% to 0.4 for the last two years, the total expected QALYs is (3 x 0.8)+(2 x 0.4)=3.2 QALYs. Utility values can be measured directly, using preference measurement methods such as a rating scale, standard gamble (SG) and time trade-off (TTO), or indirectly using questionnaires such as the Euroqol EQ-5D, Health Utilities Index (HUI) and the Short Form SF-6D. [149-151]

3.2.1.1 Direct Utility Measurement

Direct preference measurement methods generally involve providing individuals with health state descriptions, or vignettes, and then valuing those health states by measuring the strength of preference of individuals for the states. Typical vignettes describe numerous health attributes such as physical, social and cognitive functions, psychological well-being, symptoms and pain. Health states are valued using cardinal preference measurement methods such as standard gamble (SG), time trade-off (TTO) rating scales or person trade-off. A visual analogue scale (VAS) between zero and one, with zero regarded as equivalent to dead and one as best imaginable health has also

been used to value health states, although it is not strictly speaking a preference-based technique. [152]

3.2.1.1.1 Standard Gamble

The SG approach is based directly on expected utility theory first presented by von Neumann and Morgenstern, and is sometimes considered the gold standard of utility valuation. [153] In SG, individuals express preferences by choosing between alternatives in which outcomes are associated with probabilities of occurrence e.g. between a health state that is associated with a certain outcome and an alternative health state in which a worse outcome would be received with probability (p) and a better outcome would be received with probability ($1-p$). The probability (p) is varied until the individual is indifferent between the two choices, and used to calculate the utility for the certain health state relative to the alternatives. The SG method can be time-consuming and costly to administer and it imposes a significant cognitive burden as probabilities may not be easy for individuals to interpret.

3.2.1.1.2 Time-Trade Off

The TTO method was developed by Torrance *et al* in the 1970s specifically for the purpose of valuing health states. [154] As with SG, the TTO method also involves individuals expressing a preference by choosing between two alternatives, however each alternative is associated with a certain amount of time e.g. a health state associated with a certain outcome would be received for the remaining life expectancy t, or alternatively a health state with a better outcome would be received for a shorter duration of time $x<t$. The duration x is varied until the individual is indifferent between the two choices. [154] A review of utility values from 995 chronic and acute health states found a strong tendency for VAS to yield the lowest, TTO the middle and SG the highest utility values for the same health states. [155]

3.2.1.1.3 Whose Preferences should be Used?

Whether to use valuations obtained from patients or the general population is a source of some debate. [156] [157] Community preferences from the general public are generally considered appropriate for health care decisions on reimbursement and funding, on the basis that the public represent the taxpayer who bears the cost of those decisions. [156]

However, without first-hand experience of a particular disease or health state, members of the public may over- or under-estimate the impact of the disease compared with patients. This has been demonstrated in both directions by Boyd et in the case of colostomy post surgery for rectal carcinoma (public gave lower preferences than patients) and by Pyne *et al* in the case of depression (public gave higher preferences than patients). [158 159]

3.2.1.2 Indirect Utility Measurement

As an alternative to the direct approach to utility measurement, multi-attribute health status classification systems use a generic descriptive system which allows patients to describe their perceived health state and then valuations derived from the general public are placed on these described health states. Examples of multi-attribute health status classification systems include the EQ-5D, Health Utilities Index (HUI) and the Short Form SF-6D.[149-151] The use of indirect preference-based methods such as the EQ-5D or SF-6D is recommended to measure utilities in Irish and other national HTA guidelines. [7]

3.2.1.2.1 The Euroqol Five-Domain (EQ-5D) Questionnaire

National guidelines on health technology assessment, in both Ireland and the UK, recommend use of the EQ-5D. [7 160] The EQ-5D is a generic, validated, preference-based, self-report HRQoL instrument developed by the EuroQol Group. [149] The EQ-5D has become one of the most widely used instruments of its type, since it was first developed in the 1980s and has been used extensively in MS QoL research. [1 160 161] The EQ-5D consists of 2 elements, the EQ-5D descriptive system and the EQ visual analogue scale (VAS) (Appendix 1). The descriptive system comprises five dimensions (mobility, self-care, usual activities, pain/discomfort, anxiety/depression). Respondents record their level of problems in each of the five domains of health indicating no problems (1), some problems (2) or severe problems (3). Based on the combination of responses, respondents are classified into one of 243 unique EQ-5D health state profiles e.g. 12111, 22313, 33123 etc. Each health state is associated with a utility value representing general population preferences. Country-specific preferences, reflecting trade-offs that individuals are willing to make between health outcomes, have been elicited directly from general populations. In the absence of Irish public preference

data, the UK population valueset has generally been used in Irish studies. [162] [163] Utilities are measured on a cardinal scale anchored between 1 (perfect health) and 0 (absence of life or dead). Valuations less than zero (as low as -0.594), reflecting health states WTD, can exist. Results may be summarised as mean utility values per patient or per subgroup based on a particular characteristic. In addition, descriptive information on the proportion of respondents with or without problems in a specific domain may also be reported. On the EQ-5D VAS, respondents record their self-rated health on a vertical scale where the endpoints are labelled 'Best imaginable health state' and 'Worst imaginable health state'. Information from the EQ-VAS can be used as a quantitative measure of health outcome as judged by the individual respondents, and can be used to assess the face validity of results obtained from the descriptive system.[6]

3.2.1.2.2 Limitations of the EQ-5D

Different measurement systems, like the valuation methods described above, can give different results. EQ-5D valuations range from 1.0 to as low as -0.594 whereas SF-6D health state utility values range from 1.0 to 0.296 at the lowest point. The EQ-5D-3L descriptive system may suffer from a ceiling effect in that significant numbers of respondents may cluster in the highest health states due to a reluctance to report "moderate problems" if problems are very mild. Conversely the SF-6D suffers from a floor effect with significant numbers of respondents clustered in the lowest health states. [149] [164] In addition, the ability of the EQ-5D to measure small changes in health, particularly in patients with milder conditions, has been questioned.[164]

As a generic preference-based instrument, there are inevitable limitations on the extent to which the EQ-5D can address all of the health domains of relevance to all diseases. For example, low coverage of QoL domains relevant to MS such as fatigue has been reported by some reviewers of the EQ-5D. [165] [166] Condition-specific, preference-based measures are in the early stages of development. [167]

3.2.1.2.3 The Five-level EQ-5D (EQ-5D-5L)

The EQ-5D-5L has been developed for better discriminative capacity and sensitivity to change than the original three-level version of the EQ-5D (EQ-5D-3L) as well as smaller ceiling effects. [168] As with the EQ-5D-3L, respondents record their level of problems in five domains of health: mobility, self-care, usual activities, pain or

discomfort and anxiety or depression. In contrast to the EQ-5D-3L, within each domain of the EQ-5D-5L there are five levels of response, indicating no problems, slight, moderate, severe or extreme problems on that domain. Based on the combination of responses, respondents are classified into one of 3125 unique EQ-5D-5L health state profiles. Preference elicitation studies based on the EQ-5D-5L are underway in a number of countries. Until these studies are complete, a "crosswalk" between the EQ-5D-3L index values and the new EQ-5D-5L descriptive system has been undertaken by the EuroQol.[168]

3.2.1.2.4 Measuring the Discriminatory Capacity of the EQ-5D-5L

Increasing the number of response categories, as has been done with the EQ-5D-5L, is an intuitive way of enhancing discriminatory capacity; however if the additional levels are underutilised or don't represent the population, this will not be achieved. Janssen *et al* have proposed Shannon's indices as suitable measures of discriminatory power of multi-attribute utility instruments such as the EQ-5D-5L. [169] This methodology originates from the field of information theory. Shannon's index of informativity (*H'*) is defined by:

$$H' = -\sum_{i=1}^{L} pilog_2 p_i$$

where *L* is the number of possible levels in the system and *pi* is the proportion of responses in the *i*th level of the sample. *H'* is calculated separately for each domain of the EQ-5D-5L. The higher *H'*, the more information is captured by the system. Shannon's index has an upper limit (*H'max)* when the optimal amount of information is captured, occurring if the responses of a sample are evenly distributed among the five available response categories of the domain. The maximal value of *H'* for the EQ-5D-3L is 1.58. By comparison, *H'max* for the EQ-5D-5L is 2.32 as the five-level system offers greater potential to discriminate between respondents. Shannon's Evenness index *(J'=H'/H'max)* reflects the relative informativity of a system given its potential. Janssen *et al* compared the EQ-5D, HUI2 and HUI3 using Shannon's Indices and found that absolute informativity was highest for HUI3, and lowest for EQ-5D while the opposite was true for relative informativity. [169] The same authors also compared the performance of the EQ-5D-5L and the EQ-5D-3L using this method and found that that

discriminatory power (informativity) improves considerably with the EQ-5D-5L without loss of evenness.[170]

3.2.2 Populating Decision Analytic Models with Utility Values

Utilities are incorporated into decision analytic state-transition models as health state utility values (HSUV), from which total expected QALYs may be calculated by summing the product of these HSUVs and the proportion of the cohort in each state. Similarly, in a decision tree, total expected QALYs are calculated as the sum of products of the probability of events occurring and the utility associated with the event. For example, many CEAs of DMT in MS have structured decision models on health states representing aggregate scores on the EDSS scale. In this case, mean utility values for patient groups falling within each EDSS category may be used to estimate HSUVs. Utility decrements, or disutilites, associated with drug treatment or adverse events may also be incorporated into decision models.

3.2.2.1 Source of Utility Data

As with efficacy data, the most appropriate source of HSUV data is often clinical trials, where treatment related events and adverse effects may be combined in one score. [171] However, for a chronic condition such as MS, a clinical trial may not be long enough to cover all health states of interest and indeed the clinical trial population may have specifically excluded some patients, particularly those with more severe disease. Therefore, for treatment related utilities, clinical trial estimates can be useful where collected, otherwise observational studies are often used to obtain HSUVs. In the absence of preference-based utility values, a non-preference based clinical measure for which data is available, may be used to predict utilities, provided a relationship between the EQ-5D and the clinical measure has been established. Mapping studies are considered acceptable in certain circumstances and are included in the Irish HTA Guidelines as acceptable in the absence of relevant utility data from an indirect preference-based measure such as the EQ-5D or SF-6D. [7] Mapping functions have shown a tendency to overestimate the HSUVs as health states become more serious and overestimate HSUVs of good health states. [172]

3.2.3 Summary

As described above, the use of indirect preference-based methods is recommended to measure utilities in national Irish HTA guidelines. [7] The EQ-5D has proven utility in the setting of MS. Compared with other indirect preference-based methods such as the SF-6D, the EQ-5D imposes minimal cognitive burden on the patient, and is quick to complete. The EQ-5D is also freely accessible. Drawbacks of the EQ-5D include the potential for a ceiling effect and insensitivity to small changes in health, particularly in mild disease, aspects which the EQ-5D-5L has been developed to address. The EQ-5D-5L will be used in this thesis to elicit preference-based utilities from a cohort of Irish MS patients. To date, there has been no reported use of the EQ-5D-5L in an MS population. The discriminatory capacity of the instrument will therefore be assessed using Shannon's Indices. Further details on the application of this methodology will be outlined in Chapter 6.

3.3 Evidence Synthesis

Invariably, all of the evidence required to inform a population-based CUA, will not be available from a single study. [173] In practice it is common to combine evidence from a number of different sources e.g. CoI studies for resource utilisation and cost parameters, utility valuation studies for utility parameters, often together with expert opinion and clinical experience. The synthesis of evidence from RCTs in order to estimate relative efficacy parameters is of particular importance in CUA, often having a significant influence on the cost effectiveness of competing alternatives.

3.3.1 Synthesising the evidence on relative efficacy

Where available, it is recommended that evidence from high quality RCTs should be used to quantify efficacy for CEAs.[174] RCTs often compare investigational drugs to placebo or standard care, and rarely incorporate all available comparators. Treatment efficacy estimates for the same technology may be reported in multiple trials, but may vary due to differences in study design, patient population etc. Evidence synthesis methods should therefore be applied where multiple relevant RCTs exist. Standard pairwise meta-analysis methods may be used to derive a pooled estimate of efficacy where the research question considers just two competing alternatives. [175] For reimbursement-related research questions however, numerous comparators may be relevant to the decision problem, and evidence on the comparative efficacy of all treatments must be considered. RCTs comparing all treatments of interest in the relevant population are rarely available. Network meta-analysis (NMA) allows multiple pairwise comparisons across a range of different treatments facilitating the estimation of relative effects in the absence of head-to-head RCTs. [176] Both placebo-controlled and direct-comparative evidence contribute to the NMA network, within which treatments may be connected via one or more common comparators. Given this connected network of trials, simultaneous estimation of the comparative efficacy of multiple treatments may be made.

3.3.2 Network meta-analysis

NMA is an extension of traditional meta-analysis by including multiple pairwise comparisons across a range of different treatments. Traditional pairwise meta-analysis

might seek to estimate the relative effect of treatment *A* versus placebo (*B*) using a network of placebo controlled trials of *A*. However the decision problem often requires consideration of the relative efficacy of *A vs B* and also *vs* treatment C and potentially many other active treatment comparators. In the absence of RCTs directly comparing *A* with *C* or other active treatments, an indirect estimate for the relative effect of *A vs C* can be estimated from the individual relative efficacy estimates of *A vs B* and C *vs B* (Figure 3.2a). Relative treatment-effects (e.g. odds ratio) of *A* vs *B* and C *vs B*, must be compared in order to preserve the randomisation within each trial. Simply comparing absolute effects of individual arms from different trials as if they were from the same RCT is incorrect as different baseline risks and possible placebo effects are ignored. [177] In this simple example, *A* is a common comparator between *B* and *C* An active treatment *D* may also constitute a common comparator, given the available network of trials. The network may be extended to include further treatments connected via a common comparator (Figure 3.2b) or indeed treatments which do not share a common comparator but are nonetheless connected to at least one other treatment in the network (Figure 3.2c), Relative efficacy between treatments connected via longer paths, such as *A vs G* in Figure 3.1c, will be estimated with less precision than, for example *A vs E.* [178] Using this approach, relative efficacy estimates can be obtained for pairwise comparisons which have not been investigated in a head-to-head RCT. A further advantage is that indirect comparisons may be used to support evidence obtained from the direct comparisons.

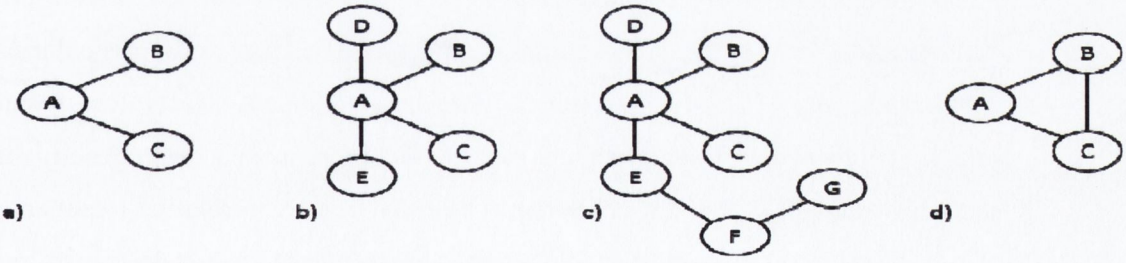


Figure 3.2a-d: Possible Evidence Networks

3.3.2.1 Bayesian Approach

Classical frequentist or Bayesian methods can be applied when performing an NMA. Bayesian methods involve a formal combination of a prior probability distribution, reflecting prior belief/knowledge of the potential values of the treatment-effect, with a likelihood distribution of the treatment-effect based on observed data, to give a corresponding probability distribution. Frequentist methods result in a treatment-effect point estimate and 95% (CI). The 95% CI cannot be interpreted in terms of probabilities, rather it contains the true population parameter 95% of the time under repeated sampling. In contrast, Bayesian models incorporate the prior distribution and the actual data to generate a result which is presented as a distribution. This "posterior distribution" can be interpreted in terms of probabilities, such as the probability that one drug is the best or second best etc. or the probability of experiencing a particular event given treatment with a particular drug. This allows for more intuitive interpretation and is therefore particularly suitable for medical applications with an emphasis on decision making. [179] [180] Other advantages of the Bayesian approach are summarised by Sutton and Abrams, including the capacity to incorporate evidence from a variety of sources within a coherent modelling framework, and to borrow statistical strength from the entire network of evidence in estimating an individual effect.[181] Flat, or non-informative prior distributions are sometimes incorporated to allow any value for the pooled effect to occur, minimising the influence of the prior.

3.3.2.2 Fixed effects or Random effects

In common with traditional frequentist meta-analysis, NMA can take a fixed-effects or random-effects approach. A fixed-effects model assumes that, for a particular pairwise comparison, any observed differences in relative treatment-effects across studies is solely due to chance (sampling error). In the presence of heterogeneity between studies, a random effects model assumes that differences in relative treatment-effects across studies are caused by heterogeneity between studies in addition to sampling error. Under the random effects approach, the *true* relative effects across studies are considered *exchangeable* and are described by the normal distribution. [182] In a frequentist meta-analysis, models may be evaluated or selected based on a measure of heterogeneity such as the I^2 statistic which estimates the proportion of total variation in the effect estimate that is due to heterogeneity rather than chance. [183] Bayesian models

incorporating different assumptions can be compared by calculating the difference between the deviance for the fitted model and the saturated model (i.e. the model which has as many estimated parameters as data points and fits the data perfectly). The Bayesian information criterion or deviance information criterion can be used to estimate goodness-of-fit in model selection.[184] Jansen *et al* recommend the use of the random-effects model if there is heterogeneity between study results, caused by different study populations across studies, or methodological differences. [185]

3.3.2.3 Similarity Assumption

Individual studies may differ in terms of patient characteristics, outcome definition, length of follow-up and other variables. If relative treatment-effects interact with study covariates and the distribution of these interactions across trials is unbalanced, this can give rise to heterogeneity in treatment-effects. The "similarity assumption" required for NMA is therefore not satisfied and analysis may be biased. Meta-regression may be used to relate the size of a treatment-effect obtained from an NMA to certain characteristics of the included RCTs, in an attempt to explain the observed between-trial heterogeneity.[186] However, treatment-effect modification from baseline covariates can be difficult to identify using aggregate study-level data.[187] Meta-regression based on patient level data is likely to have much greater power to explore differences in effect based on covariate subgroups. [188]

3.3.2.4 Consistency Assumption

Where the network of evidence supports both direct and indirect comparisons, a further NMA assumption is that there is a consistency across the evidence base i.e. the indirect estimate is not biased and that there is no discrepancy between the direct and indirect comparisons. For example, Figure 3.2d depicts a network which incorporates both direct and indirect evidence for all possible pairwise comparisons. The relative efficacy of *A vs B* (d_{AB}) can be made directly from the *A vs B* trial or indirectly via the common comparator *C*. Assuming an additive scale, the consistency assumption requires the following equation to be satisfied $d_{BC} = d_{AC} - d_{AB}$. Inconsistency, like heterogeneity, is caused by an imbalance in the distribution of treatment-effect modifiers between the direct and indirect evidence. Dias *et al* have suggested methods for the detection of inconsistency in evidence networks within a Bayesian framework, by comparing the

consistency model with an "inconsistency" model. The consistency model defines all contrasts as functions of basic parameters which estimate all treatment-effects relative to the same treatment e.g. d_{AB}. d_{AC}...etc The "inconsistency" model estimates separate relative treatment-effect parameters for each contrast e.g. d_{AB}, d_{BC}, d_{Ac} ...etc. without assuming any relationship between parameters. It is based on direct evidence only. The deviance and deviance information criterion statistics of the consistency and inconsistency models may be compared as a test of consistency.[189] Like tests for heterogeneity, tests for inconsistency are inherently underpowered and Dias *et al* state that the null hypothesis of consistency will "nearly always fail to be rejected" as the detection of inconsistency requires far more data than is needed to establish the presence of a treatment-effect. [189] They recommend measures that can help avoid inconsistency such as the avoidance of between-trial heterogeneity particularly from known potential confounders and observation of the between-trials variation in the trial baselines e.g. heterogeneity in the event rate or hazards in the placebo arms of a number of trials constitutes a warning for potential heterogeneity in relative effects.

3.3.3 Summary

In the absence of RCTs comparing all comparators of interest, evidence synthesis methods are required to combine individual components from the evidence base of relevant treatments. NMA methods allow the estimation of relative treatment effects through the combination of direct and indirect evidence from across a network of trials while preserving within-trial randomised treatment comparisons. The Bayesian approach allows for more intuitive interpretation than the classical frequentist approach, and is well suited to applications in healthcare decision making.

Synthesis of evidence from a range of placebo-controlled and direct-comparative trials is necessary in order to estimate the relative efficacy of DMT in RRMS. In this thesis, a Bayesian NMA model will be fitted in WINBugs to estimate the relative treatment effects of all DMTs of interest. The model will be extended to meta-regression to identify potential sources of treatment effect modification and the consistency assumption will be checked. Further details on the application of these methods is provided in Chapter 7.

3.4 Decision-analytic modelling for Economic Evaluation

3.4.1 Introduction

Decision analysis provides the framework for conducting economic evaluations, within which all important aspects of a decision problem may be considered. A decision-analytic model is a systematic, quantitative approach to decision-making under uncertainty. Based on an explicit structure, the alternatives available to a decision-maker, the probabilities of associated events, and the expected costs and expected outcomes of different decisions are represented together with a quantification of uncertainty. In HTA and economic evaluation, a model may be defined as "a mathematical model of the natural history, epidemiology and treatment of a disease designed with the purpose of predicting how a technology will affect clinically important outcomes". [190] In practice it is common to combine evidence from a number of different sources e.g. RCTs for efficacy parameters, Cost-of-Illness studies for resource utilisation and cost parameters, utility valuation studies for utility parameters, often together with expert opinion and clinical experience.

RCTs would appear to provide a natural framework for economic evaluations as patient-specific data on interventions and outcomes together with resource use and outcomes may be gathered prospectively to provide an unbiased estimate of the effect of interventions. However, the widespread use of RCTs for economic evaluation is limited. All relevant alternatives are often not included in the trial, the RCT may be limited to specific setting or group of patients, resource utilisation, unit cost and HRQoL data may not be collected, the time horizon is often not long enough and intermediate endpoints such as HbA1C for diabetes may be measured, instead of final endpoints such as mortality. Modelling overcomes many of these limitations to complement the trial-based approach by synthesising trial results with other sources of evidence on those parameters of interest which are not available from the trial. Furthermore, health economic modelling can handle uncertainty in a systematic way, produce evidence-based estimates for data that haven't been measured e.g. final endpoints from intermediate endpoints, and can be used to extrapolate from existing data to predict long-term outcomes. Models can also incorporate discounting of costs and benefits to reflect society's preference to incur costs later and receive benefits earlier. Irish guidelines recommend a standard discount rate of 4% for both costs and

outcomes, although opinion is divided among experts on whether outcomes should be discounted at a differential rate or at all. [191]

3.4.2 Development of a decision-analytic model

The steps involved in the model development process include: understanding the decision problem, conceptual modelling, gathering evidence to inform model parameters, model implementation and validation.

3.4.2.1 Understanding the decision problem

The population of interest, setting, perspective and time horizon are defined, and appropriate interventions, comparators and relevant outcomes are identified. This involves reviewing previous models and published literature and discussion with clinical experts and policy-makers. While all models are a simplification of reality, they should still be realistic, guided by but not dictated by data availability. Rather, the model scope and structure should be driven by the decision problem and reflect what is known about a particular disease and the impact of the alternative interventions on that disease process. [192]

3.4.2.2 Conceptual modelling

During the conceptual modelling phase, the model structure is devised including all relevant health states and disease pathways, and all necessary assumptions are identified. Involvement of stakeholders in this process contributes to the acceptability and validity of the model. A visual model i.e. a graphical representation of the disease process and the impact of interventions in the context of the decision-problem, often accompanies the mathematical model. This diagrammatic approach can also facilitate communication of aspects of the decision analysis to the decision-maker and other model-users. The main decision model types used for health economic evaluation include decision tree, state transition model (e.g. Markov model), dynamic transmission model, discrete event simulation. Decision tree and Markov models are both forms of cohort model, focusing on the expected costs and outcomes of the average patient. Decision trees are usually appropriate for decision problems with short time horizons without recurring events (Figure 3.3).

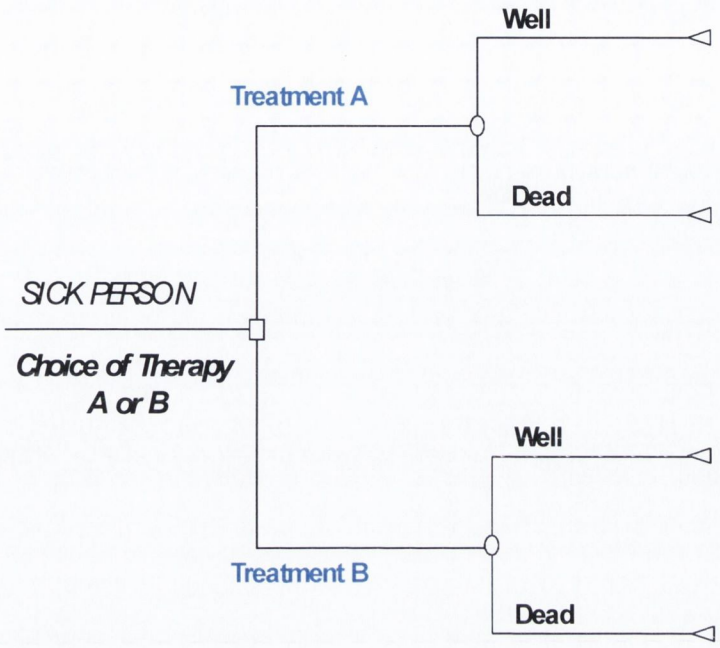


Figure 3.3: Example of a decision tree

3.4.2.2.1 Markov Models

In situations where a large number of potential consequences must be considered, decision trees can become "bushy" and unwieldy to program and present. This extra complexity is more appropriately handled using a state transition model e.g. Markov model, used where the disease process involves a series of health states and recurrent events. A simple example is graphically illustrated in Figure 3.4. Many disease processes can be described in terms of health states and transitions between these states, involve time-dependent parameters e.g. disease progression, or recurrent events e.g. relapses. As such, Markov modelling is particularly suited to decision-problems involving health technologies and is one of the most widespread modelling techniques in HTA and health economic evaluation. [192] Markov models comprise a finite set of mutually exclusive health states, defined and described according to the decision problem, across which the modelled population is distributed. Patients transition between these health states during cycles of short time intervals, depending on a set of transition probabilities. Each patient can only be in one health state in any cycle. Cycle length should reflect the natural history of the disease and should represent the

minimum amount of time that an individual should spend in a state before the possibility of transition to another state. [192] In this way, longer cycle lengths are appropriate for diseases with a low frequency of events over a lifetime horizon, while shorter cycle lengths are suited to acute illnesses or short time horizons. A cohort is simulated whereby the proportion of the cohort in one state is multiplied by the relevant transition probability to derive the proportion starting in another state. Each state is associated with state values e.g. life years, utility and cost, associated with occupying that health state for one cycle. Total expected costs and outcomes can be estimated for each cycle by summing the product of health state values and the proportion of the cohort in each state. The baseline risk of transition can be adjusted to reflect the effect of a particular treatment compared with no treatment, for example. The difference in total costs and effects is then used to calculate an ICER, as described in Chapter 2.

The main disadvantage of Markov models is that all patients in a given state are treated as a homogeneous group. Transition probabilities depend only on the state occupied by the patients at the beginning of a given cycle and not the time spent in a given state or the history of the patient prior to entering the state.

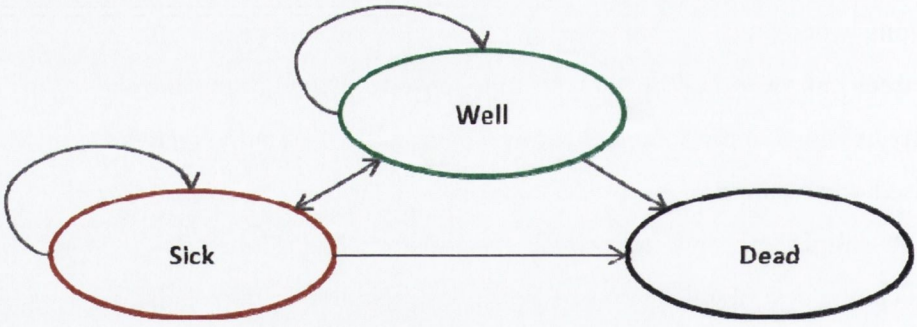


Figure 3.4: Example of a Markov Model

In this simple example patients are initially distributed between "sick" and "well" health states. At the end of each model cycle, patients can remain in their current health state (denoted by curly arrow), move between "sick" and "well" health states, or die. The "dead" state is referred to as an absorbing state, in that no transitions are allowed from it.

3.4.2.2.2 Individual Patient Simulation Models

Individual patient simulation models are alternatives to cohort models in that they track the process of individual patients through particular health states over time. Dynamic transmission and discrete event simulation models overcome the "memoryless" function of Markov models and allow full representation of the time individuals spend in a given state and individuals' history before entering that state. [193] The effect of interactions between individuals may also be evaluated using these individual patient-level simulation models. Dynamic transmission models are used to evaluate the effect of an intervention on an infectious disease process. Individual patient simulation models require more evidence and are computationally more expensive than cohort models. Barton *et al* have produced a flowchart which aids in the model-type selection process based on whether individuals can be regarded as independent, whether interaction is an important issue, if recurrent events need to be modelled and if a lot of health states need to be represented (Figure 3.5). [193]

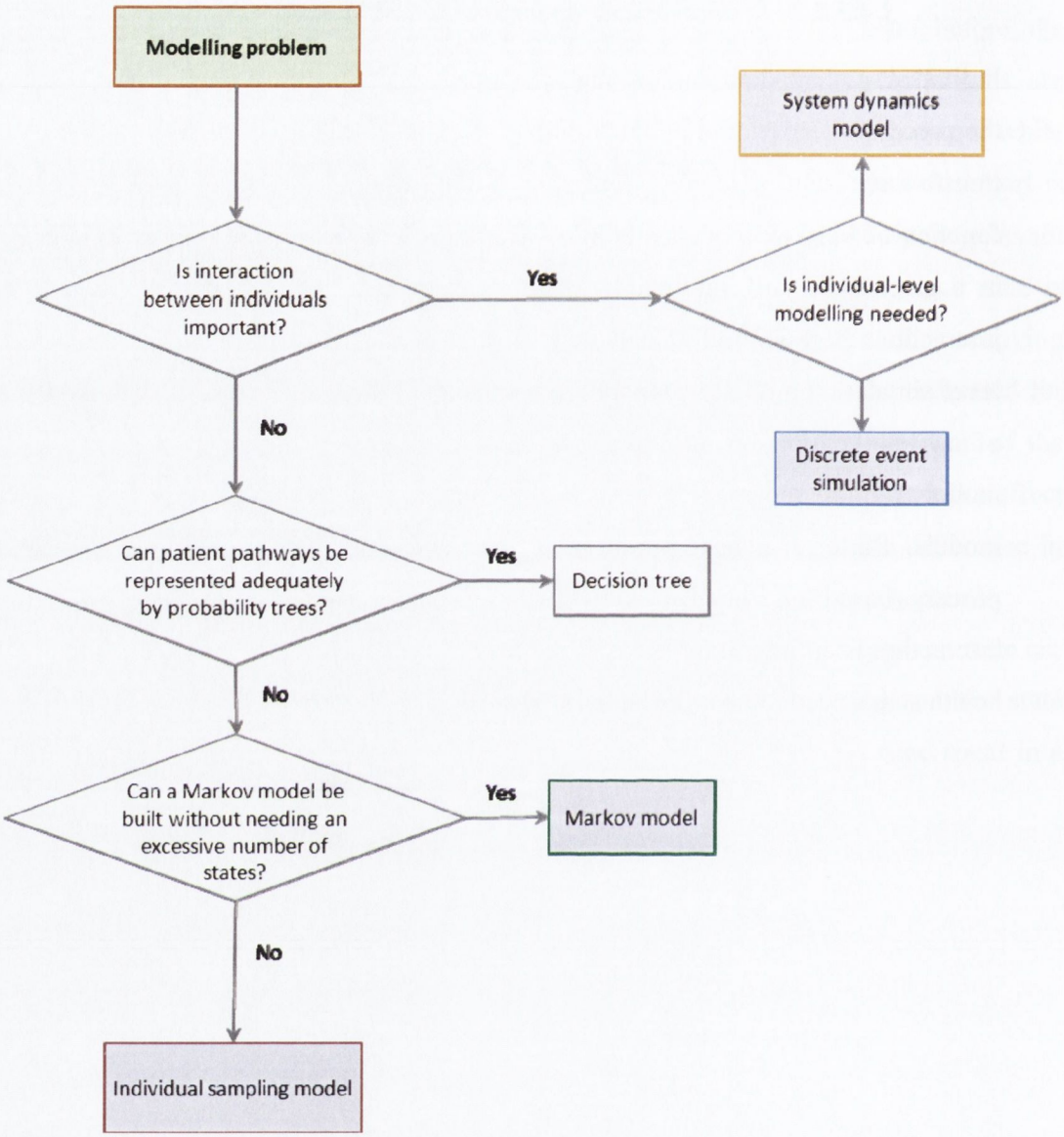


Figure 3.5: Selecting an appropriate model type

Adapted with permission from Sage Publications: Journal of Health Services Research & Policy, Barton *et al*, © 2004 [193]

3.4.2.3 Identifying evidence to inform model parameters

The model combines data on the characteristics of the target population, natural history of the relevant condition, efficacy of the intervention, resource utilisation and costs, and health state utility data. In most cases, all of the evidence required to inform these model parameters will not be available from a single study. [173] As a result, evidence must be obtained from a disparate range of sources e.g. RCTs, observational studies, registry data, administrative claims databases and expert opinion. Identification of data sources to inform model parameters should be systematic and conform to the principles

of evidence-based medicine e.g. endeavour to incorporate all available evidence and avoid potential biases. [194] It is recommended that data sources should be mutually consistent but this is not always possible. [195] Data should be clear, transparent and justified and reported in sufficient detail. [196] [197] For parameters where evidence is available from multiple sources e.g. RCTs for relative efficacy of comparators, appropriate statistical techniques must be used to synthesise the evidence base e.g. meta-analysis, indirect treatment comparisons and network-meta analysis. [132] [176] [198] In recognition of both the scarcity of data sources for some parameters and the multiplicity of evidence for others, Briggs *et al* recommend that the choices made should reflect uncertainty in estimation of the parameter via deterministic sensitivity analysis (DSA) or probabilistic sensitivity analysis (PSA). [194]

3.4.2.4 Model implementation

The spreadsheet is the predominant software platform for the implementation and calculation of health economic models although various software packages are available, differing in their ease of use, flexibility and access. Menn and Holle compared the strengths and weaknesses of three commonly used packages, TreeAge®, Microsoft® Excel and Arena® with regard to ease of implementation. They found that for simpler models, Excel offers an intuitive spreadsheet interface and is widely accessible, making co-operation and public access to the model easier. TreeAge® or Arena® were found to facilitate implementation of more complex models and offer greater flexibility than Microsoft® Excel. [199]

3.4.2.5 Model Validation

In order for the model to be fit for purpose, it is essential that results are reliable and credible to decision-makers. It has been recognised that errors in mathematical decision models are unavoidable. [7] A study by Chilcott et al found that errors in HTA models arise from the understanding of the decision problem, the structure and methodology used, the use of evidence, implementation and operation of the model and/or presentation and understanding of results. [200] Validation is a set of methods for judging a model's accuracy in making relevant predictions. [201] Face validity examines whether model assumptions, structure and results are sensible and intuitive. [202] Internal validity or verification checks whether the model has been correctly implemented, whether

model inputs relate to model outputs and how the model compares the evidence used for its development. External validation independently compares the model with other models, and model-predicted events with actual events. [201]

3.4.3 Dealing with Uncertainty

Uncertainty must be systematically examined and reported in order for decision-makers to have confidence in applying model results to a particular decision problem. Various forms of uncertainty must be captured in the model including: stochastic uncertainty (also referred to as first-order uncertainty or random variability in outcomes between identical patients), parameter uncertainty (also referred to as second-order uncertainty, relates to precision of parameter estimates), heterogeneity (the variability between patients that can be attributed to observed differences) and structural uncertainty (model assumptions). [194] The various types of uncertainty can be dealt with through deterministic Sensitivity Analysis (DSA), scenario analysis, and probabilistic sensitivity analysis (PSA)

3.4.3.1 Deterministic Sensitivity Analysis

Parameter uncertainty is dealt with through both DSA and PSA. In DSA a measure of precision such as standard error of 95% confidence interval will inform a plausible range over which the parameter can be varied. In one-way DSA, parameters are varied singly and independently to observe the impact on model results. Multi-way analysis involves changing multiple parameters according to a specific scenario. Structural uncertainty and variability may be handled through scenario analysis in which the set of base-case parameter values and assumptions are substituted for an alternative set associated with different subgroups of interest. DSA is useful for identifying the parameters which are driving the decision or identifying the critical parameter values above which the decision may be expected to change i.e. threshold analysis, but is most useful when presented alongside PSA results. [194]

3.4.3.2 Probabilistic Sensitivity Analysis

PSA is required for a complete assessment of uncertainty as it permits the joint uncertainty across all the parameters in the model to be assessed at the same time. Instead of using mean values of input parameters, in PSA a probability distribution is

specified for each parameter of interest, representing both the range of values that the parameter can take as well as the probability that it takes any particular value. [194] Uncertainty is then propagated through the model by randomly selecting values from these distributions for each model parameter using Monte Carlo simulation. 1000 iterations are typically used although this can vary depending on the degree of uncertainty and computational requirements. [203] Probabilistic analysis is particularly important in the case of Markov and other non-linear models where the expected values generated by models using mean values of the input parameters can differ from probabilistic models using input distributions. [204] Probabilistic assessment of uncertainty can also address bias which may be inherent in some mean parameter values e.g. from manufacturer-funded studies (the NCPE requires probabilistic models to be included in manufacturer submissions). [7] Finally, the consequences of making an incorrect decision in terms of benefits foregone and associated costs can be captured in a probabilistic model. [205]

3.4.3.3 Defining Distributions for various types of data

Standard statistical methods, using parametric or non-parametric assumptions, can be used to fit a distribution where primary, patient-level data are available. Often, only summary statistics for certain parameters will be available e.g. published treatment-effects from randomised controlled trials, to which a distributional form can be applied. Distributions are assigned to all uncertain parameters in order to represent second-order parameter uncertainty. The type of distribution for each parameter is typically chosen from among commonly used distributions including normal, log-normal, gamma, beta and uniform. The choice of distribution should reflect the characteristics of the distribution and the nature of the data, be they cost, utility, probabilities, treatment-effects etc. Convenient to fit distributions such as triangular or uniform distributions are inappropriate as they rarely reflect the nature of the data or the prior knowledge of how the distribution should look. [194]

3.4.3.4 Cost Data

Cost data are constrained on the interval zero to positive infinity and are often highly skewed. Both the log normal distribution and the gamma distributions may be used to represent uncertainty in skewed cost parameters.

3.4.3.5 Utility Data

Utility values are theoretically constrained between 1 (perfect health) and negative infinity (worse possible health states). If health state utilities are expected to be far from zero, the beta distribution may be used. In the event that states close to or worse than death are possible, a transformation of utility to utility decrement (or disutility) i.e. 1-utility, now constrains values on the interval zero to positive infinity and a gamma or log normal distribution can be fitted.

3.4.3.6 Probabilities

Probability parameters such as transition probabilities are constrained on the interval zero to one. A further constraint is that probabilities of mutually exclusive events must sum to one. The beta distribution is recommended to represent uncertainty in a probability parameter where the data informing the parameter are binomial, as it is similarly defined on the interval zero to one and is characterised by two parameters, alpha and beta. Alpha and beta can be interpreted as counts of the event of interest occurring (r) versus not occurring (n-r). In the case of multinomial data where greater than two events can occur, the dirichlet distribution, may be used. The dirichlet distribution is the multivariate equivalent of the beta distribution with number of parameters equal to the number of categories in the multinomial distribution. [206]

3.4.3.7 Efficacy Data

Treatment-effects are often applied in models as relative risks or hazard ratios. The ratio nature of these parameters is well reflected by the log-normal distribution.

3.4.4 Analysis and Presentation of Results

3.4.4.1 Deterministic Analysis

The "ICER" was introduced in Chapter 2, and defined as the difference in costs divided by the difference in effects of competing alternatives. More specific terminology is suggested by Gray *et al* who suggest reserving the term "ICER" for comparisons with the next best alternative (as determined in a fully-incremental analysis, described below).(REF) The term "average cost-effectiveness ratio" (ACER) is suggested for

cost-effectiveness ratios that are calculated versus a "do-nothing", "best-supportive care" or "baseline" option. In a fully incremental analysis, all treatments options should be included and, calculation of cost-effectiveness ratios relative to the next best alternative is recommended after exclusion of options subject to dominance (more costly and less effective) and extended dominance (combinations of other options can provide more benefit for the same cost). [207] An illustrative scenario is depicted in Table 3.1 and Figure 3.6. Five mutually exclusive treatment options are listed in Table 3.1 in order of increasing total cost. Initial ICERs are first calculated for each option compared with the previous less expensive alternative. Any options that are both more expensive and less effective than the previous alternative (Option D) are dominated and are eliminated. Second ICERs are recalculated (with dominated options excluded), and it is clear that now the ICER for option C is higher than that of option E. Under the principle of extended dominance the option with the higher ICER (option E) should be eliminated from consideration as a cost-effective strategy, even though it is a less costly option based on total cost. This is based on the assumption that if the decision-maker is willing to pay a specified incremental amount for health benefit, they should be willing to pay a smaller incremental amount to obtain the same benefit. After eliminating all dominated and extended dominated options the final ICERs are calculated. In the final scenario all ICERs will rise as the options become more costly. This process is depicted graphically in Figure 3.6. The ICERs of the remaining alternatives may be considered relative to the WTP of the decision-maker e.g. €45,000 per QALY.

Table 3.1: Incremental cost effectiveness ratios and identifying dominated/extended dominated options

Option	Total Costs	Incremental Costs	Total QALYs	Incremental QALYs	Initial ICER	2nd ICER	Final ICER
A	€1,074	-	10.961	-	-		
B	€1,077	€3	10.966	0.005	€600	€600	€600
C	€1,107	€30	10.972	0.006	€5,000	€5,000	ED
D	€1,110	€3	10.967	-0.005	D	-	-
E	€1,114	€4	10.984	0.017	€235	€583	€83

Values are for illustrative purposes and have been adapted from an Irish HTA of a population-based colorectal cancer screening programme in Ireland. [208]

Abbreviations: ICER=incremental cost-effectiveness ratio (euros per QALY); QALY= Quality adjusted life year; D=dominated; ED=extended dominated

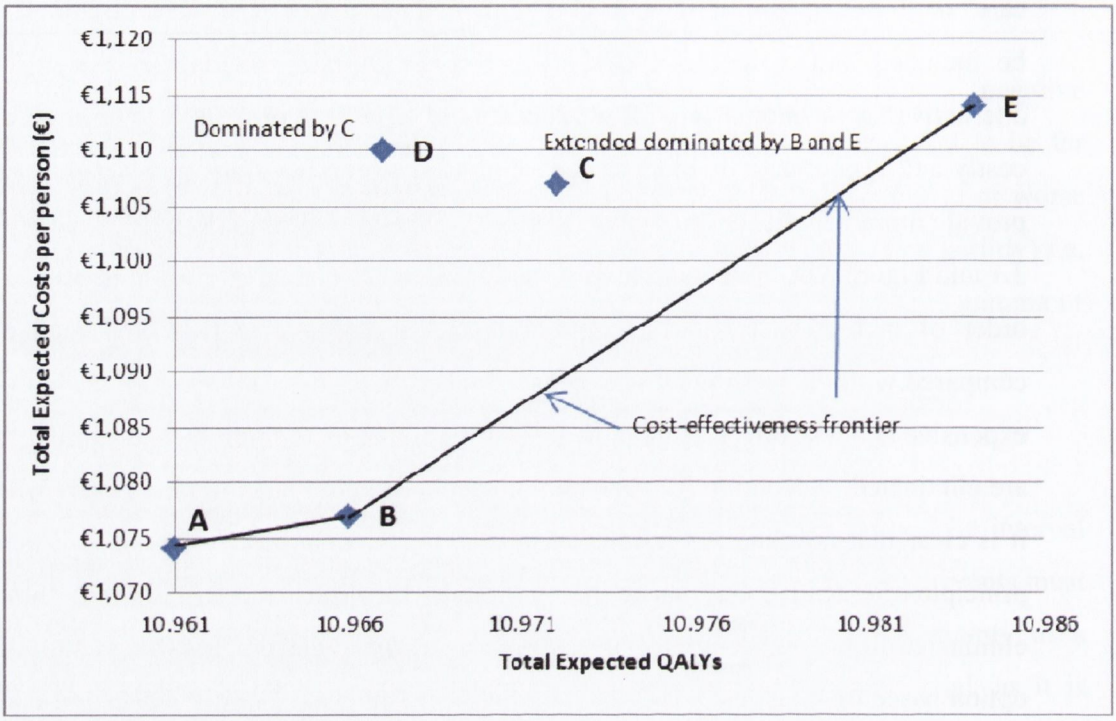


Figure 3.6: Graphic illustration of Table 3.1

Options which lie on the cost effectiveness frontier, or "efficiency frontier" represent those which maximise health gain for a given level of health spending.
QALY= Quality adjusted life year

This thesis refers to all cost-effectiveness ratios as ICERs as every comparison involves a calculation of incremental costs and effects whether or not the comparator is the next best treatment, BSC, or another option among available alternatives. In addition, despite the rules of dominance and extended dominace which have been described, it may not be feasible or appropriate to eliminate alternatives from the decision-making process, particularly if they are already reimbursed.

The results of univariate sensitivity/scenario analysis can be reported in a tornado diagram, where ICERs based on low and high estimates of each parameter are presented as horizontal bars to each side of the central base-case ICER (Figure 3.7). Very wide bars indicate the variables for which uncertainty has the biggest effect on the ICER.

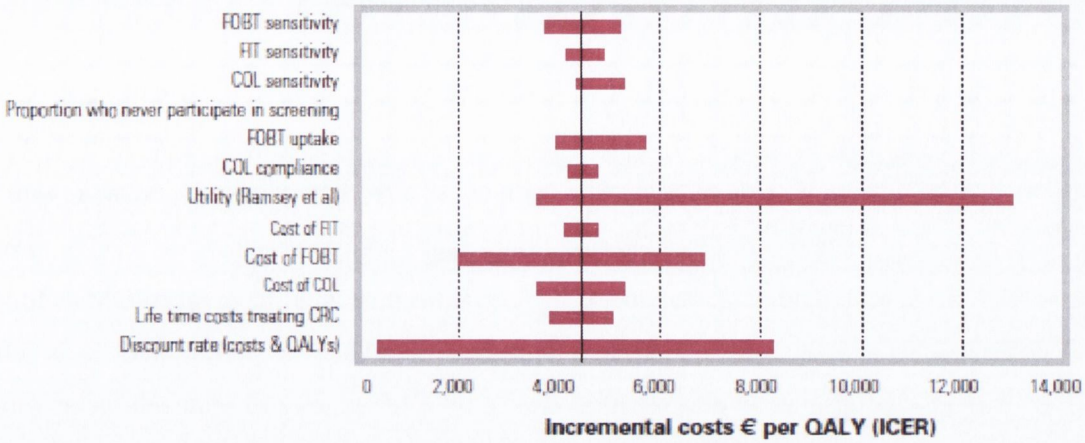


Figure 3.7: Example of a tornado diagram for one-way sensitivity analysis

The example is that of gFOBT at 55-74 years, a colorectal cancer screening strategy included in the HTA of a population-based colorectal cancer screening programme in Ireland. [208] Key parameters, listed on the left of the graph, are varied independently. The base case ICER was €4428 per QALY and was most sensitive to variation in utility and discount rate.
Abbreviations: ICER= Incremental cost effectiveness ratio; QALY= Quality adjusted life year

3.4.4.2 PSA Results

A scatter-plot of PSA simulated cost and effect pairs can be presented on the incremental cost-effectiveness plane, the spread of the points illustrating the degree of uncertainty surrounding the estimates. CEACs and CEAFs are among the most common methods of presenting the results of PSA. [16] For each option, a CEAC plots the proportion of cost and effect pairs which have the highest NMB among all available options, for a range of values of λ (willingness to pay threshold). The NMB is equal to λ*total effects – total costs. Fenwick *et al* point out that use of the CEAC should be restricted to estimating the probability of cost-effectiveness given the associated uncertainty, and not used to identify the optimal treatment option. This is because the option with the highest probability of being cost-effective is not necessarily the option with the highest expected NMB. [209] Instead, a CEAF plots the optimal option over a range of λ. The optimal option is that which has the highest expected NMB at different levels of λ. The CEAF can be used to identify "switch-points" at which there is a change in the optimal option corresponding to the ICER between different options. Value of information (VoI) analysis etimates the opportunity cost of an incorrect decision. [16]

3.4.5 Summary

Decision-analytic models provide a framework within which all evidence on a decision-problem may be synthesised to provide estimates of the cost-effectiveness of health technologies together with an assessment of the uncertainty associated with those estimates. Decision-analytic modelling is a core component of HTA processes internationally and has been utilised in decisions on reimbursement of DMTs for MS in Ireland, the UK and elsewhere. Markov modelling is well-suited to a chronic, progressive disease like MS where multiple health states and recurrent events must be accounted for. In Chapter 8, the development of a Markov model for an economic evaluation of DMT for RRMS in Ireland will be described, together with an outline of the various deterministic and probabilistic sensitivity analyses applied.

CHAPTER 4 – LITERATURE REVIEW

CHAPTER 4 – LITERATURE REVIEW

This chapter reviews the existing research which is relevant to this thesis. Relevant research is grouped according to the broad issues related to the thesis; the economic burden of MS, HRQoL utilities in MS, and the relative efficacy and cost-effectiveness of DMT for MS. The approaches and findings of individual studies are compared, with particular focus on studies which overlap with my research.

4.1 The Economic Burden of Multiple Sclerosis

MS is associated with significant economic burden. Healthcare resource utilisation in MS has significant financial consequences for the healthcare system, patients and their families. DMT, used to prevent relapses and delay disease progression, are among the most costly pharmaceuticals on the market in Ireland ranging from €11,000 to €23,000 per patient per year. Ongoing magnetic resonance imaging and laboratory investigations are required during treatment to monitor disease activity and response. Symptoms including pain and loss of sensation, fatigue, impaired muscle control, balance and postural problems, visual loss, cognitive impairments, and bowel and bladder disturbance, require both pharmacological and non-pharmacological management in the form of physiotherapy, occupational therapy, counselling and rehabilitation. As the disease progresses, symptom management predominates with the aim of maintaining independence and functioning both at work and at home. This often requires a complex multidisciplinary approach including inpatient, ambulatory, and home-based rehabilitation interventions under medical supervision.[84] As the leading cause of non-traumatic neurological disability in young adults, MS imposes an additional indirect cost burden on society. Neurological symptoms of varying severity can result in functional limitations which can severely impact patients' physical activity, employment capabilities and opportunities. These limitations can result in prolonged absences from work, early retirement from the labour force and significant care requirements from both professional caregivers and informally from family and friends.

4.1.1 Cost of Illness Research in Multiple Sclerosis

The economic burden of MS has been widely studied internationally. [1 134 138 141 210] A literature review of the global economic impact of MS published in 2010 by the International Multiple Sclerosis Federation identified 215 articles on the economic burden of MS. [211] For the 15 countries for which complete estimates were found (Australia, Austria, Belgium, Canada, France, Germany, United Kingdom, Italy, the Netherlands, Norway, Spain, Sweden, Switzerland, and the United States), the average total annual cost per person with MS in 2007 varied from $16,400 to 54,500 U.S. international dollars. When costs were converted to euros using purchasing power parity (PPP) and inflated to 2012 values using statistics from the OECD , the weighted average is €45,446 per person (Figure 4.1). [211 212] Extrapolations from a multinational cost study estimated the total annual cost of MS in Europe at €12.5 billion in 2005. [213]

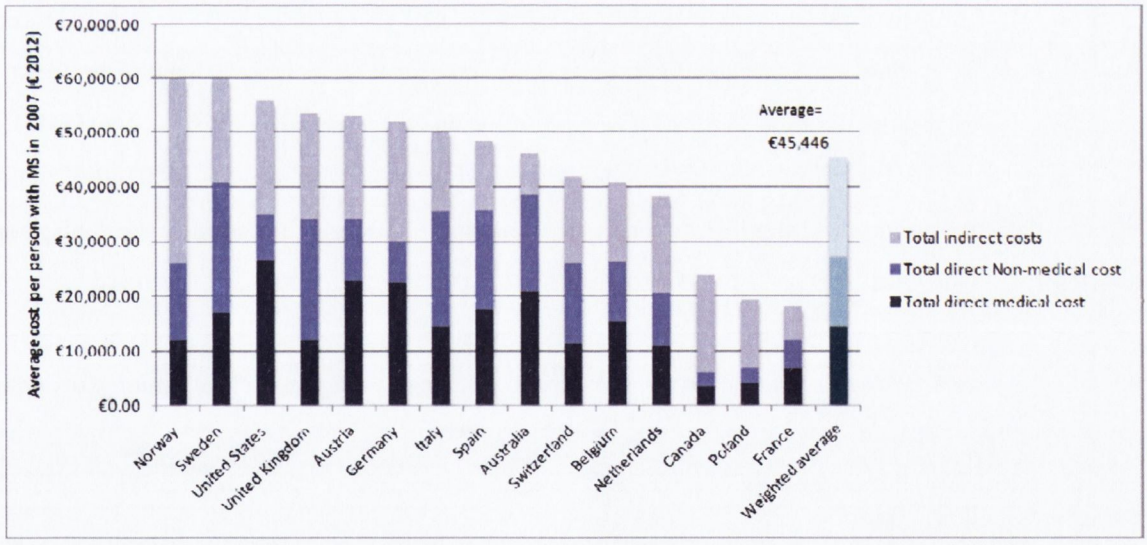


Figure 4.1: Mean annual cost per person with MS in 2007

Data for each cost component extracted from Trisolini *et al* and converted to €2012[211]

4.1.2 European Studies on the Cost of Multiple Sclerosis

Two large European studies investigated the economic burden of MS across a number of countries in 2005 and 2009 from the societal perspective. [1 134] The 2005 study by Kobelt *et al* recruited 13,186 patients predominantly via MS society mailing lists from

nine countries including Austria, Italy, Spain, Sweden, Switzerland, UK, Belgium, Germany and The Netherlands. The 2009 TRIBUNE study by Karampampa *et al* recruited 1261 patients from treatment centres in France, Germany, Italy, Spain and the United Kingdom (an additional study was conducted in the Netherlands in 2011). Both the Kobelt and TRIBUNE groups of studies utilised self-administered questionnaires to capture data on disease status and history, resource utilisation and costs. The earlier study was a mail survey in contrast with the more recent study which captured data using a web-based electronic system. The results of these studies are summarised in Table 4.1 and 3.2. Mean direct costs per patient per year were similar in both groups of studies (€13,822-€30,721 in the Kobelt *et al* studies, €12,819-€24,578 in the TRIBUNE studies, all costs inflated to 2012). [1 134] The Kobelt *et al* cohort had more severe disease on average (mean EDSS 3.8-5.1; 45.5%-67.7% progressive disease) than the 2009 study (mean EDSS 1.8-3.9; 12-29% progressive disease), reflecting the mode of patient recruitment (MS society mailing lists versus treatment centres respectively) and partly explaining the trend towards higher mean costs in the Kobelt study. Higher levels of DMT utilisation in the 2009 study (75%-94% vs 21%-52% in 2005 study) is in keeping with evolving international practice in response to clinical trials demonstrating improved outcomes with DMT use early in the disease course. [96-98] DMT costs therefore contribute to the higher than expected costs in the TRIBUNE study in comparison with the more severely disabled patient cohort included in the Kobelt study.

Table 4.1: Mean annual direct and indirect costs per patient with MS in nine European countries, 2005 (societal perspective)

Country	Direct costs	Indirect Costs
Sweden	€30,721	€28,419
Switzerland	€28,441	€30,559
Austria	€22,149	€23,280
Germany	€20,343	€23,215
Spain	€16,418	€21,054
Belgium	€16,415	€20,012
Italy	€15,026	€28,830
United Kingdom	€13,876	€23,940
Netherlands	€13,822	€18,925

Data extracted from individual studies of Kobelt *et al* and inflated from 2005 to 2012. [161 214-221] Direct and indirect costs have been adjusted from the original studies to include informal care as an indirect cost in keeping with costing classification employed in this thesis.

Table 4.2: Mean annual direct medical, non-medical and indirect costs per patient with MS in six European countries by level of disability, 2009 (societal perspective)

Country	Patient subgroup (level of disability)			
Germany	**All**	**Mild**	**Moderate**	**Severe**
Direct medical costs	€18,396	€17,451	€18,364	€31,237
Direct non-medical costs	€1,223	€343	€2,446	€6,180
Total Direct costs	€19,619	€17,794	€20,809	€37,417
Total indirect costs	€9,797	€4,001	€20,284	€28,736
Spain	**All**	**Mild**	**Moderate**	**Severe**
Direct medical costs	€16,519	€15,051	€19,516	€16,344
Direct non-medical costs	€1,253	€245	€2,342	€11,464
Total Direct costs	€17,772	€15,296	€21,859	€27,808
Total indirect costs	€12,418	€6,010	€23,465	€33,400
United Kingdom	**All**	**Mild**	**Moderate**	**Severe**
Direct medical costs	€9,959	€8,861	€10,692	€7,997
Direct non-medical costs	€2,860	€63	€3,175	€25,628
Total Direct costs	€12,819	€8,925	€13,867	€33,625
Total indirect costs	€16,028	€6,703	€20,308	€44,268
France	**All**	**Mild**	**Moderate**	**Severe**
Direct medical costs	€15,944	€13,581	€20,352	€19,989
Direct non-medical costs	€1,156	€349	€2,170	€12,324
Total Direct costs	€17,100	€13,929	€22,523	€32,314
Total indirect costs	€4,266	€2,488	€7,477	€12,799
Italy	**All**	**Mild**	**Moderate**	**Severe**
Direct medical costs	€24,319	€22,536	€32,099	€14,358
Direct non-medical costs	€259	€22	€890	€4,068
Total Direct costs	€24,578	€22,558	€32,989	€18,426
Total indirect costs	€3,224	€1,075	€10,493	€23,232
Netherlands*	**All**	**Mild**	**Moderate**	**Severe**
Direct medical costs	€12,822	€11,480	€13,918	€14,234
Direct non-medical costs	€5,303	€1,268	€5,253	€22,471
Total Direct costs	€18,125	€12,748	€19,172	€36,705
Total indirect costs	€28,033	€18,757	€31,074	€55,307

Total direct costs include direct medical and direct non-medical costs

Data extracted from individual TRIBUNE studies and inflated from 2009 to 2012 (*from 2011 to 2012).[222-227]

"All" figures based on sample proportions reported by Karampampa *et al.* [134]

Direct and indirect costs have been adjusted from the original studies to include informal care as an indirect cost in keeping with costing classification employed in this thesis.

Mild: EDSS score (0-3), moderate: EDSS score (4-6.5), severe: EDSS score (7-9)

4.1.2.1 Differences Between Countries

Kobelt found that healthcare utilisation was quite variable across countries, reflecting differences in the organisation of healthcare systems, financial incentives, access and traditions. Hospital admissions were substantially more frequent and longer in duration in countries where payment for hospitalisations was by a daily rate. Ease of access to medical or paramedical practices led to higher numbers of medical visits e.g. Belgium and Germany, compared with countries where specialist consultations are largely limited to hospitals e.g. Sweden. The extent of informal care was found to be dependent on the extent to which homecare services and personal assistants are funded by the healthcare system (higher in Sweden than in Italy or the UK, for example), and family structures e.g. lower usage of informal care in countries were more women are employed outside the home. [1] The COMS study established the cost of MS in the Czech Republic from the societal perspective. [141] The mean direct cost per person was €6753, significantly lower than those cost estimates from Western European countries. The difference may be attributed to the lower unit costs and lower average wages (resulting in less productivity losses) in the Czech Republic.

4.1.2.2 The Impact of Increasing Disability on Costs

Studies have consistently shown that costs increase in line with increasing disability. In a 2008 study on the cost of MS in UK and Northern Ireland, McCrone *et al* identified a similar pattern of increasing costs between relapsing remitting and progressive phases of the disease.[138] TRIBUNE explicity categorised patients by disease severity into mild (EDSS score ≤ 3), moderate (EDSS score 4 – 6.5) and severe (EDSS ≥ 7). Costs varied across countries from €13,534-€22,461, €28,524-€43,948 and €39,592-€65,395 for mild, moderate and severe subgroups respectively. [134] Kobelt found that costs for patients with severe disease (EDSS >7.0) increased by a factor of 2.2-2.5 in Germany, Austria or Belgium, and by a factor of 3.9–4.9 in other countries (e.g. Sweden, Switzerland or UK) compared with patients with earlier disease (EDSS <4.0). [1] The COMS study established the cost of MS in the Czech Republic from the societal perspective. [141] The average annual costs in COMS study patients with mild, moderate and severe disability were to €9905, €14,064 and €22,880, respectively.

4.1.2.3 Indirect Costs and Definition of "Total Cost"

In many cost-of-illness studies "total cost" refers to the sum of direct and indirect costs, with indirect costs outweighing direct costs in later stages of the disease. [228] Indirect costs arise from the productivity losses associated with short and long-term work absences, reduced working hours and changing type of work, presenteeism and early retirement. Productivity losses are also associated with informal care provided by family and friends. In addition to differences in employment rates, provision of formal home-care, and average wages between countries, cross-study comparisons are further complicated by the varying definitions of direct and indirect cost. Indirect costs in both Kobelt and TRIBUNE studies include informal care as a direct cost. [1 134] Indirect costs in the TRIBUNE study ranged from 6.52% of total costs in Italy to 38.06% of costs in Spain, reflecting the extremes of employment level in these country cohorts. [224 226] In the Kobelt study, 26.23%-45.80% of total costs comprised indirect costs. By including informal care among indirect costs, the proportion of indirect costs in the Kobelt studies increases to 48.05%-65.74%. [1] In McCrone *et al.* UK study, lost production costs and informal carer costs are reported separately and account for 33% and 48%, respectively, of the total. [138]In the COMS study the productivity losses of both patients and informal caregivers were included among indirect costs which represented 45% of total costs. [141]

4.1.2.4 Factors which influence Costs in MS

Two UK cost studies highlighted associations between patient characteristics and variations in costs. [138 229] Tyas *et al* found that disability severity (as measured on the EDSS scale), disease type, relapse status, treatment type and time of treatment, sex, age, educational status, and time since diagnosis, were significant cost factors. [229] McCrone showed that service costs were higher if patients had an advanced disease type, low HRQoL scores, high levels of disability, male, or married/cohabiting. [138] Higher costs for men are associated with higher mean wages compared to women, while those who are married or cohabiting are more likely to be in receipt of informal care. [138]

4.1.3 The Cost of MS Relapse

The cost of relapses in MS can be substantial and includes GP and emergency department care, outpatient or inpatient treatment costs, follow-up and rehabilitation. [86] Relapse management can vary in intensity from GP-provided care to hospitalisation for

acute treatment followed by intensive outpatient follow-up, rehabilitation or nursing home care. [86] Due to the variability in severity and setting of care, the estimation of an accurate cost of MS relapse is problematic. [230] A study on the direct medical cost (2003 USD) of managing MS relapses in the US stratified relapses by the intensity of the episode ranging from $243 for a mild relapse, $1847 for a moderate relapse and $12,870 for a high intensity episode. [86] Studies such as the Kobelt and TRIBUNE studies have calculated the mean cost of a relapse in patients with an EDSS <5.0 as the difference in costs between patients with a relapse and those without and ranged from €3116 and €6537 in the Kobelt studies and €4568 and €6355 in TRIBUNE (€2012). [1 134]

4.1.4 Health State Costs for Economic Evaluations

Since the publication of the ScHARR model for IFN beta and GA in 2002 subsequent CEAs have invariably used the same modelling approach in which health states are structured on different levels of the EDSS scale. [231]

4.1.4.1 Source of Health State Costs

Published CEAs have typically derived health state costs from a core set of observational CoI studies which report mean MS-related cost associated with EDSS disability. CEAs conducted from the perspective of the UK healthcare payer or society including manufacturer submissions to NICE for natalizumab and fingolimod have used costs reported by the CoI study conducted in the UK by Kobelt *et al.*[48 232 233] The Kobelt CoI study conducted in Germany has also been used in a CEA originating from this country. [234] CEAs by Tappenden *et al* and by Noyes *et al* have modelled health state costs based on the Sonya Slifka Longitudinal Multiple Sclerosis Study in the US. [235 236] US CEAs by Bell, Lee and Earnshaw have referenced costs to a 2003 abstract which is not publicly available. [52 54 56]

4.1.4.2 Linearity of Health State Costs

While CoI in MS studies have consistently shown that costs increase in line with increasing disability, the linearity of this relationship across the EDSS scale is not clear. Tappenden *et al* mapped Activities of Daily Living (ADL) – related resource use from the Sonya Slifka study to the EDSS scale and found that the expected pattern of

increasing resource use with increasing disability was not obvious. [236] This was hypothesised to be due to the exclusion of nursing care costs from the Slifka dataset and the declining number of respondents in the more severe ADL categories. [236] A simple straight line relationship was assumed and an exponential relationship used in sensitivity analysis. The original UK Chilcott model assumed that costs increase exponentially alongside worsening on the EDSS and estimated costs for each EDSS state relative to the costs of EDSS 9.5 (note: the Chilcott approach was reported in the Tappenden report for AHRQ as cost data was reported as confidential in the original Chilcott report). [231 236] Goldberg *et al* used a fixed direct medical cost per increase in EDSS step ($1788) based on a US CoI study, also conducted by Kobelt and colleagues in 2006. [55 210] Goldberg *et al* state that the authors of the cost study showed that mean annual costs per patient increased linearly by EDSS level. This assertion is not evident from the original costing study. Significant fluctuations in medical costs are apparent as disability increases, reflecting the changing distribution of costs as the disease progresses. Costs of homecare and inpatient care increase with advanced disease while outpatient, tests and drug costs decrease. [219] A drop in annual costs at EDSS 4 was demonstrated in many of the studies included in the Kobelt series of CoI studies. [161 215 217 219 221] This drop is represented in health state costs in NICE submissions for natalizumab and fingolimod which include a lower cost for EDSS 4 compared with EDSS 3. [48 233]

4.1.5 Summary

Large European multi-national studies have contributed to our understanding of the economic burden of MS, however there are no CoI studies from Ireland. It is clear that significant variation in cost estimates exist between studies reflecting differences in study methodologies, resource consumption, prices or tariffs, organisation and delivery of healthcare in different countries, and different rates of withdrawal from the labour force. Because of this variation the degree to which CoI results across individual studies and countries can be generalised to other settings is limited. In Chapter 4, various methodologies for the measurement and valuation of MS costs will be discussed and the application of specific methodologies in an Irish cohort will be described in Chapter 5.

4.2 Preference-based HRQoL Utility in Multiple Sclerosis

The HRQoL burden of MS, like the economic burden, has been widely studied. This is partly due to the practice of conducting CoI and HRQoL studies in parallel, obtaining data from the same patient cohort. As a result, a number of studies have published utility values derived from generic preference-based instruments.

4.2.1 Preference-based HRQoL Health State Utilities in MS

A systematic review by Naci *et al* in 2010 investigated the changes in utilities associated with the increasing neurological disability of different stages of MS, as measured by the EDSS. [237] Of the 18 studies identified by the review, 16 reported health utilities by EDSS scores and none of the included studies was conducted in Ireland. Fourteen out of 18 studies used the EQ-5D-3L. The authors identified a clear inverse relationship between health utilities and EDSS scores (Table 4.3)

Table 4.3: Utility Range by EDSS Score

EDSS Score	Utility Range
0-1	0.80 to 0.92
2	0.68 to 0.84
3	0.49 to 0.71
4	0.56 to 0.71
5	0.52 to 0.97
6.5	0.38 to 0.54
7	0.27 to 0.45
8-9	–0.19 to 0.70

Data extracted from Naci et al, 2010 [237]

EDSS=expanded disability status scale

A large proportion of the studies included in the Naci review were undertaken by one group, Kobelt *et al*, as part of the multinational European study on the costs and QoL in MS discussed earlier in this chapter. [1] The study was conducted in 2005 and recruited 13,186 patients predominantly via MS society mailing lists from nine countries including Austria, Italy, Spain, Sweden, Switzerland, UK, Belgium, Germany and The

Netherlands. The authors found that utilities were almost identical across countries illustrating the consistency of disease definition across geographies and the strong correlation between disability and QoL (Figure 4.2). [1]

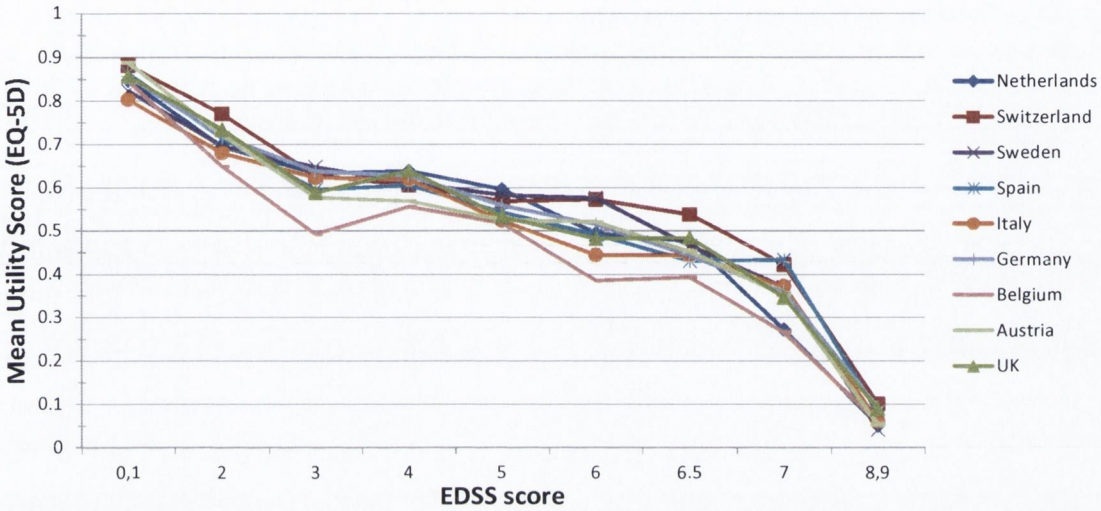


Figure 4.2: EQ-5D-3L Utilities from nine European countries

Data extracted from figures in Kobelt *et al*, 2006.[161 214-221] The authors reported mean values for EDSS 6 and 6.5 separately, and combined mean values for EDSS 0 and 1, and EDSS 8 and 9. Utility values were truncated at zero.

Abbreviations: EQ-5D=EuroQol 5-domain. EDSS=expanded disability status scale

Many of these studies calculated a utility decrement associated with relapse. However, as Naci comments, methodological inconsistencies render reported relapse-associated utility losses inaccurate. [237] The utility results of the UK study were further analysed by Orme *et al* to determine the association between utility and various factors. [238] In addition to the impact of disease severity, the type of disease (SPMS), a recent relapse, and length of time since diagnosis also have an effect on utility. Participants of this study classified their own disease course. Self-classification of disease has been identified as a difficult task. The main source of censoring in the study described by Orme *et al* was due to patients' inability to classify their type of disease. [217 238 217] Gottberg *et al* also found a significant association between EQ-5D-3L utility and severe MS (defined as EDSS 6-6.5), progressive course of MS and a disease duration >10 years in a population-based sample of 166 people with MS in Stockholm.[239] The

TRIBUNE study by Karmampampa *et al*, also described earlier in the context of CoI of MS, assessed EQ-5D-3L utility and reported results for mild (EDSS 0-3.5), moderate (EDSS 4.0-6.5) and severe (EDSS 7.0-9.5) MS subgroups. As with other studies, utility decreased with advancing disability (mild 0.78, moderate 0.57, severe 0.37) and no statistically significant differences in the mean utility scores were observed when comparing the results across countries. [134]

4.2.2 Generic Preference-based HRQoL Instruments

The practical application and psychometric properties of the EQ-5D-3L, HUI3 and the SF-6D, three generic measures of health utility, were evaluated by Fisk *et al* in a sample of 187 MS patients with a broad range of neurological disability. [240] The full range of utility was represented in the responses to both the HUI3 and the EQ-5D-3L, and both had a strong relationship with the clinical measures. However, the EQ- 5D was unable to distinguish mild from moderately impaired patients due in part to the higher proportion of ceiling effects in the EQ-5D-3L. For individual subscales of the SF-6D, floor effects were reported by 41% of subjects in physical function and 16% in role limitations. For the HUI3, ceiling effects were present in 3% of subjects for individual subscales and there were no floor effects on the subscales. The EQ-5D-3L and HUI3 demonstrated strong concordance with clinical measures of neurological disability. The same pattern was found for the SF-6D but evidence of construct validity was moderate, suggested by the authors to reflect the more limited decline in SF-6D utility with increasing disability. The authors concluded that all three measures were found to be generally feasible and reliable but the HUI3 demonstrated highest concordance with the EDSS across the full range of neurological disability. [240]

4.2.3 MS-specific Preference-based HRQoL Instruments

An MS-specific preference based measure, the MSIS-PBM has been generated from the Multiple Sclerosis Impact Scale 29 (MSIS-29).[241] The MSIS-29 is a MS-specific self-reported measure, which measures the physical and psychological impacts of MS on individuals. [242] Versteegh *et al* compared the MSIS-PBM with the EQ-5D-3L and found that the PBM was more sensitive than the EQ-5D-3L to very mild impairment and did not suffer from the ceiling effect found in the EQ-5D-3L questionnaire. [167] This was not surprising as the authors had previously shown that the physical scale of the MSIS-29 is

better capable of discriminating between subcategories of the EDSS than is the EQ-5D-3L. [241] The mean utility values of the MSIS-PBM were higher than those of the EQ-5D-3L and the MSIS-PBM showed better discriminative properties in EDSS subcategories. The authors state that the MSIS-PBM could make a contribution to CUA, however without convincing empirical evidence on the insensitivity of a generic instrument, the authors conclude that using a condition specific-PBM introduces confusion about the appropriate outcome measures in CUA and health-care decision making.[167]

4.2.4 Summary

Studies have consistently demonstrated a significant negative association between increasing MS disability and HRQoL utility. EQ-5D-3L has been used extensively in MS QoL research, however a potential ceiling effect has been identified and there may be issues regarding its ability to measure small changes in health. MS-specific, preference-based measures, which suggest greater sensitivity to MS-specific changes in health, appear to have potential but are in the early stages of development. There are no HRQoL in MS studies from Ireland. In Chapter 4, various methodologies for the elicitation of HRQoL utilities will be discussed and the application of specific methodologies in an Irish cohort will be described in Chapter 6.

4.3 Relative Efficacy of Disease-modifying Therapies in MS

The efficacy of various interferons and GA, compared with placebo, has been established in several placebo-controlled RCTs, briefly summarised in Chapter 2. In addition, several direct comparative studies have compared the relative efficacy of the various interferons and GA. [243-246] A number of systematic reviews and meta-analyses of DMTs for MS have been published, including both traditional pairwise meta-analysis and network meta-analyses (NMAs). The results of pairwise meta-analyses conducted by the Multiple Sclerosis Group of The Cochrane Collaboration are described here, in addition to all studies which employed indirect comparisons or NMA. Details of a selection of these reviews are summarised in Table 4.4a and 3.4b.

4.3.1 Cochrane Meta-Analyses

The Cochrane Collaboration is an internationally recognised independent, not-for-profit network with a core mission of producing systematic reviews of primary research in human health care and health policy. Cochrane meta-analyses of randomised, double-blind, placebo-controlled trials include "Interferon in relapsing-remitting multiple sclerosis" (2001, updated 2009) and "Glatiramer acetate for multiple sclerosis" (2004, updated 2010). [94 95] Randomised, double-blind controlled trials, not restricted to placebo controls, were included in reviews of "Natalizumab for relapsing remitting multiple sclerosis" (2010) and "Teriflunomide for multiple sclerosis" (2012). [247 248] The efficacy of other immunosuppressants azathioprine, methotrexate and mitoxantrone has also been reviewed by Cochrane in addition to the efficacy of IFN β in progressive forms of MS and the efficacy of both IFN β and GA for delaying conversion of the first demyelinating event to MS. [249] The first review of the Cochrane MS Group to employ NMA methods was published in 2013, entitled "Immunomodulators and immunosuppressants for multiple sclerosis: a network meta-analysis". [250] Pairwise meta-analyses were performed using a frequentist approach in addition to a NMA within a Bayesian framework. Randomised trials of DMTs for use in MS were included, without specification on blinding or controls.

4.3.1.1 Included Outcomes

All reviews included relapse-related and disability progression outcomes among their primary efficacy outcomes in addition to safety outcomes. Most of the reviews stated that definitions of relapse/progression given in the original studies were accepted. The Cochrane NMA disability progression outcome was defined as at least 1 point EDSS increase (or 0.5 point increase if baseline EDSS was ≥5.5), confirmed during two subsequent neurological examinations separated by an interval of at least *six months* free of attacks. However the authors accepted the definition of disability progression given in the original papers, which required an interval of just *three months* in over half of included studies.[250] The specific relapse-related outcome varied across reviews, from frequency of clinical relapses and number of patients relapse free (GA review), proportion of participants who experienced new relapses during the schedule treatment and follow-up period (IFN review), in two years (natalizumab review), or over 12, 24, or 36 months (NMA review), and ARR, mean number of confirmed relapses per patient adjusting for the duration of follow-up to annualise it (teriflunomide review). All reviews used the same primary disability related endpoint i.e. the proportion of patients free of disability progression as assessed by the EDSS, over various timeframes (24 or 36 months) (IFN and natalizumab reviews). Other disability related endpoints included in some reviews were mean change in disability score (EDSS) and time to progression in disability. The natalizumab and teriflunomide reviews also included MRI endpoints among their secondary outcomes. Safety outcomes focussed on the number of patients experiencing adverse events and withdrawals or dropouts due to adverse events.

4.3.1.2 Results of pairwise meta-analyses

The results of Cochrane pairwise meta-analyses are summarised in Table 4.4a. Six RCTs contribute to the GA review, including four in RRMS. [95] "Partial efficacy" was demonstrated for GA in RRMS in reducing the mean number of relapses without any significant effect on sustained disability. A "modest" effect on exacerbations (20% reduction in the relative risk) and disease progression in patients with RRMS was found for IFN two years after randomisation (31% reduction in relative risk). [94] The IFN review included eight trials but only 71% of participants contributed to the results due to incomplete reporting. The significance of the effect of progression disappears in sensitivity analysis in which dropouts are assumed to have progressed. The

natalizumab review found evidence of a reduction in the risk of relapse at two years by 30%-50% and of progression at two years by about 25%. [248] Meta-analysis of teriflunomide efficacy was not conducted because only two RCTs were eligible for inclusion, of which one included teriflunomide as an add-on to IFN β. [247] The authors of the IFN review found that the correct assignment of dropouts was essential to the demonstration of efficacy, particularly concerning the effect of the drug on disease progression. The authors concluded that most trials of IFN had major weaknesses, including high dropout rates and a failure to do an intention-to-treat analysis. A likelihood that patients could become unblinded during RCTs of IFN and GA was identified due to the well documented side effects of the treatments. In the pivotal RCT of IFN β-1b, 80% of patients in the high dose IFN β-1b arm, 51% in the low dose IFN β-1b arm and 30% in the placebo arm had correctly guessed their treatment at the end of follow up. [69] The duration of trials is also a limitation, as clinical efficacy of all DMTs beyond two years is uncertain.

4.3.1.3 Results of Network Meta-Analysis

The bayesian NMA by Filippini *et al* included 44 RCTs, mostly short-term trials with median duration of 24 months. In addition to estimating the relative efficacy of DMTs on risk of relapse and progression, the authors provide a ranking of treatments according to their effectiveness and risk-benefit balance, using the "Surface Under the Cumulative RAnking curve" (SUCRA). This measure is expressed as a percentage and shows the relative probability of a treatment being among the best options. [251] Thirty three RCTs related to RRMS. Trial arms involving different doses of the same agent (e.g. IFN β-1a SC 22mcg and 44mcg, both Rebif®) were converted into a single arm. Detailed results are outlined in Table 4.5. Mitoxantrone and other unlicensed medicines were included in this NMA. Mitoxantrone was found to be the most effective agent in reducing the risk of relapse at 24 months (OR 0.14, 95% C I 0.03 to 0.55; SUCRA = 92%) followed by natalizumab, IFN β-1a SC (Rebif®), IFN β-1b SC 250mcg (Betaferon®) and GA. Mitoxantrone was also the most effective in reducing the number of patients with disability progression at 24 months (OR 0.11, 95% CI 0.01 to 0.65; SUCRA = 96%), followed by GA (OR 0.52, 95% CI 0.28 to 0.88; SUCRA = 70%). On the basis of pairwise meta-analysis, the authors found Natalizumab and IFN β-1a SC (Rebif®) to be superior to all other treatment for preventing clinical relapses in

RRMS and disability progression in RRMS in the short-term (24 months) compared to placebo (high quality evidence). Natalizumab and GA showed a similar effect on disability progression over 24 months (median OR versus placebo 0.61, 95% CI 0.41 to 0.91; 0.67, 95% CI 0.49 to 0.88, respectively) Moderate quality data support the efficacy of IFN β-1b and GA for preventing relapse and disability progression in RRMS in the short-term, but a lack of convincing efficacy data showed that IFN β-1a IM has an unfavourable benefit-risk balance in RRMS. Given that all treatments are associated with long-term serious adverse events it was stated that their benefit-risk balance might be unfavourable. A dose-effect relationship was not found for any of these treatments. All agents were associated with a statistically significant higher rate of withdrawals due to adverse events, but there was no difference between DMTs. All agents were associated with a non-significantly higher rate of total serious adverse events compared with the control treatment during a median two years' follow-up period. Confirmation of disability progression at three months was used in the majority of studies included in the Filippini NMA. The authors attach a high risk of bias to this definition criterion as it may result in patients who recover slowly from relapses being regarded as having unremitting disability progression. Short duration trials and poor reporting of adverse events were identified as major limitations in determining the overall balance between benefits and risks of the included treatments. [250] Filipini *et al* recommend that safety data from observational and registry studies need to be considered for medium and long-term serious adverse events associated with these treatments.

4.3.2 Other Indirect Comparisons and Network Meta-Analyses

The results of indirect comparisons and NMAs of treatments for RRMS are summarised in Table 4.4b and 3.5. Roskell *et al* conducted a systematic review and NMA (termed a mixed treatment comparison in this study) to compare ARRs of the beta interferons, GA, and fingolimod using data from 14 placebo-controlled and head-to-head comparative trials in RRMS. [252] A significant reduction in relapse frequency with fingolimod compared with other DMTs was found. Disability progression was not included as an outcome. Natalizumab was not included in this study as the authors state that natalizumab is generally recommended for patients who have an inadequate response to, or are unable to tolerate, alternative DMT. All active treatments were statistically superior to placebo and fingolimod was found to be statistically superior to

all comparators for the ARR outcome with relative rate reductions ranging from 30.1% versus GA to 48.2% versus IFN β-1a IM 30mcg. Covariate analysis showed baseline EDSS score and year of publication to be statistically significant covariates, but repeat analysis adjusting for these covariates made no material difference.

Tappenden *et al* explored the impact of synthesising evidence using an NMA model (termed a mixed treatment comparison in this study) in place of placebo-controlled RCT results, in their economic evaluation of IFN β and GA for RRMS and SPMS for the Medicare population in the US in 2006. [236] Two head-to-head trials were added to the evidence base of placebo-controlled RCTs for the NMA analysis. The authors recommend that the NMA estimates should be interpreted "tentatively" due to both known and unknown heterogeneities between trials and differences in definitions of sustained progression (increases in EDSS score sustained for 3-months and 6-months were both accepted). Incorporation of head-to-head trials had a substantial impact on the relative hazard ratio for progression. Both IFN β-1a SC 44μg and IFN β-1b SC 250mcg were found to be more effective in slowing progression than IFN β-1a IM 30mcg. In general, NMA estimates of the effectiveness of IFN β-1a SC 44μg were broadly consistent with the placebo-controlled data, estimates for IFN β-1b SC 250mcg were favourable, and estimates for IFN β-1a IM 30mcg were substantially reduced. Relapse rates from the NMA were very similar to those obtained from the basecase analysis. Particular concern was raised over the lack of an intention-to-treat estimate of the efficacy of IFN β-1a IM 30mcg compared with placebo, as the published estimate is based on an analysis of data only for patients who finished two years in the trial as it was stopped early at this point.

An NMA of 109 trials including 145 treatments for relapsing MS was performed by Zintzaras *et al* in 2012. [253] Most of the included treatments are unlicensed for use in MS. Outcomes included proportions of patients who were relapse-free, without disease progression, or without magnetic resonance imaging progression. Natalizumab and fingolimod showed a better response than placebo for all three efficacy outcomes while alemtuzumab had a better response than IFN β-1b (the chosen reference treatment) for the relapse-free patients and disease progression outcomes.

Smith *et al*, from the Oregon Health & Science University Oregon, conducted a review on disease-modifying drugs for MS on behalf of the Canadian Agency for Drugs and Technology in Health and other Medicaid agencies. [254] As part of the review the authors conducted an "exploratory Bayesian analysis" to compare the efficacies of

DMTs for which there were no head-to-head comparisons and where there was a common comparator intervention across studies. This approach did not allow comparison of treatments across a network which did not have a common comparator. The authors used the adjusted indirect analysis of the placebo-controlled trials as the "prior" assumptions and the direct evidence from head-to head trials as the primary evidence. Both IFN β-1a SC and IFN β-1b SC were superior to IFN β-1a IM in percent relapse-free, and IFN β-1b SC was superior to IFN β-1a IM in progression rates.

4.3.3 Conclusions on the Relative Efficacy of DMT in MS

The existing evidence on the relative efficacy of DMTs for RRMS has been synthesised largely using traditional pairwise meta-analysis. Analyses have focussed on relapse and disability progression as the main clinical hallmarks of the disease. Overall, comparisons with placebo have shown "modest" efficacy for IFN β and GA in the prevention of relapses (reduction in relapse rate in the range 20%-30%) with minimal impact on the progression of disability. Deficiencies in the conduct of the pivotal RCTs include the integrity of blinding and the dropout rate. A limited number of NMAs have been published. The Cochrane NMA found that natalizumab and IFN β-1a SC were superior to other treatments, however most reviews have found little differences between therapies, possibly with the exception of IFN β-1a IM which may be less efficacious than other interferons and GA.

The evidence-base is limited by the lack of comparative studies between all DMTs of interest, and by the short duration of RCTs which provide little insight into the efficacy of these agents in the long-term. Of those studies that have employed NMA methods, not all outcomes of interest have been selected or relevant comparators have been omitted. The Cochrane NMA by Filippini *et al* was comprehensive in its approach but is outdated, despite its publication in 2013 as fingolimod, teriflunomide and other new oral therapies are not included. In Chapter 4, bayesian NMA methodology will be described. The application of this methodology in the estimation of the relative efficacy of all DMTs of interest will be described in Chapter 7.

Table 4.4a: Summary of Cochrane Pairwise Meta-analyses of DMT for RRMS

Author, Year	Intervention, Population	Primary relapse and disability Outcomes	Results *(versus placebo)*	Conclusions
Rice, 2001 (updated 2009) *Cochrane*	Interferons *(all* alfa- or beta-recombinant interferons), MS	number of patients who continued to experience exacerbations during the scheduled treatment period and the follow-up period	RR of relapse during the first year of treatment: 0.73, 95% CI 0.55 to 0.97, p = 0.03 RR during the first 2 years of treatment:0.80, 95% CI 0.73 to 0.88, p < 0.001. Worst-case scenario (all dropouts deemed to have progressed) RR 1.11, 95% CI 0.73 to 1.68, p = 0.6.	The efficacy of IFN on exacerbations and disease progression in patients with relapsing remitting MS was modest after one and two years of treatment. Longer follow-up and more uniform reporting of clinical and MRI outcomes among these trials might have allowed for a more convincing conclusion.
		number of patients who progressed during the first two years of treatment.	RR of progression during the first 2 years of treatment RR 0.69, 95% CI 0.55 to 0.87, p = 0.002. Worst-case scenario (all dropouts deemed to have progressed) RR 1.31, 95% CI 0.60 to 2.89, p =0.5	
		mean change in disability score (EDSS) in treatment groups at the end of the follow-up period	weighted mean difference in disability score (EDSS) at 2 years = -0.25, 95% CI -0.05 to -0.46, p = 0.01 *(questionable clinical significance as impossible to measure this very low degree of EDSS change in clinical practice)*	
		the number of patients who were unable to walk without aid (EDSS greater than 5.5) at the end of the follow-up period	No data available	

Table 4.4a Summary of Cochrane Pairwise Meta-analyses of DMT for RRMS Continued

Author, Year	Intervention, Population	Primary relapse and disability Outcomes	Results *(versus placebo)*	Conclusions
La Mantia, 2004 (updated 2009) *Cochrane*	GA, MS	Patients who progressed	Risk of progression: 0.75 (95% CI 0.51 to 1.12, p=0.16) at 2 years, and 0.81 (95% CI 0.50 to 1.29) at 35 months	No significant effect on clinical progression of disease measured as sustained disability.
		Mean changes in EDSS disability score.	Results of change in disability score could not be combined	Partial efficacy in RRMS in term of relapse-related clinical outcomes
		Number of patients relapse free	RR of experiencing no exacerbation were: 1.28 (95% CI 1.02 to 1.62, p= 0.03) within 1 year of treatment, and 1.39 (95%C I 0.99 to 1.94 , p=0-06) at 2 years, and 1.33 (95% CI 0.86 to 2.06) at 35 months	
			Results of relapse-free survival could not be combined	
		Number of patients relapse free over time	A significant reduction in relapses at 1 year (-0.35) at 2 years (-0.51) and at 35 months (-0.64) however significant heterogeneity between studies	
		Frequency of clinical relapses		
Pucci *et al*, 2011 *Cochrane*	Natalizumab, RRMS	Number of patients experiencing at least one relapse at 2 years	RR of at least one relapse during 2 years of treatment versus control group not receiving natalizumab 0.57 (95% CI 0.47 to 0.69)	Robust evidence in favour of a reduction in relapses and disability at 2 years in RRMS patients treated with natalizumab. Well tolerated.
		Number of patients who progressed at 2 years.	RR of progression at 2 years versus control group not receiving natalizumab 0.74 (95%CI 0.62 to 0.89),	Significant safety concerns due to reporting of an increasing number of PML cases

Table 4.4b: Summary of Network meta-analyses of DMT for RRMS

Author, Year	Intervention, Population	Primary relapse and disability Outcomes	Results	Conclusions
Filippini *et al*, 2013 *Cochrane*	Natalizumab IFN ß-1a (Rebif) GA IFN ß-1b (Betaseron) IFN ß-1a (Avonex), MS	proportion of participants who experienced new relapses over 12, 24, or 36 months after randomisation or at the end of the study. proportion of participants who experienced disability progression over 24 or 36 months after randomisation or at the end of the study.	Results (in table 4.5 below)	Natalizumab and IFN ß-1a (Rebif) superior to other treatments for preventing clinical relapses and disability progression in RRMS in the short-term (24months) vs placebo. (high quality evidence) Moderate quality data support the efficacy of IFN ß-1b (Betaseron), GA, for preventing relapse and disability progression in RRMS in the short-term. A lack of convincing efficacy data showed that IFN ß-1a (Avonex) has an unfavourable benefit-risk balance in RRMS All treatments are associated with long-term serious adverse events and their benefit-risk balance might be unfavourable.
Roskell *et al*, 2012	Fingolimod 0.5mg, IFN β -1a, IFN β -1b, GA	ARR	Relative ARR (95% CI) vs fingolimod: GA: 1.43 (1.16 to 1.77) IFN β-1b: 1.51 (1.22 to 1.86) IFN β-1a 44: 1.55 (1.26 to 1.90), IFN β-1a 22: 1.67 (1.32 to 2.10), IFN β-1a 30: 1.93 (1.59 to 2.34) Placebo: 2.32 (1.95 to 2.77).	All active treatments were statistically superior to placebo Fingolimod was statistically superior to all comparators

Table 4.4b Summary of Network meta-analyses of DMT for RRMS Continued

Author, Year	Intervention, Population	Primary relapse and disability Outcomes	Results	Conclusions
Smith *et al*, 2010 (only results of NMA model presented here)	IFN β -1a IFN β -1b GA Natalizumab	Multiple effectiveness outcomes including disability, relapse	RR (95% CI) of progression: IFN β -1b vs IFN β -1a SC 22mcg; 1.18 (0.80 to 1.71) IFN β -1b vs. IFN β -1a IM; 0.48 (0.27 to 0.86) IFN β -1a SC 22mcg vs. IFN β -1a IM 1.05 (0.93 to 1.22) EDSS change (weighted mean difference): IFN β -1b vs IFN β -1a SC 22mcg; −0.30 (−0.60 to +0.015) RR (95% CI) of relapse free: IFN β -1b vs IFN β -1a SC 22mcg: 0.85 (0.56 to 1.25) IFN β -1b vs. IFN β -1a IM; 1.48 (1.11 to 2.02) IFN β -1a SC 22mcg vs. IFN β -1a IM: 1.22 (1.06 to 1.41)	Both IFN β -1a SC (Rebif®) and IFN β -1b SC (Betaferon®) were superior to IFN β -1a IM (Avonex®) in percent relapse-free, and IFN β -1b SC IFN β -1b was superior to IFN β -1a IM (Avonex®) in progression rates

Table 4.4b Summary of Network meta-analyses of DMT for RRMS Continued

Author, Year	Intervention, Population	Primary relapse and disability Outcomes	Results	Conclusions
Tappenden *et al*, 2009 (only results of NMA model presented here)	IFN β-1a 6 MIU IFN β-1a 22 mg IFN β-1a 44 mg IFN β-1b 8 MIU GA 20 mg.	sustained disease progression risk of relapse (estimated from ARR)	Relative hazard (SE) for progression vs placebo: GA 20 mg. 0.86 (0.23) IFN β-1a 6 MIU 0.79 (0.12) IFN β-1b 8 MIU 0.52 (0.09) IFN β-1a 22 mg, 0.72 (0.19) IFN β-1a 44 mg 0.70 (0.11) Relative relapse rate (SE) vs placebo: GA 20 mg. 0.70 (0.11) IFN β–1a 6 MIU 0.83 (0.07) IFN β–1b 8 MIU 0.66 (0.07) IFN β–1a 22 mg, 0.71 (0.08) IFN β–1a 44 mg 0.68 (0.05)	NMA estimates of the effectiveness of IFNβ-1b 8MIU appear to be more favourable than those obtained from the analysis of the placebo-controlled trial data. By contrast, the head-to-head trials suggest that the placebo-controlled data for 6MIU IFNβ-1a result in an overestimate of its true effect on progression Heterogeneities between the trials mean that the results of this analysis should be approached with caution.

Results from non-RRMS patient populations and immunomodulators which are not of interest (Mitoxantrone, Immunoglobulins, Azathioprine, Corticosteroids) are excluded from the summary in Table 4.4a and b
IFN β = interferon beta. GA=glatiramer acetate. RRMS: Relapsing Remitting Multiple Sclerosis; RR=relative risk. SE=standard error. ARR: Annualised Relapse Rate; Median OR: Median Posterior Odds Ratio. CI:Confidence Interval

Table 4.5: Summary of Filipini NMA results of all active interventions versus placebo for patients with RRMS

Treatment	Recurrence of relapses over 12 months		Recurrence of relapses over 24 months		Disability progression over 24 months	
	Median OR (95%CrI)	SUCRA	Median OR (95%CrI)	SUCRA	Median OR (95%CrI)	SUCRA
Mitoxantrone	0.13 (0.01 to 1.32)	85%	0.14 (0.03 to 0.55)	92%	0.11 (0.01 to 0.65)	96%
Natalizumab	0.35 (0.07 to 1.67)	65%	0.31 (0.19 to 0.55)	75%	0.62 (0.33 to 1.24)	55%
Immunoglobulins	0.36 (0.08 to 1.28)	63%	0.34 (0.13 to 0.69)	70%	0.63 (0.24 to 1.67)	52%
Azathioprine	0.76 (0.08 to 7.40)	36%	0.34 (0.08 to 1.30)	65%	0.51 (0.13 to 1.95)	61%
IFN β-1a (Rebif®)	0.65 (0.19 to 2.29)	46%	0.46 (0.25 to 0.71)	53%	0.74 (0.40 to 1.32)	40%
GA	0.36 (0.07 to 1.54)	63%	0.50 (0.29 to 0.71)	46%	0.52 (0.28 to 0.88)	70%
IFN β-1b (Betaferon®)	0.54 (0.09 to 3.33)	47%	0.50 (0.31 to 0.82)	45%	0.67 (0.38 to 1.13)	50%
Corticosteroids	0.44 (0.04 to 4.86)	54%	1.17 (0.02 to 50.83)	31%	-	-
IFN β-1a (Avonex®)	0.81 (0.23 to 2.90)	29%	1.10 (0.69 to 1.82)	10%	1.11 (0.64 to 2.16)	10%

IFN β = interferon beta. GA=glatiramer acetate. RRMS: Relapsing Remitting Multiple Sclerosis; Median OR: Median Posterior Odds Ratio. CrI: Credible Intervals. SUCRA: Surface below the Cumulative Ranking Curve (The larger the SUCRA value for a treatment, the higher its rank among the available treatment options).

4.4 Cost effectiveness of Disease-modifying Therapies in RRMS

In the era prior to the widespread use of "personalised" therapies such as monoclonal antibodies, IFN β and GA were among the mostly costly drugs available in Ireland, reimbursed under the high-tech drug scheme. Their high cost likely stimulated early research on the cost effectiveness of these agents, and MS has become a widely studied disease area in cost effectiveness research. A further potential stimulus for such research was the HTA of IFN β and GA conducted by NICE in 2002. [255] Although NICE issued negative guidance on the use of these agents, the Department of Health in the UK agreed a "risk-sharing scheme" which would see the drugs funded on condition that their effect on disease progression was monitored in a cohort of patients for ten years. Eleven years on, this scheme has still not concluded, and the question of the cost effectiveness of these agents continues to be the subject of research. In the following sections, the existing research on the cost effectiveness of DMTs for MS is summarised with particular emphasis on the decision-analytic modelling approach taken, the application of treatment-effects, the estimation of natural history progression and relapse rates, and study results.

4.4.1 Setting and General Characteristics of published Cost effectiveness analyses

Numerous CEAs have estimated the cost effectiveness of DMT for the treatment of MS since the introduction of IFN β-1b in 1993. A large proportion of the studies were based on US or UK data, with all but one UK study published prior to 2002, and all but one USA study published after 2005, reflecting the growing interest in CEA in the USA over the last decade. [48-55 210 231 232 256-260] The majority of studies adopt a societal base case. Six studies included natalizumab [54 232 257 261-263] and three included fingolimod. [56 256 263] Just one study included both natalizumab and fingolimod. [263] No study included all currently approved DMTs as comparators.

4.4.2 Decision-analytic modelling approach

The majority of the studies used cohort simulation Markov models. One study was implemented as a discrete-event simulation while another was a retrospective

multivariate cohort analysis. [259] [264] Since the publication of the model for RRMS by Chilcott *et al* in 2003 (which was developed for the original NICE HTA of IFN β and GA), subsequent CEAs have invariably used the same modelling approach. [231] This approach is graphically outlined in Figure 4.3. The model is based on a state transition matrix simulating the natural history of MS disease. Each health state represents a level of disability defined by an EDSS score, using either the full scale (0.0, 0.5…9.5, 10.0) or aggregate scores (0, 1…9, 10). Patients enter the health states of the model and experience progressive disability to more severe health states based on transition probabilities. Backwards transitions are typically not allowed. Separate health states may be included for patients at the same EDSS level but with different types of disease i.e RRMS or SPMS. Costs, utilities and risk of relapse are applied to each cycle in each individual EDSS health state. Cycle length varies from one month to three years and during each cycle patients are at risk of progression, treatment discontinuation or death from background or MS-related mortality. [234] [265] DMT treatment-effects may be applied to slow the rate of progression through the EDSS health states, and reduce the risk of relapse or death.

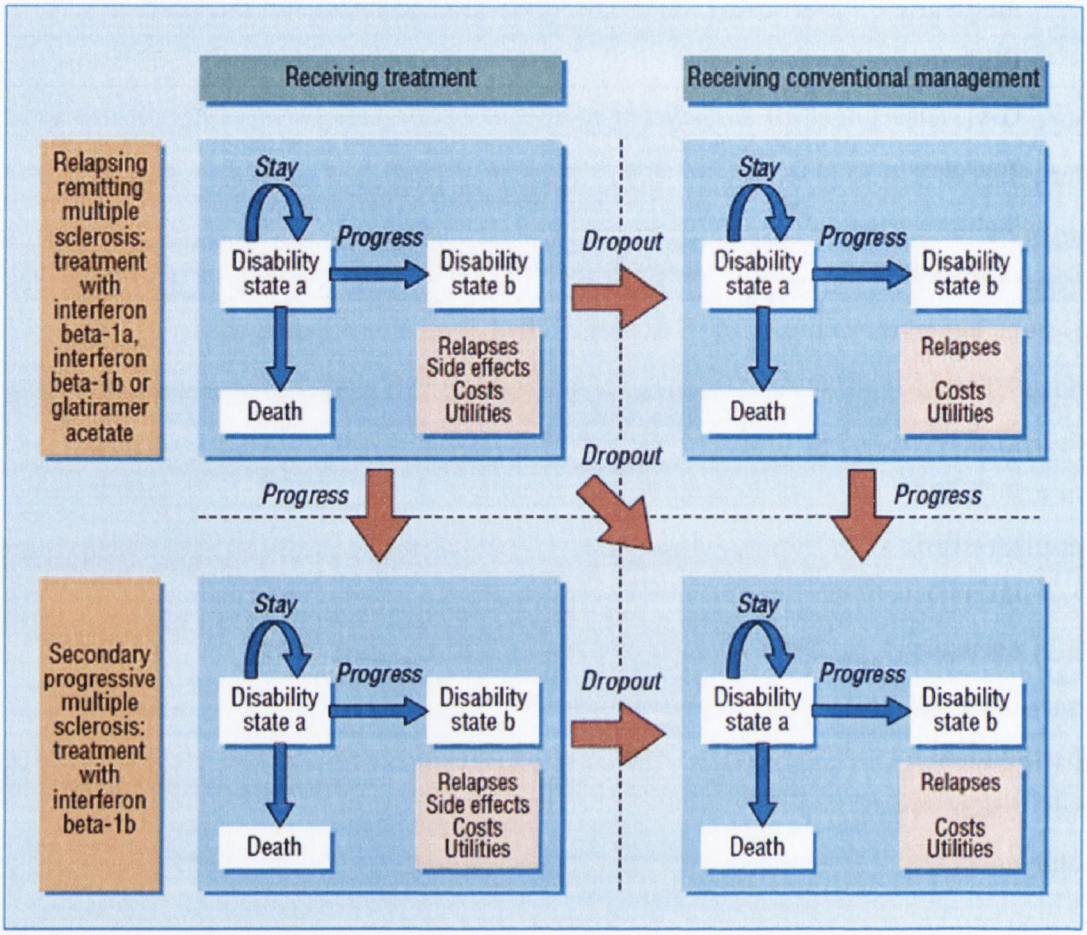


Figure 4.3: Schematic of Chilcott *et al* cost effectiveness model

Reproduced from BMJ, Chilcott *et al*;326:522-525 ©2003, with permission from BMJ Publishing Group Ltd[231]

4.4.3 Application of treatment-effects

Most CEAs applied treatment-effects to both relapse rate and disability progression, and included the QALY as the primary outcome of effect. Studies with shorter time horizons were more likely to include relapses-avoided as the primary outcome. The general approach has been to derive treatment-effects from placebo-controlled RCTs or extension studies. These effects are then applied to baseline rates of relapse or progression, variously termed best supportive care (BSC) or no treatment, using evidence on the natural history of disease from observational cohort studies. Under this approach, assumptions must be made regarding the longevity of treatment-effects and the similarity of RCT populations to the observational cohort. Earnshaw *et al* applied RCT efficacy estimates for the first two years of their lifetime horizon model and

prediction curves were derived from prospective extension studies and long-term follow-up to estimate changes in efficacy over subsequent years. [54] An alternative approach by Kobelt *et al* utilised effectiveness data from individual patients in the Swedish MS registry for two CEAs in Sweden and in France, while Noyes *et al* used data from a longitudinal MS Survey, the 2000–2005 Sonya Slifka Longitudinal Multiple Sclerosis study, to simulate disease progression paths for an MS cohort on and off treatment. [235 262 266] As an alternative to using placebo-controlled RCT efficacy estimates, Tappenden *et al* synthesised data from both placebo-controlled and head-to-head trials using MTC methods in a CEA of IFN β and GA. [267]

4.4.4 Natural history of MS relapse and disability progression

Historical MS registries provide valuable insights into the rate of disability progression, the factors which influence accumulation of disability MS and changes in mortality. The longitudinal dataset of patients with MS from the LO MS clinic in Canada has been the most widely used source of natural history of progression data in CEAs. [268] The observation period for the LO database began in 1972 and ended in 2000, with much of the data collected before the widespread use of DMTs. The shortest follow-up was 16 years. [29] Individual patient-level data from this dataset was obtained by Chilcott *et al* for their IFN β and GA model for NICE, by Tappenden *et al* for a model commissioned by AHRQ in the US, and also by the manufacturers of natalizumab and fingolimod for subsequent submissions to the NCPE and NICE. [49-51 233 236 255] In 2004, Prosser *et al* were the first authors to use published data from the LO study to estimate transition probabilities for BSC arm of a CEA. [265] Median time from disease onset to DSS 3, 6, 8 and 10 were used to derive transition probabilities for progression to the next level of disability from EDSS 0-2.5, EDSS 3-5.5, EDSS 6-7.5 and EDSS 8-9.5, respectively. The data on which the Prosser *et al* estimates were based were obtained from studies published in 1989 and 1993, and were based on patients followed up between 1972 and 1984. [37 39] Many subsequent CEAs published since 2004 have used the transition probabilities estimated by Prosser *et al*. [52-56] Kobelt *et al*, in a CEA of DMT in France, estimated BSC disease progression from individual data from patients followed in the Lyon cohort of EDMUS (European Database for Multiple Sclerosis) (n=1562). Kobelt *et al* chose the EDMUS cohort in preference to the older LO cohort as they suggest that there are indications that the disease may have changed over time. [269] The natalizumab

manufacturer's submission to NICE incorporated data from both the placebo arm of the AFFIRM trial and the LO cohort to inform progression between EDSS states. In keeping with the trial data, both backward and forward transitions between EDSS health states were allowed. [48]

Data for the LO cohort were collected under the assumption that patients could only show a decline in disability (i.e. no improvement in EDSS score was allowed). After initial analysis of data from the UK MS risk-sharing scheme, patients were found to commonly show improvements in disability from one year to the next. As a result, the study co-ordinators decided to change from the LO natural history dataset to a different natural history comparator, the British Columbia MS Dataset, in which patients' disease can get better or worse from year to year, as with the Risk-sharing Scheme. Additional analysis using this comparator have not been published. As Tappenden *et al* surmise in their CEA for AHRQ, it is unclear whether observed improvements in disability are "noise", due to misspecification of initial or subsequent disability, or variations in patients' attitudes to their underlying level of functioning. [236] Improvements in disability have typically not been considered in the majority of clinical trials, although the advent of therapies such as alemtuzumab may dictate changes in future study design. In the CARE MS II RCT, patients on alemtuzumab were more likely to improve from baseline than worsen or remain stable.[111] Most models have based probabilities of relapse on data from pivotal trials of DMTs although some have used various prospective studies to estimate relapse rates. [52 235 259 262]

In general, the relevance of historical cohorts to current standard of care, given improvements in disease management over time, is uncertain. The application of progression rates from specific settings to cohorts in other countries may also be an issue. However, given the widespread use of DMTs, the existence of a current untreated cohort from which to derive relapse and progression rates which are reflective of current natural history, is highly unlikely. Even for studies with shorter time horizons, the continued availability of data from placebo arms from RCTs is in question, given the questionable ethics of conducting placebo-controlled trials in MS given the availability of treatments with proven efficacy. [270]

4.4.5 Time horizon

Time horizons of greater than ten years have been adopted in most studies, and those with shorter horizons have typically included relapses avoided as the health outcome. [55] [234] [256-259] Long time horizons are appropriate when modelling a chronic disease such as MS but difficulties arise from the lack of RCT efficacy data beyond two years and the scarcity of direct comparative trials. In studies reporting relapses avoided as an outcome, time horizons of two to four years have been used. [55] [234] [258] [259] [261] [263] Yamamoto *et al* suggest that short-term time horizons reflect the average insured time horizons for the populations of US insurers and are thus of interest from their perspective. [271] Of the existing studies which include fingolimod only one looked at the QALY as an outcome, adopting a ten year time horizon.[56]

4.4.6 Comparison of CEA Results

A summary of methods and results from various CEAs discussed in this section is presented in Table 4.6.

Table 4. 6: Summary of the CEAs of disease-modifying therapies in RRMS

Study / Base year	Country	Population	Time horizon	Perspective	DMT	Health outcome	Base-case ICER (vs no treatment unless otherwise specified)	Sensitivity Analysis: Drivers of ICER
NCPE and NICE Assessments								
NICE / 2012 [51]	UK	Highly active RRMS	50 yrs	Payer	**Fingolimod**, IM IFNβ-1a	QALY	£55,634 per QALY	• Relative risks of disease progression of DMT • Relative risk of relapse for IFNβ-1a
NCPE / 2011 [49]	Ireland	Highly active RRMS			**Fingolimod**, IM IFNβ-1a, NAT	QALY	• €87,814 to €99,523/ per QALY (IM IFNβ-1a) • €55,492 savings per QALY lost (NAT)	• Fingolimod price • Fingolimod relative risk of progression
NCPE / 2007 [50]	Ireland	Highly active RRMS: RES and SOT	20 yrs	Societal	**NAT**, IFN β, GA	QALY	• RES: NAT dominant(IFN β and GA) • SOT: €4,400 per QALY (IFN β), dominant (GA)	Time horizon
NICE / 2007 [48]	UK	Highly active RRMS (RES and SOT)	20 yrs	Payer	**NAT,** IFN β, GA	QALY	RES: £44,600 (IFN β), £32,000 (GA) £34,600 (BSC) per QALY SOT:£56,100 (IFN β) (£43,400 (GA) £44,300 (BSC) per QALY	Time horizon
NICE / 2002 [255]	UK	RRMS	20 yrs	Payer	**IM IFNβ-1a, SC IFNβ-1a, SC IFNβ-1b, GA**	QALY	• £106,150 (IM IFNβ-1a) • £58,859 (SC IFNβ-1a 22mcg) • £78,556 (SC IFNβ-1a 44mcg) • £38,782 (SC IFNβ-1b) • £97,690 (GA) per QALY	• Use of equal discounting for costs and benefits • Dropout rate
Other Published CEAs								
Agashivala *et al* / 2012 [256]	US	RRMS	2 yrs	Payer	**Fingolimod** (early and late initiation) IM IFNβ-1a	relapse avoided	• $83,125 (early initiation) • $103,624 (late initiation) per relapse avoided	• drug cost, • baseline relapse rates • fingolimod efficacy

Table 4. 6: Summary of the CEAs of disease-modifying therapies in RRMS Contd.

Study / Base year	Country	Population	Time horizon	Perspective	DMT	Health outcome	Base-case result (versus no treatment unless otherwise specified)	Sensitivity of Results
Pan *et al* / 2011	US	RRMS	Lifetime	Societal	**IFNβ-1b**	QALY	US $46,357 per QALY	• time horizon • early treatment
Lee *et al* / 2011 [272]	US	RRMS	10 yrs	Societal	**Fingolimod** IFNβ-1a IM	QALY, relapse avoided	• $73,975 per QALY, • $18,799 per relapse avoided	disutility of IFN use
Dembek *et al* / 2010 [53]	Spain	RRMS	30 yrs	Societal	IM IFNβ-1a, SC IFNβ-1a, SC IFNβ-1b, GA	QALY	• €168,629 (IM IFNβ-1a), • €231,853 (IFNβ-1b), • €295,638 (SC IFNβ-1b) • €318,818 (GA) per QALY	• DMT cost • utility values • treatment-effect
Sanchez de la Rosa *et al* / 2010 [260]	Spain	RRMS	10 yrs	Societal	**IM IFNβ-1a**, SC IFNβ-1a, SC IFNβ-1b, GA	QALY	• Dominant (SC IFNβ-1a) • Dominant (SC IFNβ-1b) • €117,914 (GA) per QALY	• incidence of neutralising antibodies • time horizon
Bakshai *et al* /not reported[257]	US	RRMS	2 yrs	Payer	**NAT**, IM IFNβ-1a, SC IFNβ-1a, SC IFNβ-1b, GA	relapse avoided	• $23,029 (**IM IFNβ-1a**), • $24,452 (SC **IFNβ-1b**), • $20,671 (GA), • $20,403 (SC **IFNβ-1a**) per relapse avoided	• relative reduction in relapse rate • baseline relapse rate
O'Day *et al* / 2010 [263]	US	RRMS	2 yrs	Payer	**NAT, fingolimod**	Cost per relapse avoided	• US$117,164 (NAT) • US $168,754 (fingolimod) per relapse avoided	willingness-to-pay threshold
Goldberg *et al* / 2008[55]	US	RRMS	2 yrs	Payer	**IM IFNβ-1a, SC IFNβ-1a, SC IFNβ-1b, GA**	Cost per relapse avoided	• US$81,000 (SC IFNβ−1a) • US $142,000 (**IM** IFNβ-1a) per relapse avoided	• Baseline relapse rate, treatment efficacy, compliance
Nuijten and Mittendorf / 2008[234]	Germany	RRMS	4 yrs	Societal	**IM IFNβ-1a, SC IFNβ-1a, SC IFNβ-1b, GA**	Cost per relapse avoided	• €51,000 (SC IFNβ-1a) • €134,000 (**IM** IFNβ-1a) per relapse avoided	treatment efficacy
Becker and Dembeck / 2008[258]	US	RRMS	2 yrs	Payer	**IM IFNβ-1a, SC IFNβ-1a, SC IFNβ-1b, GA**	Cost per relapse avoided	• US$78,000 (IM IFNβ−1a) • US$88,000 (GA) per relapse avoided	None
Earnshaw *et al* / 2007[54]	US	RRMS	lifetime	Societal	**GA,** **NAT**	QALY	• US$496,222 (GA) • US $606,228 (NAT) per QALY	time horizon, baseline disease progression drug costs treatment efficacy, compliance
Kobelt *et al* 2007 [269]	France	RRMS, SPMS	20 yrs	Societal	**IFNβ and GA**	QALY	€16,000 per QALY	Lower ICER if all patients start at EDSS 1-3

Table 4. 6: Summary of the CEAs of disease-modifying therapies in RRMS Contd.

Study / Base year	Country	Population	Time horizon	Perspective	DMT	Health outcome	Base-case result (versus no treatment unless otherwise specified)	Sensitivity of Results
Gani *et al* / 2006[232]	UK	Highly active RRMS	30 yrs	Societal	**NAT**, GA, IFNβ	QALY for NAT	• £2,000 (GA) • £2300 (IFN β) • £8,200 (BSC) per QALY	time horizon
Guo *et al* / 2006[259]	US	RRMS	4 yrs	Payer	**High-dose SC IFNβ-1a, low-dose IM IFNβ-1a**	Cost per relapse prevented; cost per relapse-free day gained	• US$11,000 (SC IFNβ−1a) per relapse avoided • US $232 (IM IFNβ-1a)per relapse-free day	• treatment efficacy, • time horizon, • drug costs
Noyes *et al* / 2005[235]	US	RRMS, SPMS	10 yrs	Societal	**IM IFNβ-1a, SC IFNβ-1a, SC IFNβ-1b, GA**	QALY	• US$901,000 (IM IFNβ−1a • US$2,179,000 (GA) per QALY	• drug cost, • early treatment initiation
Tappenden *et al* / 2005[267]	US	RRMS, SPMS	50 yrs	Payer	**IFNβ-1a, IFNβ-1b**	QALY	• US$104,000 (SC IFNβ−1a) • US $312,000 (IFNβ-1b) per QALY	• excluding head-to-head trials • stopping treatment at an EDSS score of 7 • including nursing home costs
Bell *et al* / 2005[52]	US	RRMS	lifetime	Societal	**IM IFNβ-1a, SC IFNβ-1a, SC IFNβ-1b, GA**	QALY	• US$258,000 (GA) • US $416,000 (SC • IFNβ-1a) per QALY	• baseline disease progression • health state utilities • treatment costs • time horizon
Kobelt *et al* / 2005[262]	Sweden	RRMS, SPMS	20 yrs	Societal	**NAT**, mixture of currently prescribed DMTs	QALY	Dominant	time horizon
Chilcott *et al* / 2001[231]	UK	RRMS, SPMS	20 yrs	Healthcare system	**IFNβ-1a, IFNβ-1b, GA**	QALY	£42,000 to 98,000 per QALY.	• time horizon, • incorporating disability progression after stopping treatment • drug cost
Phillips *et al* / 1999[273]	UK	RRMS	10 and 20 yrs	Societal	**IFNβ-1b**	QALY	£8,000 per QALY.	Baseline and treated progression rates

Table 4. 6: Summary of the CEAs of disease-modifying therapies in RRMS Contd.

Study / Base year	Country	Population	Time horizon	Perspective	DMT	Health outcome	Base-case result (versus no treatment unless otherwise specified)	Sensitivity of Results
Prosser *et al* /1999 [265]	US	RRMS, SPMS	10 yrs	Societal	**IFNβ-1a, IFNβ-1b, GA**	QALY	US$1,838,000 per QALY (men taking IFNβ-1a) to dominated (IFNβ-1b, GA)	• Shorter treatment duration • earlier treatment • baseline disease progression • drug costs
Nuijten and Hutton / 1998[274]	UK	Initial RRMS	Lifetime	Payer	**IFNβ-1b**	QALY	£52,000 per QALY	• Inclusion of relapses, drug cost, disability progression rate

Non-NCPE/NICE CEAs pre-2010 extracted and adapted from Thompson *et al.* [275]
Abbreviations: NAb neutralizing antibody; NAT natalizumab; QALY= Quality adjusted life year. IFNβ= interferon beta; GA= Glatiramer acetate; UK= United Kingdom; US= United States; ICER= Incremental cost effectiveness ratio US=United States; QALY= Quality adjusted life year; RRMS=Relapsing remitting multiple sclerosis; SPMS=Secondary progressive multiple sclerosis; RES=Rapidly evolving severe; SOT=Suboptimally treated

4.4.6.1 Studies Including IFN β and GA

Individual studies have yielded very wide-ranging estimates of cost effectiveness for the same DMT. For example, Phillips *et al* reported an ICER of £22,800 per QALY gained for IFN β-1b in 1999, compared with an ICER of £228,300 per QALY gained reported by Parkin *et al* in 1997. [276] [273] Both were UK-based and used a societal perspective and a 10 year time horizon. Lower ICERs in the Phillips study are a result of assumptions regarding DMT efficacy on the severity and length of relapses, in addition to rate of relapses. The first US-based CEA was published by Prosser *et al* in 2004 and estimated ICERs of approximately $2 million per QALY gained for IFN β-1a over a ten-year time horizon. [265] IFN β-1b was dominated by no treatment (i.e. less effective and more costly) and GA was ruled out through extended dominance (i.e. lower cost than IFN β-1b but higher ICER). A subsequent US study by Bell *et al* in 2007, using a lifetime horizon, estimated lower ICERs compared with no treatment from $258,465, $303,968, $310,691to $416,301 for SC GA, IM IFN β-1a, SC IFN β-1b, and SC IFN β-1a respectively. The authors attribute differences in results between their study and the Prosser *et al* study to the use of a shorter time horizon and higher utility values in the earlier study. [52] While Prosser *et al* state that a societal perspective was adopted, lost work productivity wasn't included, under the assumption that lost income is reflected in disutility weights. [265] These indirect costs were included under the societal perspective adopted by Bell *et al*. [52] The impact of time horizon is reflected in other studies indicating that shorter time horizons are associated with less favourable ICERs, as high treatment costs in early years may result in benefits accruing over time. [231] [276] Tappenden *et al* conducted a CEA for the representative Medicare beneficiary with MS, from the payer perspective, using a 50-year time horizon. [236] ICERs for IFN β and GA were in excess of $100,000 per QALY, falling significantly if treatment was discontinued at EDSS 7. When results of an MTC were incorporated in place of efficacy estimates from placebo-controlled trials, the cost effectiveness of IFN β-1a in particular was much less favourable. Tappenden attributes this to reporting of the IFN β-1a pivotal trial results which was not undertaken according to the intention-to-treat principle. [236] Lower ICERs again were reported by Pan *et al*, in the CEA published in 2012, driven by the inclusion of a mortality benefit from IFN β-1b. [277] This assumption differed from previous studies and was based on the survival advantage identified in the 21-year long term follow up (21Y-LTF) study in patients receiving early treatment with

IFN β-1b compared with placebo. [82] The ICER with IFN β-1b was $46,357 per QALY gained from the societal perspective over a 70-year time horizon. [277] Pan *et al* included productivity losses associated with premature deaths which were a significant cost component in the model. Unsurprisingly, time horizon was the most sensitive variable in univariate sensitivity analysis in the study by Pan *et al*, illustrating the dependence of the ICER on assumed survival benefits. ICERs in excess of $800,000 in 2011 were calculated by Noyes *et al* using data from the Sonya Slifka Longitudinal Multiple Sclerosis Study, a ten-year time horizon, and the societal perspective. [235] The authors attribute these higher ICERs to the use of data collected after DMTs were introduced onto the US market, and to the "funding effect" and the conflict of interest which may arise in study-conduct and interpretation of results of industry-sponsored studies. [235] This assertion is supported by a systematic review by Bell *et al* which found that studies sponsored by industry were associated with more favourable ICERs. [278]

4.4.6.2 Studies Including Natalizumab or Fingolimod

Difficulties modelling the cost effectiveness of natalizumab arise from differences between the clinical trial population and the approved indication. Natalizumab is licensed for use in patients with sub-optimally treated or rapidly evolving severe RRMS while the placebo controlled pivotal trial population was not restricted to these subgroups. Only 8% of those included in the RCT had previously received therapy with a DMT. [101] Studies have applied RCT efficacy data from the general trial population acknowledging this as a limitation in the applicability of results in clinical practice. [262] Gani *et al*, having access to patient-level trial data, utilised data for a subgroup of highly active RRMS patients to model natural history and applied pivotal trial efficacy estimates for natalizumab and other first line DMTs. [232] Societal base case ICERs of ~£2000 per QALY for natalizumab versus other DMTs, and £8200 per QALY versus BSC were reported. ICERs up to £25,500 per QALY were estimated from the healthcare payer perspective. Kobelt *et al* compared the cost effectiveness of natalizumab with current standard practice in Sweden and modelled disease progression in the current treatment arm using individual patient level data. [262] Natalizumab was found to be dominant in the societal base case and had an ICER of €38,145 from the healthcare payer perspective. The results of a CEA by Earnshaw *et al* were very different, finding GA to be dominant versus natalizumab over a lifetime horizon. [54]

Significantly lower withdrawal rates and a less stringent measure of treatment efficacy was applied to the GA arm of this study compared with natalizumab. Lee *et al* investigated the cost effectiveness of fingolimod versus IFN β-1a over a ten year time horizon from the societal perspective, resulting in an ICER of $73,975 per QALY. [56] Results were most sensitive to changes in drug costs and the disutility of receiving IFN β-1a. Assuming willingness-to-pay thresholds of $50,000 and $100,000 per QALY, the probability that fingolimod was cost-effective was 35% and 70% respectively.

In studies including natalizumab and fingolimod, incremental costs were US$24,452 per relapse avoided for natalizumab compared with IFN β-1b, and natalizumab dominated fingolimod, both over a two-year time horizon. [261] [263] Using data from an extension study of an RCT comparing fingolimod to IFN β-1a, Agashivala *et al* found that the cost per relapse avoided was $83,125 with fingolimod versus IFN β-1a compared with $103,624 if fingolimod is initiated after one year of IFN β-1a. [256]

4.4.6.3 HTAs by the NCPE or NICE

A number of cost effectiveness models of DMT in MS have been assessed by reimbursement agencies internationally, including the NCPE and NICE. In 2002, Tappenden and colleagues from the School of Health and Related Research (ScHARR) at the University of Sheffield were commissioned by NICE to undertake an economic assessment of IFN β and GA for the management of MS in England and Wales. [255] Commercial in confidence trial data was used for relative risks of relapse and progression for three of the four available DMTs. The natural history of MS was estimated using patient level data from the LO MS cohort. [77] Using a 20-year time horizon and differential discount rate (6% costs, 1.5% benefits), a range of ICERs were estimated with a lower limit in the region of £40,000 per QALY. The PSA demonstrated a high probability that all products could have an ICER over £140,000. The key determinants of cost effectiveness were the time horizon, the progression of patients after stopping treatment, differential discount rates, and the price of the treatments. Values were reported to "change radically" if costs and benefits are discounted equally. [255] NICE recommended against reimbursing these products, as they were not cost-effective. Considerable opposition from advocacy groups, professional organisations and the pharmaceutical industry led to the establishment of a risk sharing scheme in which drugs were funded on condition that their effect on disease

progression was monitored in a cohort of patients for ten years. Adjustments to the drug price would then be made on the basis of the results observed. Ten years on, this scheme has been described as a costly failure. [279] The only results published from this study have concluded that it is "too early" to reach any conclusions about the cost effectiveness of these therapies. [280] Subsequent NICE assessments of newer DMTs, natalizumab and fingolimod, have used IFN β and GA as comparators given their place in current practice, despite their questionable cost effectiveness. In 2006, the natalizumab submission to NICE found that a combination of BSC and natalizumab extendedly dominated the comparators IFN β and GA. The ICER for natalizumab versus BSC was £34,900 per QALY for the rapidly-evolving severe subgroup and £57,000 per QALY for the sub-optimally treated subgroup. [48] From the healthcare payer perspective, the probability that natalizumab was the most cost-effective agent was 25% for rapidly-evolving severe subgroup and close to 0% for sub-optimally treated, at a willingness to pay threshold of £30,000. From a societal perspective, ICERs were under £35,000 for both subgroups with much higher probabilities of cost effectiveness. Although the ICERs were above the threshold below which drugs are typically reimbursed, NICE approved natalizumab for the treatment of the rapidly-evolving severe subgroup on the basis of the high degree of clinical need among this subgroup and the innovative nature of the technology. Koeser *et al* suggest that the treatment-effect of natalizumab may be overestimated in this model due to the use of AFFIRM trial data to estimate BSC progression rates. [281] In the Irish setting, a CEA submitted to the NCPE demonstrated natalizumab to be dominant in the societal base-case for the rapidly-evolving severe subgroup. [50] The ICER was €4,400 per QALY for the SOT subgroup using a 20 year time horizon. Adopting a healthcare payer perspective reduced the cost effectiveness of natalizumab giving ICERs of €27,100 to €39,800 per QALY. Time horizon and choice of data to inform baseline disease progression had a significant impact on the results. The probability of acceptability at the €45,000/QALY threshold ranged from 63.5% and 83.8%. The NCPE conclusion was that Natalizumab could be considered borderline cost effective in the Irish healthcare setting and was recommended for reimbursement. In view of the uncertainty surrounding some of the ICERs a follow up review was advised. [50] The more favourable ICERs in the Irish setting compared with the UK may be due to higher healthcare costs in Ireland.

In the NICE assessment of Fingolimod, ICERs were presented for various subgroups. [233] In a subgroup of patients with sub-optimally treated MS, the

manufacturer's original deterministic base case ICER for fingolimod compared with IM IFN β-1a was £55,600 per QALY. After incorporating a number of changes, including a confidential discounted price of fingolimod, assuming a 50% waning of treatment-effect at five years and presenting a probabilisitic rather than deterministic ICER, the ICER was reduced to £17,275 per QALY. The probabilistic ICER versus BSC was £58,000 per QALY gained. Although the evidence review group found that IM IFN β-1a was extendedly dominated by BSC and fingolimod, IM IFN β-1a was still considered an appropriate comparator given its place in practice. A further analysis included a comparator which represented a weighted average (based on market share) of IFN β products and GA together with BSC accounting for just 5% of the average. The ICER in this scenario was £27,820 per QALY. The choice of comparator in the manufacturer's model was a key driver of cost effectiveness, and the ICER was most sensitive to the relative risks of disease progression assumed for fingolimod and IM IFN β-1a, and the relative risk of relapse for IM IFN β-1a. NICE viewed fingolimod as an "exceptional case", particularly in light of the difficulties in ascertaining the cost effectiveness of other DMTs for MS, and recommended reimbursement for the sub-optimally treated subgroup. Natalizumab was not included as a comparator in this assessment. [51]

In the NCPE assessment of fingolimod, it considered natalizumab as a comparator, in addition to IFN β-1b and BSC, as it is approved for the same indication as fingolimod. ICERs for all active comparators versus BSC were all significantly greater than €100,000/QALY. [49] The base case ICER for fingolimod compared with IM IFN β-1a in subgroups of non-responders ranged from €87,814 per QALY to €99,523 per QALY from the HSE perspective, and from €58,572 per QALY to €65,754 per QALY from the societal perspective. The main drivers of cost effectiveness are fingolimod price and the relative risk of progression with fingolimod and administration costs of natalizumab. The model was also sensitive to variation in discontinuation rates. A PSA conducted by the company found the probability of fingolimod being cost-effective at typical WTP thresholds (i.e. €20,000 per QALY, €45,000 per QALY) was 0%. Fingolimod was less effective but less costly than Natalizumab, resulting in €55,492 savings per QALY lost, from the healthcare payer perspective. The NCPE concluded that although fingolimod represents a potentially useful treatment option for patients with RRMS, particularly in those patients for whom natalizumab is considered unsuitable, the incremental benefit over other currently available DMTs does not justify

the substantial increase in price. [49] Following a confidential price revision the NCPE subsequently considered fingolimod a cost-effective therapy and recommended reimbursement.

4.4.7 Summary of the main challenges in RRMS modelling

A review of the existing literature on the cost effectiveness of DMTs for RRMS has revealed a number of challenges which face those undertaking and interpreting CEAs. The relevance of historical untreated cohorts to present-day untreated populations is unclear, due to changes in the epidemiology of MS over time. However, it is unlikely that a better source of evidence on the long term impact of untreated MS will become available given the widespread use of DMTs. The continued relevance of the BSC comparator (representing an untreated population) in itself is questionable given the growing practice of initiating DMTs early in the disease progress, even before a definitive diagnosis of MS has been made in some cases. In the absence of a disinvestment strategy where reimbursement of IFN β and GA is withdrawn, it is likely that standard of care will be dominated by these and other DMTs.

Given the growing number of available DMTs and the chronic, progressive nature of the disease, it is likely that many of these agents will be used in sequence. Natalizumab and fingolimod are specifically licensed for second-line use however there is limited data available on their efficacy in this setting. Existing CEAs have not addressed the various treatment pathways which may be taken as patients start a therapy, relapse or progress and switch to an alternative second line therapy. This is partly due to the lack of data on the efficacy of these agents in the second/third/fourth line setting, and also due to the lack of consensus on the appropriate treatment sequence once patients fail on first-or second-line therapies.

In the setting of a chronic, progressive illness, DMTs may be used for many years but the durability of DMT efficacy is unknown. Incorporation of data from observational studies such as registries or RCT extension studies may enhance our understanding of DMT efficacy over a prolonged duration of treatment. Severe adverse effects limit the duration of treatment for certain DMTs such as natalizumab and alemtuzumab, and the degree to which previously accrued benefits are retained once therapy is discontinued is unknown. All studies have assumed indefinite treatment duration, albeit with yearly adjustments for treatment withdrawals. Treatment

experience with newer DMTs is limited, however it is highly unlikely that the duration of treatment with natalizumab will be indefinite, given the increasing risk of PML with increasing duration of treatment. Current recommendations are that continued therapy after two years should be considered only following a reassessment of the potential for benefit and risk.[103] Existing CEAs have not explored a scenario in which natalizumab is discontinued after two years. This difficulty will also arise with alemtuzumab whose license is expected to restrict use to two years, reflecting the treatment duration in clinical trials.

Relapse rates are known to decrease as the disease progresses. This is reflected in the usual model structure in which relapse rate is dependent on EDSS score. However, ARRs in the placebo arms of RCTs have decreased significantly over the years. [65] Numerous reasons have been postulated for this e.g. changes in definition of MS, change in trial populations etc. but it is also possible that the epidemiology of MS has changed over time, limiting the relevance of historical cohorts from which baseline relapse rates have been derived.

4.4.8 Conclusions on the cost effectiveness of DMTs for RRMS

Different CEAs of DMT for MS have reported very different conclusions. Assumptions regarding the duration of treatment, durability of treatment-effects, discontinuation rate, time horizon, discounting, perspective and data inputs have all been shown to have a significant influence on results. The appropriateness of short time horizons (two to four years) for a chronic condition like MS, is dubious, and in general a lifetime horizon should be adopted. The inclusion of relapses as the sole outcome of interest may be misleading as the potential economic benefit associated with delaying progression of disability is not captured. The selective inclusion/exclusion of comparators can also result in misleading conclusions. All potential comparators should be included. The inclusion of various cost categories depends on the perspective of the analysis. Adoption of a societal perspective in the setting of a chronic illness like MS which affects young adults can have a significant impact on results as productivity losses may be substantial. Nevertheless, the economic impact of MS management from the perspective of the healthcare payer is often the most relevant. The source of treatment efficacy data can have a significant impact on results, as demonstrated by Tappenden *et al* who utilised both direct trial estimates and estimates from an MTC.

This can happen where results of placebo-controlled trials conflict with those of direct comparative studies. Likewise the source of natural history data is important, with particular differences arising from the inclusion of data from longitudinal observational cohorts compared with clinical trial populations.

As a result of the different methodologies and assumptions employed in existing CEAs, compounded by the variation in cost associated with study setting, interpretation of the overall evidence base can be confusing. In general, most independent (non-manufacturer-sponsored) CEAs have found that all DMTs are not cost-effective compared with BSC. Studies comparing natalizumab or fingolimod with first line DMTs have generally reported more favourable ICERs for natalizumab, although between-study comparisons must be made with caution.

CHAPTER 5 – COST OF MULTIPLE SCLEROSIS IN IRELAND

CHAPTER 5 – COST OF MULTIPLE SCLEROSIS IN IRELAND

This chapter describes a CoI study which provides the economic data for a decision analytic model for DMT in MS. The CoI study was facilitated by the neurology team in St. Vincent's University Hospital (SVUH), a research group with an international reputation in the field of MS research. [282] *Scientific abstracts based on this study have been presented at the Irish Neurological Association Annual Meeting 2013, the European Committee for Treatment and Research in Multiple Sclerosis (ECTRIMS October 2013) and the International Society for Pharmacoeconomics and Outcomes Research Annual European Conference (ISPOR November 2013).*

5.1 Introduction

At the core of a cost effectiveness assessment (CEA) is an estimation of the costs and effects associated with the health intervention under review and its comparators. The cost of the disease process on which they impact, both before and after treatment, is also relevant. Healthcare resource utilisation in MS has significant financial consequences for the healthcare system, patients and their families arising from immunomodulatory and symptomatic drug therapy, inpatient and outpatient healthcare professional services, laboratory and radiological investigations, professional and informal home supports, mobility and other living aids, home modifications and reduced work capacity. Costs included in a CEA should reflect the costs in the setting where the treatment or programme in question will be implemented. [130] Currently, however, there are no agreed Irish cost models available, nor has any study specifically estimated the costs associated with MS in Ireland.

5.2 Aims

The aims of this research are to assess healthcare and wider societal resource utilisation in a cohort of patients with MS in Ireland, to estimate both direct and indirect costs of

MS from the perspective of both the healthcare payer and society in general, and to generate economic evidence for inclusion in a decision analytic model for DMT in MS.

5.3 Methods

Methods sections 5.3.1 to 5.3.4 also apply to the study described in Chapter 6 as this CoI study was conducted in parallel with a HRQoL study in the same patient cohort.

A bottom-up, prevalence based approach was taken, whereby resource use and productivity loss was assigned to individuals with MS, from detailed data from real cases covering the timeframe of the study.

5.3.1 Ethical Approval

Prior to study commencement, a study protocol, patient information leaflet (PIL) and study questionnaire were developed in support of an ethical approval application form (Appendices 2-5). Ethical approval for the study was granted by the Research and Ethics Committee of St. Vincent's University Hospital, a major academic teaching hospital in Dublin, Ireland, on 21st July 2011.

5.3.2 Patient Recruitment and Consent

Consecutive patients attending a specialised MS outpatient clinic at St. Vincent's University Hospital, Dublin from September 2011 to February 2012 were invited to participate in the study. Prospective participants were provided with a PIL at the MS clinic reception which outlined the background to the study and included a consent form (Appendix 3). Following the patient's outpatient review, the reviewing consultant neurologist/specialist registrar/clinical nurse specialist discussed the PIL. Patients were informed that participation was voluntary. If they decided to take part, they were informed that they were free to withdraw from the study at any time, and that the decision to/not to participate or to withdraw from the study, would not affect the care they received in any way. If they decided to withdraw at any time after the interview has been conducted, they were informed that all identifiable data would be destroyed. If the patient was willing to participate they signed a consent form. Inclusion criteria included a confirmed diagnosis of MS, (based on the McDonald

Criteria)[21] and age greater than 18 years. Patients were excluded if, based on clinical judgement, their capacity to provide informed responses was compromised due to cognitive impairment.

5.3.3 Clinical Status

The recruiting consultant neurologist/specialist registrar/clinical nurse specialist recorded the type of MS (i.e. RRMS, SPMS, PPMS, Benign) and each patient's level of disability on the EDSS scale [31] The EDSS quantifies disability in a number of functional systems on a scale from 0 (normal neurological examination) to 10 (death from MS). Above EDSS 6.0, disability is almost exclusively dependent on walking function and a score of 8.0 marks the loss of ambulation. Half-points on the EDSS scale were combined to give an integer scale in line with the approach taken in many CEAs of DMT in MS, which have structured their decision models on health states represented by aggregate scores on the EDSS scale. EDSS Patients were further stratified based on the severity of disability into three groups based on EDSS score; mild (EDSS 0-3.5), moderate (EDSS 4-6.5) and severe (EDSS 7-9.5).

5.3.4 Data Collection and Storage

Following outpatient review, participating patients were individually guided through a structured interview by the author, using the study questionnaire. A carer was permitted to assist in answering questions if the patient had recall difficulty or was unable to answer certain questions. The EQ-5D-5L descriptive system and visual analogue scale were self-completed by all participants. Questionnaires did not include any patient-identifiable information and data was pseudo-anonymised using a numerical ID. Hard copies of the questionnaires were stored in a locked filing cabinet in the NCPE. Electronic data was stored in encrypted files on a desktop computer in the NCPE.

5.3.5 Study Questionnaire

The study questionnaire was based on the Client Service Receipt Inventory (CSRI), a research instrument extensively applied in psychiatry for the collection of information on costs. [283] The CSRI had previously been used by McCrone *et al* in their Cost of MS in the UK and Northern Ireland study and was kindly shared with the author on request.

[138] A list of healthcare and non-healthcare resources commonly associated with MS management was compiled following a review of the literature and discussion with clinical experts. On the basis of this research, the CSRI was adapted to suit the aims of the study and the expected medical and non-medical resource utilisation, employment and related financial matters of the Irish MS patient. Data was collected on healthcare resource utilisation and non-medical resources used as a consequence of participants' MS diagnosis during the year prior to study recruitment. The questionnaire included questions on the following:

- Basic sociodemographic details e.g. ethnicity, marital status, living arrangements, education
- History of MS diagnosis and symptoms
- Healthcare services used/received
- Professional care and informal care from family and friends
- Living and mobility aids and home adaptations
- Impact of MS on employment status

5.3.6 Perspective and Included Cost Components

Direct medical, non-medical and indirect costs are presented from the societal perspective (i.e. regardless of who pays) with further stratification based on the payer i.e. healthcare payer, patients or other non-HSE organisations or society. Only resource-use attributable to MS was collected. Direct medical costs included inpatient hospital admissions, rehabilitation, respite and nursing home care, outpatient and primary healthcare, laboratory and radiological investigations and medication. Direct non-medical costs include mobility and other living aids, major investments and home adaptations and professional help in the home. Indirect costs included lost productivity due to absenteeism from work, early retirement and informal care from family and friends.

In the Irish healthcare system, all residents are entitled to free or subsidised public hospital care and all people with MS are entitled to free MS-related prescription medication, medical and surgical appliances. The HSE provides means-tested financial support to people who need long-term nursing home care. In the absence of data on the breakdown of HSE/patient payments it is assumed that long-term care is funded by the HSE. Primary care entitlements are means-tested with ~40% of the population entitled

to free GP care. A small proportion of direct expenditure is therefore expected to be borne by patients, their families and other organisations.

5.3.7 Recall Period

The length of the recall period for resource use varied, using longer recall periods for less frequent events e.g. 12 months for inpatient admissions, six months for outpatient and primary healthcare, laboratory and radiological investigations, one month for medication, and one week for home help. For resources such as mobility and other living aids, and major investments such as home modifications, the full duration of the disease was used for recall.

5.3.8 Unit costs

Nationally applicable unit costs were applied to each resource component. The sources of unit costs are summarised in Table 5.1. A detailed summary of all unit costs and their sources are outlined in Appendix 6. A variety of sources were used for valuing resources e.g. National Casemix Programme, HSE salary scales, individual long term care and rehabilitation institutions' price-lists, Primary Care Reimbursement Service, Central Statistics Office (CSO), hospital laboratory and radiology departments.

In the absence of standard unit costs, the cost of aids and adaptations were based on patient estimates and publicly available price lists, and were annualised over a useful life of five years (aids) and ten years (adaptations) at a discount rate of 4.0%.[284] Where necessary, unit costs were inflated to 2012 values, using the consumer price index for health. [285] Productivity losses were valued using the "human capital" approach assuming that labour earnings reflect productive capacity. Productivity losses associated with reductions in working hours or sick leave and permanent withdrawal from the labour force due to MS, were based on national gender-stratified average gross hourly and annual earnings, respectively, available from the CSO. [285]

In a similar way informal care was valued, using the opportunity cost approach, as earnings foregone as a result of time spent care-giving (up to a maximum of 40 hours per week) using the national gross mean hourly wage in Ireland. A cap of 40 hours per week was imposed on the amount of time that could be valued as productivity losses to reflect the average working week of those employed in Ireland. This bottom-up

approach to cost-estimation enabled extrapolation of annual costs to the general population.

Table 5.1: Source of Unit Costs

Resource	Source of unit cost
Hospital inpatient*	HSE-Casemix (Inpatient DRG) [142]
Hospital outpatient consultation	HSE-Casemix (Average cost per case for an outpatient attendance) [142]
Nursing home/Rehabilitation/Respite^	HSE Nursing Home Support Scheme [286 287]
Laboratory and radiological investigations	University teaching hospital Laboratory/Finance Departments
Investigations and outpatient procedures e.g. OGD, colonoscopy etc.	HSE-Casemix (Daycase DRG) [142]
General Practitioner†	HSE-PCRS Statistical Analysis of Claims and Payments 2011, and Madden *et al* [288 3]
Healthcare professionals e.g. physiotherapist, nurse etc. ‡	HSE Salary Scales [289]
Medication §	HSE-PCRS [290]
Over-the-counter medication	Patient estimates
Living aids e.g. crutch, wheelchair etc.	Patient estimates, public price-lists, national procurement expert opinion
Home modifications	Patient estimates
Help at home	HSE Salary Scales [289]
Productivity losses	Central statistics office, gross gender specific mean earnings [285]

* Specific DRGs selected depending on MS-related reason for hospital admission, cost per-diem applied based on reported length of stay
^ Institution-specific costs used where reported, cost per-diem applied based on reported length of stay
† Cost per GP visit calculated from GP capitation fee and national average number of GP visits per annum
‡ Median point on relevant salary scale plus overheads, consultation assumed to be of 30 minutes duration [7]
§ Where dose not reported, average of reported doses from other study-participants used
‡ Median point on relevant salary scale plus overheads, based on reported number of hours
Abbreviations: HSE=Health Service Executive; DRG=Diagnosis Related Group; PCRS=Primary Care Reimbursement Service.

5.3.9 Analysis

All data were entered in a database created in Microsoft Excel and analysed using R version 2.12. Costs were annualised under the assumption that resource use during the recall period was representative of other periods of similar duration throughout the year. Data were summarised using the mean and standard deviation (SD) for continuous

variables and proportions for categorical variables. Mean annual costs per person for each cost component, and cost-type (direct medical, direct non-medical and indirect) were estimated for patients with mild, moderate and severe MS. Mean annual costs for patients on each level of the aggregated EDSS scale (from 0 to 9) were also estimated. Base-case EDSS health state costs include all resources funded by the HSE with the exception of those directly related to the prescription of DMT (drug, administration and monitoring costs), as DMT-related costs are independent of health state costs in the model. Societal EDSS health state costs include all direct costs, regardless of the payer, and indirect costs.

5.3.9.1 Non-parametric bootstrapping

As cost data is typically truncated (at zero) and positively skewed (due to the presence of relatively small numbers of patients with very high costs), standard parametric statistical tests are often not appropriate. This study used the non-parametric bootstrap approach to account for the skewed distribution of the data. [291] Using this approach, the observed sample is treated as an empirical distribution. Random values are selected from the sample, with replacement, to produce a bootstrap dataset of equivalent size to the original sample. This sampling with replacement process was repeated 1000 times to create a series of bootstrap datasets which were used to produce a sampling distribution of the mean from which the mean and 95% CI were calculated. Differences in demographics and between subgroups were compared by ANOVA and Kruskal-Wallis test, for parametric and non-parametric data respectively. Statistical significance is based at the 0.05 level.

5.3.9.2 Multivariate Regression Analysis

Determinants of direct costs were evaluated in multivariate analysis using a log transformation of the dependent variable. A backwards stepwise procedure was used to reduce the model to include only significant covariates ($p<0.05$). A separate model was used to extrapolate costs from the study sample to the national population assuming an overall population of 8000 MS patients in Ireland. Model covariates included age, gender, duration and MS-type using mean values from a 2007 cross-sectional study including 632 patients from three regions of Ireland.[73] Prescribing data from the Primary Care Reimbursement Service (HSE-PCRS) was used to estimate the proportion

of the MS population on DMT.[292] To account for a substantial fraction of observations at zero-indirect cost, the indirect cost model was fitted as a mixture distribution, fitting the multiple regression to non-zero values only and using a logistic regression to estimate population costs proportionally.

5.4 Results

5.4.1 Patients

214 patients completed the study. Key demographic data are summarised in Table 5.2. The mean age was 47.6 years (SD 12.75 years, median 49 years, range 19-81 years). The majority of patients were female (66.36%), living with a spouse or partner, family or friends (80.84%), had completed second-level education (60%) and were either retired or unemployed (50.93%). Responses were provided by a carer for 9 (4%) patients.

The mean (SD) EDSS score was 3.59 (2.64). 61% of patients had EDSS scores <6. The distribution of EDSS states in the population is bimodal with peaks at EDSS 1 and EDSS 6 (typical of the EDSS scale) and there were fewer numbers with EDSS scores of 5 and 9 (Table 5.2). 53.52% of patients had mild disease, 33.80% had moderate disease and 12.68% had severe disease. The mean duration of illness was 14.81 years (SD 10.80 years, median 13 years, range 0-60 years) and mean age at first symptoms was 32.69 years (SD 10.23 years, median 31 years, range 14-65 years). Some 52.30% of patients had RRMS, 33.64% had SPMS, 11.68% had PPMS and 1.87% had benign MS.

Patients with mild disability were younger compared to those with moderate/severe disability, had a shorter disease duration and were more likely to be in paid employment ($p<0.05$). There was no significant differences between age of patients with moderate or severe MS but those with moderate MS had a significantly shorter duration of illness ($p<0.05$). Patients with moderate or severe disability were more likely to have retired early because of MS-related ill-health compared with patients with mild disability ($p<0.05$)

Table 5.2: Demographics and clinical characteristics of the study population

Number	214
Age *(mean in years), (SD)*	47.6 (12.75)
Female *(%)*	66.36%
Duration of disease *(mean in years), (SD)*	14.81 (10.80)
Age at MS onset *(mean in years), (SD)*	32.69 (10.23)
On disease-modifying therapy	44.50%
Relapse in previous 6 months	15.40%
Married/cohabiting	65.44%
Age finishing full-time education *(mean in years), (SD)*	19.66 (4.32)
Disability Severity*	
Mild (EDSS 0-3.5)	53.52%
Moderate (EDSS 4-6.5)	33.80%
Severe (EDSS 7-9.5)	12.68%
Disease Type	
Relapsing Remitting	52.30%
Secondary Progressive	33.64%
Primary Progressive	11.68%
Benign	1.87%
Employment Status	
Employed	40.18%
Housewife/husband	6.54%
Student	2.34%
Retired due to age	8.88%
Retired due to MS	35.98%
Unemployed	6.07%
Habitation	
Live alone	15.89%
Live with others	80.84%
Live in a care home	3.27%
Children	
0	69.63%
1	14.02%
>1	16.36%

*EDSS score was missing for 1 patients

EDSS: Expanded Disability Status Scale

5.4.2 Medical Resource Utilisation

The proportion of patients using each resource category is summarised in Table 5.3. Some 15.4% of patients were hospitalised during the previous year (mean (SD) number of admissions per patient, 1.3 (0.60), duration 1-167 days), 5.6% of patients utilised rehabilitation or respite services and a small proportion of patients (3.27%) were in permanent nursing home care.

In addition to the incident outpatient neurological consultation, 42.5% of patients had an outpatient neurology consultation in the previous six months and 19.63% had a consultation with a non-neurology specialist physician. Among primary care health professionals, GPs were visited most frequently (48.13%), followed by physiotherapists (29.91% had an individual or group session). DMT was prescribed for 61.40% and 29.58% of patients with mild and moderate MS, respectively. Of those patients on DMT, 92% were on first line agents IFN ß or GA, 1.87% were on alemtuzumab, 1.40% were on natalizumab, and one patient (0.47%) was prescribed rituximab.

Table 5.3: Multiple Sclerosis Resource Utilisation

Hospital	**Proportion of users**	**Mean (SD) days in previous 12 months**
Hospital inpatient	15.42%	17.1 (28.77)
Outpatient/Primary Care	**Proportion of users**	**Mean (SD) visits in previous 6 months**
Hospital Consultant*	44.39%	1.46 (0.96)
Physiotherapist	30.37%	11.08 (11.64)
General Practitioner	48.13%	2.65 (2.63)
Occupational Therapist	11.21%	2.46 (1.50)
*in addition to the incident neurology consultation which all participants received		
Tests	**Proportion of users**	**Mean (SD) tests in previous 6 months**
Lumbar puncture	2.34%	1.00 (0.00)
Ultrasound	3.27%	1.00 (0.00)
Laboratory investigations	30.84%	1.74 (1.30)
Magnetic resonance imaging	21.03%	1.29 (0.82)
Medication	**Proportion of users**	
Disease-modifying therapy	44.39%	NA
Baclofen	18.22%	NA
Pregabalin	13.08%	NA
Paracetamol	12.15%	NA
Gabapentin	10.75%	NA
Mobility/Living Aids and Adaptations	**Proportion of users**	
Crutches/sticks	35.05%	NA
Wheelchair	27.10%	NA
Rollator	15.89%	NA
Home modifications	31.78%	NA
Regular Help at Home	**Proportion of users**	**Mean (SD) hours in previous week**
Professional home help	22.4%	13.84 (19.20)
Informal care	21.50%	21.86 (16.29)
Labour resources	**Proportion of users**	**Mean (SD) days in previous 6 months**
MS-related Sick-leave/reduced working hours	13.08%	23.10 (26.04)
Receiving MS disability-related social welfare	36.92%	NA

SD=standard deviation

5.4.3 Non-medical Resource Utilisation

Regular help at home, either from paid professionals or family and friends was received by 9.65%, 54.17% and 92.89% of those with mild, moderate and severe MS respectively. Professional help at home was received by 22.43% of patients, funded by the healthcare payer, other organisations or patients themselves (mean (SD) number of hours per week, 13.84 (19.20)). Informal care from friends or famaily members was

received by 21.50% of patients (mean (sd) number of hours per week, 13.84 (21.86 (16.29))).

Some 52.34% of patients reported use of a mobility or other living aid e.g. wheelchair, rollator, grabber, eating utensils, hoist etc. with 31.78% of the cohort making adaptations to their home.

23.23% of those with moderate or severe MS were in paid employment in contrast to 54.38% of mild MS patients. MS-related sick leave or a reduction in working hours was taken by 32.56% of those in paid employment (mean (SD) reduction in working days per week, 0.89 (1.0)). The majority (54.55%) of patients with moderate or severe disability were retired due to MS-related ill-health (mean (SD) age at retirement, 44.26 years (10.86)). 37.38% of patients were in receipt of social welfare disability payments including the majority of patients with moderate (54.17%) and severe MS (59.26%).

5.4.4 Direct costs

Table 5.4 summarises data on annual direct medical, direct non-medical, and indirect costs according to disease severity. The mean annual direct cost per person was €17,103 (95% CI €14,203-€20,304) varying with disease severity from €10,249 (95% CI €8,856-€11,685) in mild MS, €13,045 (95% CI €10,119-€16,238) in moderate MS and €56,528 (95% CI €43,160-€72,067) per patient with severe MS.

Table 5.4: Resource Utilisation and Mean annual Direct and Indirect Costs

	All (n=214)		mild EDSS 0-3.5 (n=114)		moderate EDSS 4.0-6.5 (n=72)		severe EDSS 7.0-9.5 (n=27)	
	Users	mean 95%CI	Users	mean 95%CI	Users	mean 95%CI	Users	mean 95%CI
Total Direct Medical		**€11,946 €10131-€13960**		**€10,040 €8674-€11454**		**€9,001 €6820-€11508**		**€27,522 €17122-€39158**
Hospital/Rehabilitation	15%	€1,922 €1045-€2807	13%	€848 €354-€1462	11%	€1,179 €319-€1356	37%	€8,416 €3047-€15626
Outpatient/Primary Care	79%	€1,218 €998-€1251	68%	€628 €521-€710	90%	€1,698 €1247-€1707	96%	€2,434 €1484-€3276
Long-term care	8%	€1,965 €641-€3876	1%	€0 €0-€31	11%	€841 €0-€3665	33%	€13,285 €4167-€24592
Lab/Rad Investigations	49%	€276 €208-€346	52%	€309 €211-€415	40%	€263 €148-€391	56%	€158 €64-€269
Medication	88%	€6,565 €5685-€7457	83%	€8,255 €7065-€9457	93%	€5,019 €3617-€6529	93%	€3,228 €1619-€5252
Total Direct non-Medical		**€5,157 €3235-€7537**		**€209 €68-€391**		**€4,044 €2353-€6017**		**€29,007 €17634-€43263**
Aids and Adaptations	55%	€924 €537-€1430	23%	€62 €12-€143	89%	€1,568 €773-€2624	96%	€2,776 €1076-€5468
Professional home help	22%	€4,233 €2363-€6470	4%	€147 €23-€323	28%	€2,476 €1088-€4190	81%	€26,231 €14730-€40097
Total Direct Costs		**€17,103 €14203-€20304**		**€10,249 €8856-€11685**		**€13,045 €10119-€16238**		**€56,528 €43160-€72067**
Informal care	21%	€6,145 €4190-€8280	5%	€820 €104-€1985	36%	€9,884 €5794-€14303	48%	€18,073 €9760-€27122
Productivity losses	50%	€14,712 €12222-€17234	35%	€8,627 €5736-€11656	68%	€21,922 €17504-€26233	63%	€21,367 €14123-€28442
Total Indirect Costs		**€20,858 €17379-€24537**		**€9,447 €6465-€12681**		**€31,806 €25287-€38452**		**€39,440 €27229-€52005**

Abbreviations: EDSS=Expanded Disability Status Scale; CI=Confidence Interval; Lab/Rad=laboratory and radiological

For most cost categories, costs increased in line with disease severity, the notable exceptions being medication and laboratory/radiological investigations for which costs were highest in mild disease. Mean annual direct non-medical costs are higher (+€3832) in moderate MS as compared with mild MS while direct medical costs were higher in mild MS (+€1235). The difference in direct medical costs between mild and moderate MS is predominantly due to the contribution of medication costs. DMT was prescribed for 61.40% of those with mild MS and 29.17% of those with moderate MS, accounting for 76.09% and 29.56% of direct costs respectively. Excluding DMT, the direct cost of moderate MS is significantly higher than mild MS (€2,454 vs €8,133 $p<0.0001$).

Patients with severe disease had significantly higher costs than those with mild or moderate disease ($p<0.0001$). Unlike mild and moderate MS, direct non-medical costs exceeded direct costs in severe MS. The provision of nursing home care, rehabilitation and respite accounted for the greatest proportion of direct medical costs in severe MS, while the cost of professional help at home was the greatest contributor to direct non-medical costs.

Patients with relapsing remitting MS (RRMS) had lower mean annual direct costs than patients with SPMS, €10,907 (€9,402-€12,358) vs €26,505 (€19,720-€34,061) ($p=0.011$) (Figure 5.1). The mean annual cost was higher among RRMS patients with a recent relapse, compared to those without, however this difference was not statistically significant (mean (95%CI), €3228 (-€221 to €6884) $p=0.18$).

The distribution of costs among the various payers is shown in Figure 5.2. Between 74%-96% of direct costs are borne by the HSE (the healthcare payer in Ireland). The remaining costs are incurred by patients, families or non-HSE organisations, and over three-quarters of these costs (78.47%) relate to non-medical resources such as living aids, home modifications and home-help.

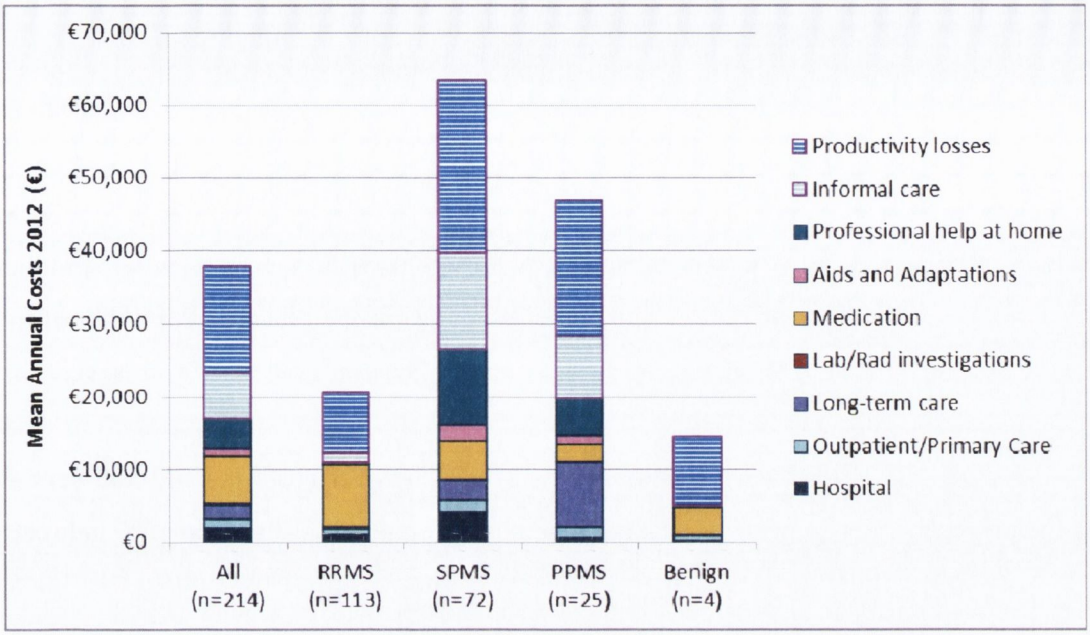


Figure 5.1: Distribution of MS cost components stratified by disease-type

Abbreviations: Lab/Rad=laboratory and radiological; RRMS=Relapsing Remitting Multiple Sclerosis; SPMS=Secondary Progressive Multiple Sclerosis; PPMS=Primary Progressive Multiple Sclerosis

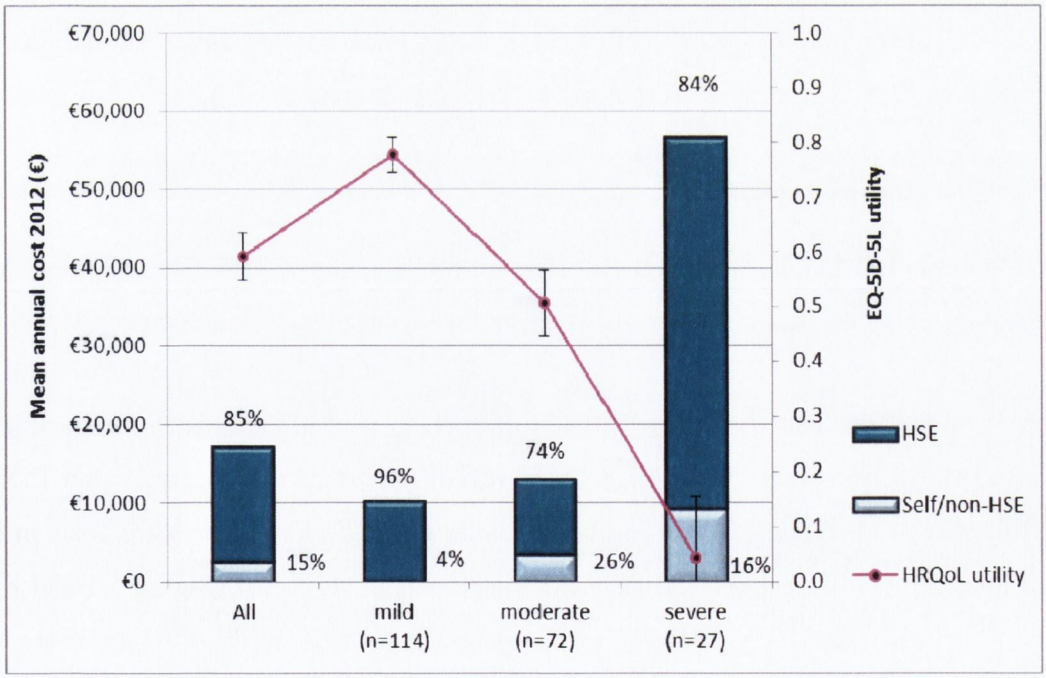


Figure 5.2: Health-related quality of life (HRQoL) and annual direct costs stratified by disease severity and payer

HRQoL results from Fogarty *et al* 2013. [163]

Abbreviations: HRQoL=Health Related Quality of Life; EQ-5D-5L=Five-level Euroqol-5D

5.4.5 Indirect costs

Indirect costs increased as MS disability increased (Table 5.4). The mean annual indirect cost per person was €20,858 (95% CI €17,379-€24,537), ranging from €9,447 (95% CI €6465-€12681) in mild disease, €31,806 (95% CI €25,287-€38,452) in moderate disease, €39,440 (95% CI €27229-€52005) in severe disease. Productivity losses of absenteeism/early retirement accounted for the greatest proportion of indirect costs (70.59%). Productivity losses are similar in moderate and severe disease indicating that the shift away from employment is largely complete before disability reaches the severe stage. Direct costs exceed indirect costs in mild and severe MS, driven by DMT and professional home-help respectively. In contrast, indirect costs dominate direct costs in patients with moderate disability (€31,806 vs €13,045) due primarily to early retirement from the workforce.

Independent predictors of total direct costs include disability, EQ5D-5L HRQoL index, DMT, and long-term care ($p<0.01$). Extrapolating costs from the study sample to the general population of MS patients in Ireland, on the basis of age, gender, duration and type of MS (the only variables reported in a national cross-sectional study, and which mirrored those of this study very closely), total national direct and indirect costs are predicted to be €127.8 million and €149.6 million, respectively.

5.4.6 EDSS Health State Costs

Mean annual EDSS health state costs together with their 95% CIs are presented in Table 5.5 from the perspective of both the healthcare payer and society. Health care payer costs increase from €871 (95% CI €446 - €1,399) per person in EDSS health state 0, to €105,091 (95% CI €68,162 - €171,024) per person in the most severe health state (EDSS 9). Extremely large increases in health care costs are observed after EDSS 7, reflecting the increase in nursing home care and professional homecare costs in these patients. The increase in EDSS health state costs is not linear (Figure 5.3 and Figure 5.4). Some fluctuations are observed as mean annual costs for EDSS 4 and 5 are lower than EDSS 3, with overlapping 95% CIs. Health state costs for mild to moderate EDSS health states, up to EDSS 4, are similar to those used in the recent NICE submission for a DMT for RRMS, fingolimod (Table 5.6).

Table 5.5: EDSS Health State Costs from both Healthcare Payer and Societal Perspective

		Healthcare Payer Costs*			Societal Costs†		
EDSS	**n**	**Mean**	**2.50%**	**97.50%**	**Mean**	**2.50%**	**97.50%**
0	**22**	€871	€446	€1,399	€5,950	€952	€12,596
1	49	€1,352	€928	€1,843	€7,244	€3,940	€11,163
2	22	€1,385	€502	€2,536	€10,426	€3,729	€18,225
3	21	€5,043	€2,439	€8,302	€30,008	€20,801	€38,673
4	15	€2,144	€1,331	€3,142	€22,518	€13,221	€31,915
5	3	€1,070	€54	€2,882	€47,183	€8,096	€96,679
6	54	€7,010	€4,286	€10,371	€45,698	€37,658	€54,090
7	10	€17,694	€8,081	€28,637	€70,813	€51,032	€91,186
8	14	€53,143	€32,185	€74,764	€99,674	€78,312	€118,434
9	3	€105,091	€68,162	€171,024	€148,268	€106,669	€221,119
All	213	€8,771	€6,059	€11,890	€32,159	€27,066	€37,401

*Includes all non-DMT related direct costs borne by the healthcare payer.

†Includes all direct costs, regardless of the payer, and productivity losses from absenteeism, early retirement and informal care.

Abbreviations: EDSS= Expanded Disability Status Scale; DMT=disease-modifying therapy; Mean = bootstrap mean; 2.50% = 2.5th percentile; 97.5% = 97.5th percentile

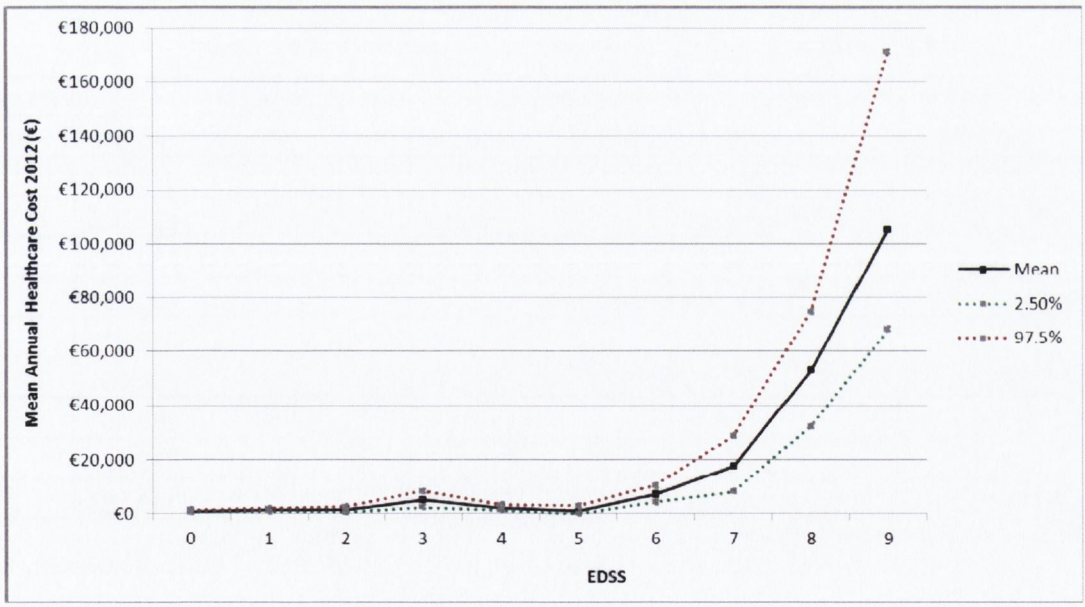


Figure 5.3: Mean annual cost per patient by EDSS level (healthcare payer perspective)

Includes all non-DMT related direct costs borne by the healthcare payer.

Abbreviations: EDSS= Expanded Disability Status Scale; Mean = bootstrap mean; 2.50% = 2.5th percentile; 97.5% = 97.5th percentile

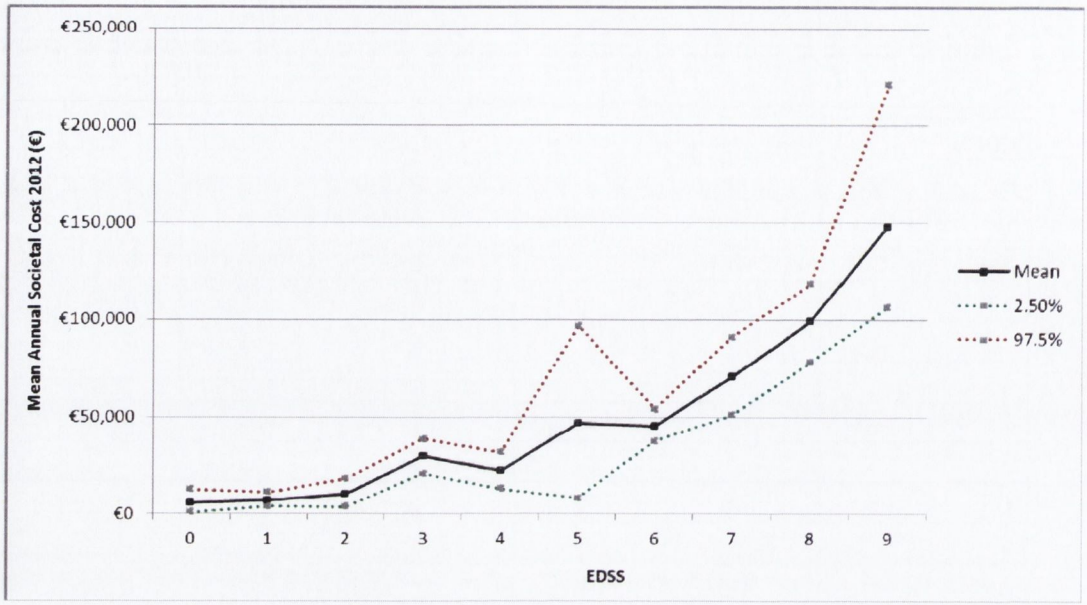


Figure 5.4: Mean annual cost per patient by EDSS level (societal perspective)

Includes all direct costs, regardless of the payer and productivity losses from absenteeism, early retirement and informal care.

Abbreviations: EDSS= Expanded Disability Status Scale; Mean = bootstrap mean; 2.50% = 2.5th percentile; 97.5% = 97.5th percentile

Table 5.6: Comparison of EDSS Health State Costs across studies

EDSS	This study	NICE 2001 [255]	AHRQ 2006 [236]	NICE 2010 [233]
0	€871	€2,326	€3,638	€995
1	€1,352	€2,757	€15,474	€1,438
2	€1,385	€3,500	€27,309	€1,370
3	€5,043	€4,787	€39,145	€4,280
4	€2,144	€7,019	€50,980	€2,725
5	€1,070	€10,890	€62,816	€3,947
6	€7,010	€17,594	€74,651	€4,883
7	€17,694	€29,220	€86,487	€11,460
8	€53,143	€49,367	€98,322	€26,959
9	€105,091	€84,287	€110,157	€25,310

*All costs inflated to € 2012

Abbreviations: AHRQ= Agency for Healthcare Research and Quality; EDSS= Expanded Disability Status Scale; NICE=National Institute for Health and Clinical Excellence

5.5 Discussion

Expenditure on MS has a clear opportunity cost with respect to other health and non-health services and goods. From the perspective of the healthcare payer, spending on MS reduces spending opportunities for other disease areas. From a wider governmental perspective, health spending reduces spending opportunities for other services and goods such as education and transport. [293] Individual patients and households also incur costs, both directly, in the acquisition of health services, as a level of co-payment is often necessary, and indirectly, due to the impact of MS on their capacity to work. Finally, reduced working capacity and early retirement due to MS can have a negative impact on labour productivity and economic growth.

5.5.1 Impact of increasing Disability on Direct Costs

MS severity was an independent predictor of direct costs, highlighting the economic priority of delaying disability progression. The economic impact of increasing disability from the healthcare payer's perspective is particularly apparent in the shift in direct costs between mild or moderate and severe disability. Mean annual direct costs increased as MS disability increased from €10,225 in mild disease, more than five fold to €56,528 in severe MS. Mean annual direct costs increased more than four fold from €13,045 to €56,528 per person with moderate and severe disease respectively, driven by the excess cost of episodic/permanent institutional care, and the provision of professional care in the home. Similarly, the mean cost of patients with SPMS was double that of those with RRMS.

5.5.2 DMT Costs and the Changing Approach to Management as Disability Increases

DMT is prescribed to reduce the rate of MS relapses and to delay progression of disability. As expected, DMT costs dominate in early MS, accounting for 74-76% of total direct costs in mild MS and RRMS. As a result, direct medical costs in mild MS exceed those in moderate MS, whereas direct non-medical costs increase in line with increasing disability. DMT utilisation falls significantly in moderate, severe and progressive disease types in line with guidelines suggesting discontinuation following

the development of non-relapsing SPMS with loss of ability to ambulate (EDSS ≥7.0).[85] [294] Excluding the cost of DMT, direct costs in moderate MS are significantly higher than mild MS.

In moderate and severe disease, there is a shift in emphasis away from expensive immunomodulator treatment, to symptomatic pharmacological treatments. As MS disability increases the overall management approach changes from acute inpatient and outpatient intervention to more supportive home-based management strategies, long-term multidisciplinary management and rehabilitation, in order to achieve the highest possible independence and HRQoL for patients. The mean cost of all cost components was higher in severe disease compared with mild or moderate disease with the exception of medication and tests. Direct costs in severe MS were dominated by the cost of providing care either in long-term care facilities or professional care at home. At this stage in the disease process, costly DMT is largely replaced by symptomatic pharmacological treatments, and there is a move away from acute inpatient and outpatient care to long-term multidisciplinary management and rehabilitation.

5.5.3 Indirect and other Societal Costs

Indirect costs exceed direct costs in moderate MS in contrast with mild and severe subgroups where direct costs dominate, driven by DMT and professional home-help respectively. The level of early retirement among patients with moderate or severe MS was similar, indicating that the shift away from employment is largely complete before disability reaches the severe stage.

Both the financial and HRQOL impact on patients with MS can be significant. Patients' out-of-pocket costs have typically not been reported in other cost of MS studies. Costs to the healthcare payer are generally included under the healthcare payer perspective, with the societal perspective including all costs regardless of who pays. The majority of direct costs in our study are borne by the healthcare payer, the HSE. However out-of-pocket spending at the individual patient level on non-medical resources, and the contribution of non-HSE organisations, can be significant and was found to be particularly so in severe disease.

5.5.4 Comparison with other MS Cost of Illness Studies

Two large European studies investigated the economic burden of MS across a number of countries in 2006 (Kobelt *et al*, included nine countries) and 2012/2013 (TRIBUNE study, included six countries). [1 134] Cross-study comparisons must take into account the differential categorisation of informal care costs. In our study, indirect costs refer to all productivity losses, including those of the informal caregiver. [295] Informal care was categorised as a direct cost in both the Kobelt *et al* and TRIBUNE studies. For the purposes of comparison, the result of these studies have been adjusted with informal care categorised as an indirect cost.

5.5.4.1 Comparison of Direct Costs

The mean annual direct cost per patient in our study, €17,103, is consistent with those reported by Kobelt *et al* (€13,822-€30,721) and in the TRIBUNE study (€12,819-€24,578) (all costs inflated to €2012). The earlier 2005 study recruited patients predominantly via MS society mailing lists and included patients with more severe disease (mean EDSS 3.8-5.1; 45.5%-67.7% progressive disease) than the 2009 study in which recruitment was from treatment centres and data was captured using a web-based electronic system (mean EDSS 1.8-3.9; 12-29% progressive disease). This may explain why there is a trend towards higher mean direct costs in the 2005 study compared to the later TRIBUNE study. The true costs of our cohort, who are more balanced in terms of progressive disease (46% progressive) and disability (mean EDSS 3.59), likely fall in between those reported in these two studies.

In keeping with our study methodology, the TRIBUNE study also reported costs stratified by disease severity.[134] The direct costs of mild and moderate groups in our study (€10,249 and €13,045 respectively) are low compared to those reported in TRIBUNE (mild €8,925-€22,558, moderate €13,867-€32,989). This is predominantly due to differences in direct medical costs, driven by the level of DMT utilisation in the TRIBUNE study.

In contrast to European comparisons for mild and moderate costs, costs for the severe subgroup of patients in our study (€56,528) were higher than those reported elsewhere (€18,426-€37,417). [134] Long-term costs associated with nursing home care are included in our study, whereas this group of patients have been excluded from most other studies. Professional care at home is also a key driver of cost in severe disease

with 81% of patients in our study receiving professional care, predominantly from the HSE and to a much lesser extent, funded privately.

5.5.4.2 Comparison of DMT Costs

Levels of DMT utilisation are not reported for severity subgroups, but DMT utilisation in the total TRIBUNE population is very high at 75%-94%. DMT is used by 29.17% of those in our moderate group, representing 29.56% of direct costs, compared with 43%-94% of direct costs for moderate subgroups in the TRIBUNE study. Mean annual costs increased between mild and moderate disease for all direct cost components in TRIBUNE however in our study there was a nominal decrease in direct medical costs between these subgroups. This finding is largely due to the low level of DMT use in moderate disease relative to mild disease in our study. The majority of our moderate MS population had progressive disease (87.5%). The efficacy of DMT in the setting of progressive disease is unproven, and discontinuation of DMT in these circumstances has been advocated. [85 294] DMT utilisation has increased over the last decade in light of clinical trials reporting evidence of benefit when used early in the disease course. [296] Substantial investment in DMT in the early stages of MS aims to prevent or delay progression to advanced disease, thereby avoiding the cost associated with severe disability. DMTs have proven efficacy in reducing short-term disability progression in the setting of RCTs of one to two years duration. Despite advances in therapies, there is little evidence on the long-term efficacy of DMTs on reducing disability progression and conflicting results have been reported for the first-line DMTs IFN ß and GA. [123 124] Long-term studies are required to assess the benefits of DMT over time.

5.5.4.3 Comparison of Indirect Costs

The mean cost of informal care in this study is similar to that reported elsewhere, despite lower levels of informal care provision in our study.[1 134 222] In the present study, 21% of patients reported receipt of informal care compared to 22-63% in TRIBUNE and 48-62% in Kobelt *et a*l. This discrepancy is due to the valuation methods used. The opportunity cost method was used to value informal care in both our study and the TRIBUNE study. Unlike TRIBUNE, productivity losses were calculated for time spent providing informal care, irrespective of whether the caregiver was in employment or otherwise. Kobelt *et al* used the concept of loss of leisure time of family members,

using the net disposable income after taxes, which yields lower unit costs. Average annual wages are higher in Ireland compared with many other OECD countries which would be expected to lead to relatively higher indirect unit costs when using the human capital approach. [297]

Productivity losses from absenteeism and early retirement are higher than TRIBUNE (with the exception of the Netherlands study) and similar to Kobelt due to similar levels of early retirement in these studies. 36% of our study population were retired early due to MS. In Ireland, the qualifying age for state pensions is 66 years. In our study cohort, the mean age at which people retired due to MS related ill health was 44.26 years, resulting in significant productivity losses. Mean productivity losses per person were similar in moderate and severe disease indicating that the shift away from employment is largely complete before disability reaches the severe stage, as defined in this study.

5.5.4.4 Relapse-related Costs

Although other studies have used findings from studies such as this to estimate the costs associated with an MS relapse, this has not been attempted in this study. Details of relapse severity, duration or management etc. were not collected. Attributing costs to recent relapses based on overall annual resource utilisation is problematic. Furthermore, inclusion of recent relapse in our regression model did not reveal this variable as a significant predictor of mean annual costs.

5.5.5 Health State Costs

5.5.5.1 Linearity of Health State Costs

As expected, in line with the trend demonstrated by the mild, moderate and severe subgroups, EDSS health state costs generally increased as EDSS disability increased. This relationship was not linear however, with deviations particularly occurring among the moderate disability health states EDSS 4 and 5. The small patient number in EDSS 5 (n=3) may have contributed to the observed trend. However the variability among individual health states representing patients with moderate disability (EDSS 4.0-6.5) has been demonstrated in other studies. The Kobelt series of CoI studies include figures graphically illustrating the relationship between costs and EDSS score. A visual inspection of graphs illustrating costs by EDSS level from the nine studies included in

the Kobelt series of studies indicates a non-linear trend of increasing cost with increasing disability. [161 214-221] The graphs also reveal some reductions in total (direct and indirect) mean annual costs across the EDSS spectrum, most commonly between EDSS 3 and 4 [161 215 217 219 221] and between EDSS 5 and 6. [161 216 219] More widespread fluctuations are apparent in direct medical costs.

As discussed earlier, the distribution of costs changes as disease progresses and increasing disability may have different impacts on the utilisation of different resources. The overall management approach may change from active intervention involving pharmacological treatments, regular investigations and consultations to more supportive long-term multidisciplinary management and rehabilitation which becomes more intensive in the severe stages of the disease as patients' independence diminishes.

5.5.5.2 Comparison with other MS Health State Costs

EDSS health state costs for patients with mild to moderate disease up to EDSS 4 are very similar to those included in the manufacturer's submission for the NICE fingolimod assessment (Table 5.6). [51] Thereafter health state costs in our study are higher than equivalent UK costs, particularly for EDSS 8 and 9. The costs included in the fingolimod submission were obtained from the Kobelt UK CoI study. [214] As described above, patients in nursing homes were not represented in this study and therefore would be expected to underestimate the cost of very severely disabled patients. On the other hand, as outlined in the methods section, this study assumes that 100% of nursing home costs are covered by the HSE, which may overestimate healthcare payer costs for these patients.

5.6 Limitations

Our study has a number of limitations. Our sample was recruited from a specialist MS outpatient clinic and as such may be considered biased towards those early in the disease course. However, the clinic also cares for patients with very severe disability, including those permanently resident in nursing homes, and this patient group are also represented in our sample. Stratification of patients and reporting of results according to mild, moderate and severe disease attempts to mitigate any overall sample bias. Postal survey of those registered with patient organisations is an alternative method of patient recruitment. Self-administration methods have been shown to impose a greater

cognitive burden on respondents than face-to-face interviews and in general report higher item non-response.[135] Face-to-face interview based surveys can increase motivation of respondents to respond through clarification, pausing and encouragement, and can ensure that questions are not missed. However interviewer and social desirability bias can also be a feature of face-to-face interviews. [137] Our study-design did not require the use of exhaustive lists of resources e.g. medication lists, healthcare professional types etc. which are often necessary in postal surveys in order to standardise responses and would therefore be expected to encompass a more complete range of resources. [138]

Additional patient costs revealed in interview narrative include clothing and heating expenses, travel and insurance costs. These were not reported in a quantitative manner and as such have not been included in these results.

Patients were recruited from just one centre and the extent to which our sample is representative of the general population of MS patients cannot be definitively assessed. However the demographics of our sample are highly comparable with those of a cross-sectional epidemiological study that includes 632 patients with MS from three different regions of Ireland. [73]

The study relies on patient recall in order to obtain complete information on a wide variety of resources. Different recall times have been used in order to facilitate recall of events which are expected to happen with different frequency, under the assumption that the recall period is representative of other periods of similar duration throughout the year.

The opportunity cost approach employed in this study values care-giving at the wage the caregiver would earn if in paid employment, based on national mean annual earnings. No distinction was made between carers who were in paid employment and those who were not. This approach may potentially lead to an overestimate of the actual productivity losses to society. However, a conservative approach to quantifying care-giving time was also taken, by placing a cap on care-giving hours in line with the average number of working hours per week. Valuing the time of just the working care-giver underestimates the contribution of those who may be retired, look after the family or home, or other carers not in paid employment. Alternative approaches to the opportunity cost method include the replacement cost approach which values care-giving at the cost of procuring care from a professional, and the loss of leisure time approach which uses net disposable income to value time spent care-giving.

5.7 Conclusions

MS is a high cost therapeutic area, with significant economic implications for society as a whole, and for individual patients whose HRQoL is also adversely affected. Economic consequences are most associated with progression from mild or moderate to severe disease, loss of independence in the home and early withdrawal from the workforce. It follows that interventions which aim to prevent or delay disease progression, support independent living at home and maintain workforce participation have the potential to reduce overall costs associated with MS. Information on the total direct and indirect costs of MS provides the economic framework upon which questions of resource allocation and expenditure on such interventions can be based. Such questions require further information on the costs and benefits of possible health interventions in order to estimate efficiency and cost effectiveness.

Health state costs obtained in this study will be applied in the decision-analytic model of DMT in RRMS, developed for this thesis and described in Chapter 8.

CHAPTER 6 - RELATING HEALTH RELATED QUALITY OF LIFE TO DISABILITY PROGRESSION IN MULTIPLE SCLEROSIS, USING THE FIVE-LEVEL EQ-5D

CHAPTER 6 – RELATING HEALTH RELATED QUALITY OF LIFE TO DISABILITY PROGRESSION IN MULTIPLE SCLEROSIS, USING THE FIVE-LEVEL EQ-5D

This chapter describes the derivation of health state preference values for inclusion in a decision analytic model for DMT in MS, from a cohort of patients with MS in Ireland. The study draws on methods described in Chapter 4 and draws comparisons with the international evidence on HRQoL in MS reviewed in Chapter 3. This study was conducted in parallel with a CoI in MS study and was facilitated by the neurology team in St. Vincent's University Hospital (SVUH), a research group with an international reputation in the field of MS research.[282] A paper based on this study has been published in the Multiple Sclerosis Journal (See Appendix 7). Scientific abstracts based on this study have been presented at the Irish Neurological Association Annual Meeting 2012 and the International Society for Pharmacoeconomics and Outcomes Research Annual European Conference (ISPOR Berlin, November 2012).

6.1 Introduction

Multiple sclerosis (MS) is a chronic debilitating disease associated with significant economic and HRQoL burden.[1 237] Neurological symptoms of varying severity can result in functional limitations which can severely impact patients' physical activity, employment capabilities and opportunities. Such limitations can arise from both acute and chronic disability and are compounded by psychological, social and psychiatric consequences which further reduce HRQoL.[298]

In order to inform resource-allocation decision-making through the application of the QALY, clinical outcomes must be related to HRQoL. Change in the EDSS remains the standard definition for disease progression in MS clinical trials and MS disease models are commonly structured on health states representing scores on the EDSS scale. The relationship between the EDSS and HRQoL, as a reflection of patients' overall well-being, is therefore of significant importance. The original EQ-5D-3L is the most widely used method to obtain preference-based valuations for

HRQoL and has been widely used in MS where studies have consistently shown a decrease in utility with increasing neurological disability. [10, 11] HRQoL has, to date, not been reported for an Irish MS population. The EQ-5D-3L has been criticised for its ceiling effects and insensitivity to change, particularly in patients with milder conditions.[149 164] This chapter describes a study in which Health state utility values (HSUVs) based on the EDSS scale were derived for a Irish cohort of patients with MS using the five-level EQ-5D (EQ-5D-5L).

6.2 Aims

The aims of the study were to:

- derive HSUVs based on the EDSS scale using the EQ-5D-5L
- explore the relationship between EDSS score and EQ-5D-5L HRQoL utility
- assess the discriminative capacity of the EQ-5D-5L in its first reported use in MS

6.3 Methods

Information on ethical approval, patient recruitment and consent, clinical status and data collection and storage is described in Chapter 5, sections 5.3.1 to 5.3.4 as this HRQoL study was conducted in parallel with a CoI study in the same patient cohort.

6.3.1 HRQoL Measure

The five level version of the EQ-5D (EQ-5D-5L) was used. The EQ-5D-5L is a generic, preference-based, self-report HRQoL instrument developed by the EuroQol Group.[149 168] Respondents record their perceived level of problems in five domains of health: mobility, self-care, usual activities, pain or discomfort and anxiety or depression, indicating no problems, slight, moderate, severe or extreme problems in each domain. Based on the combination of responses, respondents are classified into one of 3125 unique EQ-5D-5L health-state profiles. Each health state is converted to a single utility value representing general population preferences. [299] Utilities are measured on a cardinal scale anchored at 1 (perfect health) and 0 (absence of life/dead). Valuations less than zero (as low as -0.594), reflecting health states worse than death (WTD), can exist. Country-specific preferences, reflecting trade-offs that individuals

are willing to make between health outcomes, have been elicited directly from general populations for the EQ-5D-3L. Preference elicitation studies based on the EQ-5D-5L are ongoing. Until the preference elicitation studies are complete, a "crosswalk" between EQ-5D-3L index values and the new EQ-5D-5L descriptive system has been undertaken by the EuroQol group. The "crosswalk" UK population valueset has been applied in this study. [300 301] Respondents rated their overall health status on a visual analogue scale (VAS) between 0 and 100, representing worst and best imaginable health, respectively.

6.3.2 Clinical Status

As described in Chapter 5. In brief, the recruiting consultant neurologist/specialist registrar/clinical nurse specialist recorded the type of MS (i.e. RRMS, SPMS, PPMS, Benign) and each patient's level of disability on the EDSS scale [31]

6.3.3 Data Collection and Storage

As described in Chapter 5. In brief, patients self-completed EQ5D-5L and VAS. Hard copies of the questionnaires were stored in a locked filing cabinet in the NCPE. Electronic data was stored in encrypted files on a desktop computer in the NCPE.

6.3.4 Analysis

6.3.4.1 Summary Statistics and Multivariate Linear Regression

Baseline patient characteristics were summarised using the mean, standard deviation (SD), median and interquartile range for continuous variables and proportions for categorical variables. Baseline factors predictive of utility score were identified using a multivariate linear regression model including age, gender, EDSS, MS type, recent relapse, duration since diagnosis and employment status. Half-points on the EDSS scale were combined to give an integer scale in line with the approach taken in many CEAs of DMT in MS which have structured decision models on health states representing aggregate scores on the EDSS scale. Data were analyzed using R version 2.12. [302]

6.3.4.2 Piecewise Linear Regression

The association between EDSS and utility was determined using a piecewise linear regression, with the constraint that the function be monotonic, that is increases in EDSS are associated with a disimprovement in utility. Means and 95% credible intervals are presented. The model was fitted in WinBUGs 1.4.3.[303]

6.3.4.3 Meta-analysis of MS Utilities

A meta-analysis of MS utilities reported in nine European studies was conducted to assess comparability of our results.[161 214-221] Utility values were collected in these studies using the EQ-5D-3L. SDs were reported in a follow-up to one of these studies (UK) but otherwise are not reported. [238] The variability of the utility measurements for this sample was therefore used as the SD in pooling the results from the remaining eight studies. Data were analysed using the package rmeta[304] in R version 2.12. [302]

6.3.4.4 Shannon's Indices of Evenness and Informativity

The discriminatory power of the EQ-5D-5L was assessed using Shannon's indices.

6.4 Results

6.4.1 Patients

Two hundred and fourteen patients were recruited for the study. Sixty six per cent of respondents were female and the mean (SD) age was 47.6 years (12.75 years). The distribution of EDSS scores in the population was bimodal with peaks at EDSS 1 and EDSS 6 and fewer numbers with EDSS scores of 5 and 9 (Figure 6.1). Mean (SD) EDSS score was 3.59 (2.64). Fifty three per cent of patients had relapsing-remitting MS. Further demographic details are provided in Chapter 5, section 5.3.1 and key demographic data are summarised in Table 5.2.

6.4.2 EQ-5D-5L Profile

Complete EQ-5D-5L health state profiles were described by 213 patients. The proportions of patients indicating responses at each level in each domain are presented (Table 6.1). Patients who were retired or currently not working were significantly more likely to have problems in each domain (anxiety Odds Ratio (OR) 1.97, pain OR 4.79, self-care OR 4.83, usual activities OR 7.11, mobility OR 10.18 ($p<0.05$)). Males were

significantly more likely to have problems with mobility (OR 2.24 $p<0.05$) and usual activities (OR 2.71 $p<0.05$). Those with progressive disease and those with EDSS$\geq$6 were significantly more likely to have problems in all domains except anxiety ($p<0.01$).

Table 6.1: EQ-5D-5L descriptive system: ratings in each domain n(%)

Level of problems	Mobility	Self-care	Usual Activities	Pain or Discomfort	Anxiety or Depression
None	64(29.9%)	136(63.8%)	63(29.4%)	70(32.7%)	98(45.8%)
Mild	53(24.8%)	35(16.4%)	45(21.0%)	65(30.4%)	72(33.6%)
Moderate	44(20.6%)	21(9.9%)	59(27.6%)	52(24.3%)	35(16.4%)
Severe	30(14.0%)	6(2.8%)	27(12.6%)	22(10.3%)	9(4.2%)
Extreme	23(10.7%)	15(7.0%)	20(9.3%)	5(2.3%)	0(0.0%)

*Complete EQ-5D-5L responses were available for 213 patients and partial responses were available for one patient.
EQ-5D-5L=Five-level Euroqol-5D

6.4.3 EQ-5D-5L Utilities

The mean EQ-5D-5L utility value for the cohort was 0.59 (SD 0.33, median 0.67, IQR 0.47-0.83). An EQ-5D-5L utility value could not be calculated for one patient due to incomplete data. The distribution of utility values was bimodal, typical of EQ-5D scores, and right skewed with 73% of patients scoring ≥0.5. Utility values of 1.0 were calculated for the 25 (11.7%) patients who reported no problems in all domains of the EQ-5D-5L. Conversely, values below zero, representing states "worse-than-death" (WTD), were found for 21 (9.9%) patients *(Figure 6.1)*.

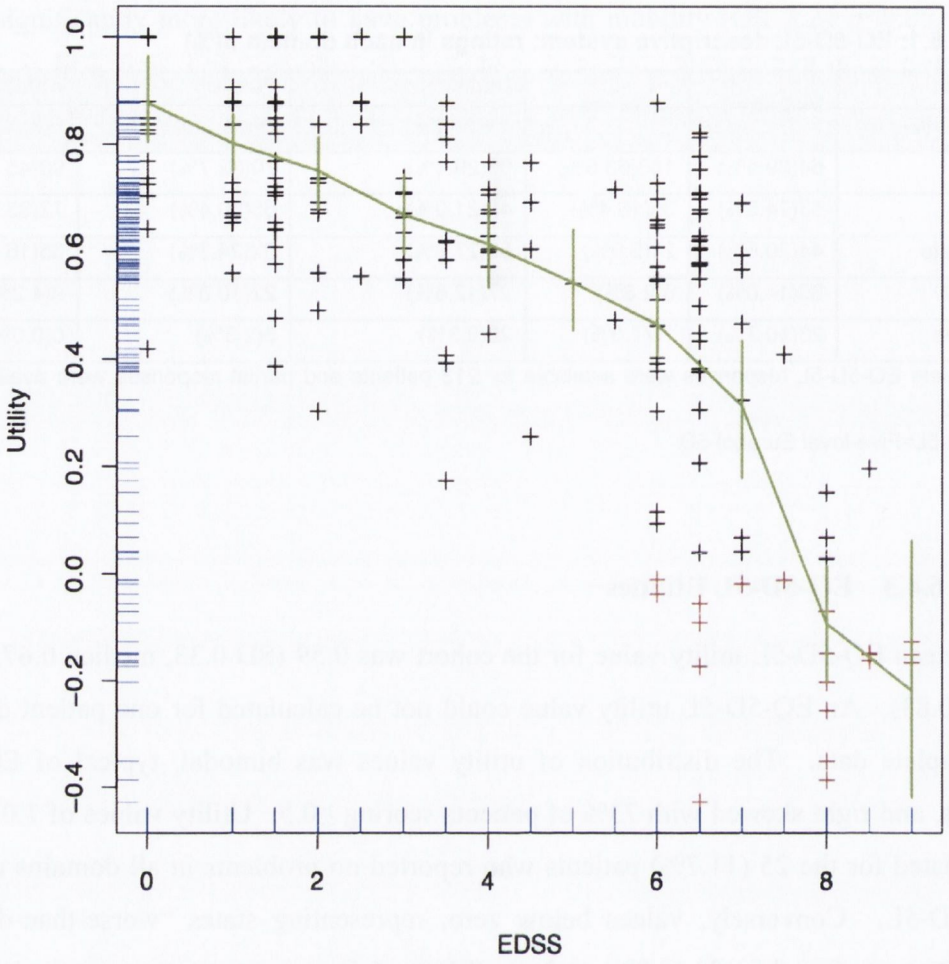


Figure 6.1: Relationship between EDSS and Utility

Scatterplot of patient data with superimposed regression line showing the relationship between EDSS and utility. A linear decline in utility is observed as EDSS progresses from 0 to 6, followed by sharp declines in utility, falling below 0 at EDSS 8 and 9. Rug plots illustrate the marginal distributions of EDSS scores on the x-axis and of utility values on the y-axis. Both distributions are typical of the respective scales, with bimodal peaks in patient numbers at EDSS 1 and 6, and in utility at ~0.7 and ~-0.2.
EDSS= Expanded disability status scale

There was a significant inverse relationship between EDSS score and utility ($p<0.001$). The mean VAS score, representing patients' own valuation of their health state on a scale of 0-100 was 65 (SD 22.38) and was consistent with EQ-5D-5L utility (Pearson correlation 0.69, $p<0.0001$). Piecewise linear regression coefficients for EQ-5D-5L utility based on EDSS score are summarised in Table 6.2. In the piecewise regression model a linear decline in utility was observed from EDSS 0 to 6. Thereafter larger utility decrements were observed with progression from EDSS 6 to 9 (*Table 6.2*). Mean utility values from the piecewise linear regression ranged from -0.22 (EDSS 9) to 0.88

(EDSS 0), and were associated with smaller standard errors than a simple linear model. The greatest utility decrease was between EDSS 6 to 7 (decrease of 0.15) and EDSS 7 to 8 (decrease of 0.41).

Table 6.2: Piecewise linear regression coefficients for EQ-5D-5L utility

EDSS	0	1	2	3	4	5	6	7	8	9
n	22	49	22	21	15	3	54	10	14	3
Utility	0.88	0.80	0.75	0.67	0.61	0.54	0.46	0.31	-0.09	-0.22
95% CI										
Lower	0.80	0.75	0.68	0.60	0.53	0.45	0.41	0.18	-0.20	-0.42
Upper	0.96	0.85	0.81	0.74	0.69	0.64	0.52	0.43	0.01	-0.06

Abbreviations: EDSS: Expanded Disability Status Scale. 95% CI: 95% credible interval.

Age, duration since diagnosis and progressive disease were significantly negatively correlated with utility ($p<0.001$), but had no additional predictive value beyond that provided by the EDSS. Utility values for patients who were retired or currently not working were, on average, 0.133 lower ($p<0.001$) than those who were in employment or full-time education. There was no significant difference in utility between males and females. Mean utilities for each EDSS score were consistent with those of a European study involving nine countries which used similar methodology (EQ-5D-3L instrument using UK population preferences) (Figure 6.2).

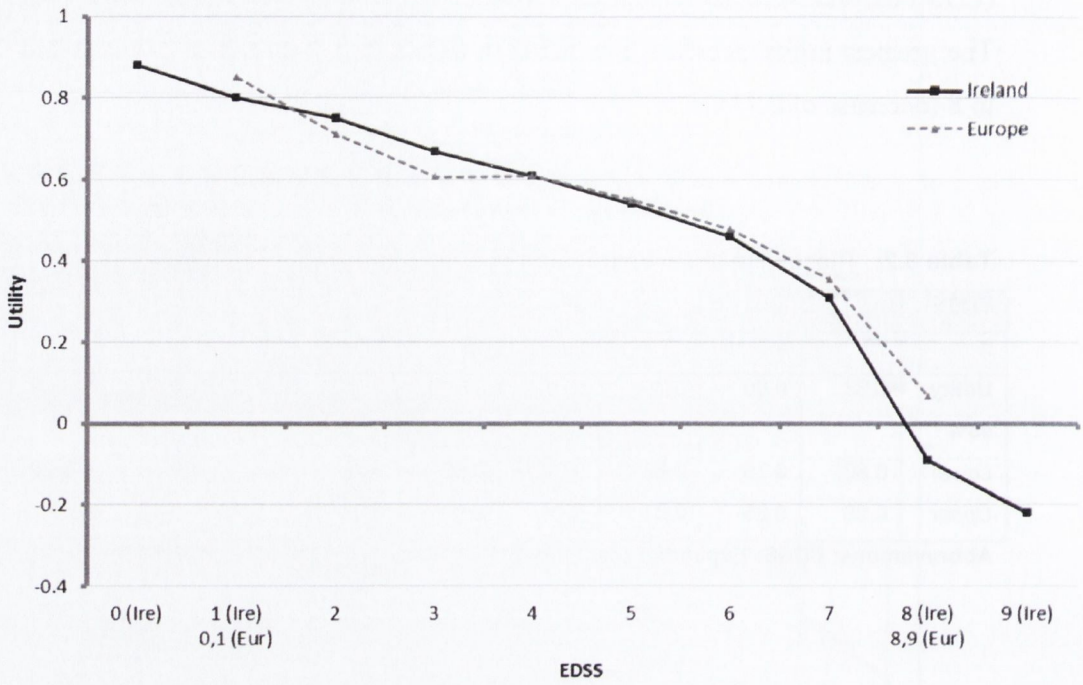


Figure 6.2 Comparison of health utilities by EDSS scores

Comparison of utility values from figure 6.1 above (Ireland) and Kobelt *et al* (Europe). [161 214-221] Mean values reported by Kobelt *et al* were combined by meta-analysis. Mean values for EDSS 6 and 6.5, reported separately by Kobelt *et al*, were weighted by population size to give a value for EDSS 6, prior to meta-analysis. Kobelt *et al* combined EDSS 0 and 1, and EDSS 8 and 9 and also truncated utility scores at zero, prohibiting comparison of the most severe health states between studies.

EDSS=expanded disability status scale

6.4.4 EQ-5D-5L Performance

Shannon's index *(H')*, representing absolute informativity, and Shannon's Evenness index *(J')*, representing relative informativity, are presented for each domain of the EQ-5D-5L in Table 6.3. Both indices were considerably higher for mobility, activity and pain/discomfort domains (*H'* 2.01-2.23, *J'* 0.57-0.96) compared with the domains self-care and anxiety/depression (*H'* 1.58-1.66, *J'* 0.68-0.72).

Table 6.3: Shannon's Indices for the EQ-5D-5L

Domain	*H'*	*J'*
Mobility	2.23	0.96
Self-care	1.58	0.68
Usual Activities	2.20	0.95
Pain/ Discomfort	2.01	0.87
Anxiety/ Depression	1.66	0.72

Shannon's index (H') and Shannon's Evenness index (J')

6.5 Discussion

6.5.1 Relationship between EQ-5D-5L utility and EDSS

A comparison of normative population mean health state utilities (0.86 and 0.87 for the UK and the US, respectively) with that of our sample (0.59) confirms the deleterious effect of MS on HRQoL. [305] [306] Our sample of MS patients comprises a heterogeneous group with wide-ranging health-profiles and utility scores. Nevertheless the variation in health utility appears to be primarily explained by the severity of disability, represented by EDSS. While other predictive variables including type and duration of disease were correlated with utility, they had no additional predictive value beyond that provided by EDSS. Despite the criticism of the EDSS in terms of the equivalence of change at different levels of the scale, change in EDSS score remains the standard definition for disease progression in clinical trials - often defined as a 1.0 step increase for individuals with an overall EDSS $\leq$6.0 confirmed at 3 months. In this study, the linearity of the EDSS scale with respect to HRQoL was maintained for EDSS scores $\leq$6. The significant explanatory value of EDSS 0-6 for utility, observed in this study, supports use of this outcome in clinical trials, particularly in trials of DMT for relapsing-remitting MS which have limited application in patients in more advanced disability states. [85] A dramatic fall in utility was observed above EDSS 6 at which point the relationship between EDSS and HRQoL exhibits greater variability. The magnitude of this drop in utility after EDSS 6, together with the small patient numbers in these advanced health states in our study, contributes to this variability.

6.5.2 Comparison with other studies and validity of Worse-than Death (WTD) utilities

Mean utilities for each EDSS score were consistent with those of a study by Kobelt *et al* in which utility data was derived from EQ-5D-3L results of a cross-sectional postal survey of MS patients in nine European countries. [307] In the reported analysis of this survey however, utilities (measured using the EQ-5D-3L) were truncated at zero, prohibiting comparison of the most severe health states between studies. Approximately 10% of our sample had utility scores <0 i.e. perceived to be in health states WTD according to the EQ-5D scoring methodology. WTD valuations of health-state utility arise in population studies when respondents indicate a preference for immediate death rather than spending any time in the described health state. Perfect health is therefore anchored at 1.0, immediate death is 0, and health states WTD are assigned negative weights. While the validity of WTD health states as a reflection of population preferences is supported, the valuation of these very severe health states is to a large extent an artefact of the scoring methodology due to problems of scaling and measurement. [308 309] Weaknesses have been identified in existing protocols for eliciting valuations of states WTD, including that of the UK EQ-5D valueset, whereby negative values can be extremely negative.[309] The questionable face validity of the WTD states obtained when using EQ-5D has been highlighted in other chronic diseases.[310] Alternative mappings are available in the literature and the impact of these is most notable for severe disease states. [162] The approach taken by Kobelt *et al*, among others, truncates utility values at zero. [1] In contrast, in a study on the cost effectiveness of DMT in MS, requested by the Centers for Medicare and Medicaid Services (CMS) in the United States, it was assumed that individuals at EDSS 9.5 would fulfil the criteria for the worst health state in the EQ-5D classification, to allow for informative censoring in severely disabled individuals. The utility for this state was therefore assumed to be -0.594. [236] The mean utility valuation for the worst health state in our study is -0.22. The results of our study are highly consistent with those of Kobelt *et al*, with the exception of the most severe health-states, most likely due to this truncation of WTD scores.[1] In countries such as Ireland, where CUA based on preference-based instruments are used to inform policy decisions, acknowledgement of these very severe health states can have important consequences. Large differences in health-state utilities can result in substantial differences in QALYs, depending on the length of time

a patient may be expected to remain in the relevant health state. Given that MS patients progress slowly once EDSS 6 is reached, the impact of including or excluding utilities <0 on subsequent cost-per-QALY calculations may be significant. A new DMT which delays progression to health states associated with WTD utility values may yield substantially more QALYs in a CUA compared with an older DMT which delays progression to a lesser extent, or compared with BSC. Greater QALY gains are achievable if WTD utility values are allowed than if these values are truncated at zero, ultimately leading to more favourable estimates of cost-effectiveness for the new DMT. Methodological advances for the elicitation of health preferences, particularly for very severe health states, should therefore be a priority.

6.5.3 First reported use of the EQ-5D-5L in MS

EQ-5D has been widely used in MS QoL research. A ceiling effect has been reported for the EQ-5D-3L and there may be issues regarding its ability to measure small changes in health, particularly in patients with milder conditions. [164] A number of European studies on costs and QoL in MS have incorporated EQ-5D-3L however a similar study has not been undertaken in a cohort of Irish patients. To our knowledge, this is the first time the redesigned EQ-5D-5L has been used in the MS patient population. [168] The EQ-5D-5L has been developed for better discriminative capacity and sensitivity to change than the original EQ-5D-3L, as well as smaller ceiling effects. [168] Increasing the number of response categories is an intuitive way of enhancing discriminatory capacity, however if the additional levels are underutilised or don't represent the population, this will not be achieved. As this is the first reported use of this instrument in MS, its discriminative capacity has been assessed.[170] Janssen *et al* have proposed Shannon's indices of informativity as suitable measures of discriminatory power of multi-attribute utility instruments such as the EQ-5D-5L and have used this method to compare the performance of the EQ-5D-5L and the EQ-5D-3L. [169 311] Shannon's indices for the domains mobility, usual activities and pain/discomfort in our study are in line with EQ-5D-5L results reported by Janssen *et al* (2.05-2.26), and higher than those reported for the EQ-5D-3L instrument in the same study (1.44-1.55). [170] However discriminatory power for the domains self-care and anxiety/depression was lower than the other three domains with index values similar to those of the EQ-5D-3L observed by Janssen *et al.* [170] This finding reflects

underutilisation of the severe/extreme levels in these domains of health in the setting of MS. Extending the descriptive system to five levels for these two domains did not lead to a gain in absolute informativity *(H')* and decreased the relative informativity *(J')* of the instrument. Further study is required to ascertain if underutilisation of the available levels in these domains, despite the availability of two additional levels in the EQ-5D-5L, is particular to our sample or a feature of the performance of this instrument in MS in general.

6.6 Limitations

6.6.1 Absence of Longitudinal Data

The capacity of the EQ-5D-5L to detect changes in health status within individuals was not investigated as observations were obtained from our cohort at just one timepoint. A longitudinal study design involving serial evaluations of both EQ-5D-5L utility and EDSS at different intervals would yield valuable information on the usefulness of this instrument for both clinical practice and CUA.

6.6.2 Absence of Irish Population Preferences

A large-scale national study eliciting Irish population preferences for EQ-5D health-state profiles has not been conducted. The transferability of utilities from one country to another has been questioned as studies differ in valuation methodologies used and cultural dissimilarities between countries. Methodological differences can influence the valuation of health states using different scoring systems, particularly for very severe health states. [312] In the absence of Irish public preference data, the UK population valueset was used in this study. [301] The similarity of UK population preferences to those of the Irish population has not been investigated.

6.6.3 Use of "Crosswalk" Dataset of Population Preferences

Preference elicitation studies based on the EQ-5D-5L are underway in a number of countries. Until these studies are complete, a "crosswalk" between the EQ-5D-3L index values and the new EQ-5D-5L descriptive system has been undertaken by the EuroQol group and "crosswalk" value set have been used in this study.

6.6.4 Relevance of EQ-5D domains in MS

Low coverage of quality of life domains relevant to MS has been reported by some reviewers of the EQ-5D. [298] As a generic preference-based instrument, there are inevitable limitations on the extent to which the EQ-5D can address all health domains of relevance to all diseases. Condition-specific instruments do not incorporate preferences in the scoring algorithm and therefore can not be used in cost-utility analyses. Condition-specific, preference-based measures are in the early stages of development. [167] National guidelines on health technology assessment, in both Ireland and the UK, recommend use of the EQ-5D. [7 160]

6.6.5 Relevance of Results to General Population of MS Patients

Our sample was restricted to one MS outpatient clinic with limited coverage of patients in the most severe health states. In contrast to population studies which typically show peak distributions at EDSS 3 and 6, a peak in our cohort was observed at EDSS 1 reflecting a bias towards those early in the disease course. Nonetheless, the demographics of our sample are highly comparable with those of a cross-sectional epidemiological study including 632 patients with MS from three different regions of Ireland. [73] Our HRQoL results are also comparable with those of the European studies of Kobelt *et al* and other international studies.[1 237]

6.7 Conclusion

The detrimental impact of MS-related disability on utility highlights the need for innovative DMT which will delay or potentially halt the dramatic deterioration in HRQoL which occurs as the disease progresses. HSUVs obtained in this study will be applied in the decision-analytic model of DMT in RRMS, developed for this thesis and described in Chapter 8. The EQ-5D-5L offers a promising alternative to the EQ-5D-3L for use in both population-based studies and clinical trials. Significant uncertainty in valuing very severe health states remains however and further methodological research in this area is warranted. The EQ-5D-5L in general displayed good discriminatory capacity in our MS cohort although performance varied over the domains of health covered by the instrument. As the use of the EQ-5D-5L becomes more widespread the

peculiarity of this finding to our cohort, to the MS population, or to respondents in general will become apparent.

CHAPTER 7 – RELATIVE EFFICACY OF DISEASE-MODIFYING THERAPIES FOR MULTIPLE SCLEROSIS

CHAPTER 7 – RELATIVE EFFICACY OF DISEASE-MODIFYING THERAPIES FOR MULTIPLE SCLEROSIS

This chapter describes the process by which evidence on the relative efficacy of all relevant DMTs was identified and synthesised using systematic review and network meta-analysis methods. Dr. Susanne Schmitz, Assistant Professor of HTA in the Department of Pharmacology and Therapeutics in Trinity College Dublin, designed the statistical methodology applied in this chapter. Professor Niall Tubridy provided clinical advice and reviewed the study for clinical integrity. Scientific abstracts based on this study have been presented at the International Society for Pharmacoeconomics and Outcomes Research Annual European Conference (ISPOR Berlin, November 2012), the European Committee for Treatment and Research in Multiple Sclerosis (ECTRIMS Copenhagen. October 2013) and at ISPOR, Dublin November 2013.

7.1 Introduction

Treatment efficacy is a core component of all CEAs. High quality RCTs are considered the gold standard for quantifying relative efficacy, and meta-analysis of RCTs is recommended to combine quantitative results from multiple studies to summarise the available evidence. [174 182] Numerous comparators must be considered in the case of RRMS and an RCT comparing all treatments of interest is not available, nor is such an RCT likely to be conducted. The existing evidence on the relative efficacy of DMTs for RRMS (described in Chapter 3) has been synthesised largely using traditional pairwise meta-analyses. In contrast to traditional meta-analysis where all RCTs compare the same intervention with the same comparator, NMA allows multiple pairwise comparisons across a range of different treatments facilitating the estimation of relative effects in the absence of head-to-head RCTs. [176] A limited number of NMAs have been conducted but have selected specific outcomes or trial designs, or were completed before data on relevant comparators were available. Consideration of all evidence on comparative efficacy with existing therapies is required to inform not just

health policy but also clinical care. As such, the work described in this chapter is intended to be applicable to both CEA and comparative effectiveness research.

7.2 Aims

The aim of the work described in this chapter is to evaluate the efficacy of DMTs for RRMS compared with placebo and compared with each other, by conducting a:

- Systematic review of RCTs of all DMTs for RRMS
- Network meta-analysis of RCT evidence to allow simultaneous estimation of relative efficacy of multiple treatments and ranking of treatment strategies

Relevant DMTs include those which have been approved by US and European regulatory agencies for the treatment of RRMS or are currently under evaluation, including:

- IFN β-1b SC 250mcg subcutaneous injection (SC)
- IFN β-1a IM 30mcg intramuscular (IM) injection
- IFN β-1a SC 22mcg
- IFN β-1a SC 44mcg
- GA 20 mg
- natalizumab 300mg intravenous infusion (IV)
- alemtuzumab 12mg IV
- fingolimod 0.5mg once daily (od) oral
- teriflunomide 7mg oral
- teriflunomide 14mg oral
- laquinimod 0.6mg oral
- BG-12 480mg oral
- BG-12 720mg oral

7.3 Methods

A systematic review of RCTs of DMTs in RRMS was performed in line with the PRISMA statement. [313] Network meta-analysis was performed within a Bayesian framework.

7.3.1 Eligibility Criteria

Inclusion criteria were based on the PICOS approach: population (P), intervention (I), comparator (C), outcomes (O) and design of the studies (S), as follows:

- Population: Adult patients with RRMS. Studies targeting patients with SPMS or PPMS were excluded.
    - Some studies, while specifying RRMS as an inclusion criterion, also recruited a small number of patients with progressive disease. In these cases, studies which included >10% progressive patients were excluded.
- Interventions: DMTs which have been approved by US and/or European regulatory agencies for the treatment of RRMS or are currently under evaluation, including those DMTs listed under "Aims" above.
    - DMTs were categorised as "first-generation" or "second-generation". First-generation DMTs include all IFN ß products and GA, reflecting the timing of their introduction into clinical practice and their current place in therapy as first-line agents. Second-generation DMTs include natalizumab and fingolimod, established as second-line agents in current practice, and all other new and emerging DMTs which are in the final stages of the regulatory approval process including teriflunomide, laquinimod, BG-12 and alemtuzumab.
    - Unlicensed agents such as mitoxantrone and azathioprine, occasionally used for severe, rapidly worsening MS but not licensed for use in RRMS were excluded.
- Comparators: DMT for RRMS as outlined in "Interventions"; placebo
- Outcome: ARR (defined as the mean number of confirmed relapses per patient adjusted for the duration of follow-up to annualise it) and the proportion of patients free of disability progression as assessed by the EDSS, sustained over three months.
    - The definition of 'relapse' is subject to slight variation across trials but it is commonly defined as new or worsening symptoms that last 24 hours and occur in the absence of fever or infection.

  - Definitions of disability progression also vary between trials, but it is commonly defined as at least 1 point EDSS increase, or a 0.5 point increase if the baseline EDSS was $\geq$ 5.5, confirmed during two subsequent neurological examinations separated by an interval of at least three to six months free of attacks. [31] Change in EDSS score, sustained over at least three months is reported most commonly in RRMS RCTs.
  - Definitions of relapse and three-month confirmed disability progression reported in individual studies were accepted.
- Study Design: Randomised controlled trials.
  - Single-arm trials, DMT combination therapy trials, switching studies and trials using historical controls were excluded.

7.3.2 Information Sources

The following databases were searched from inception to September 2012 for relevant studies: EMBASE (1980-present), MEDLINE (1966-present, via PubMed), CENTRAL (via Cochrane Library issue 9/2012). The search strategies used a combination of database-specific indexing and free text words combined with Boolean operators. Date limits were not used but trials not in the English language were excluded. See Appendix 8 for an example of the search strategy. The reference lists of papers and existing systematic reviews identified by the database searches were assessed for additional relevant studies. The contents of a selection of neurology journals were hand searched to identify any very recent publications which had not yet been included and indexed by electronic databases (New England Journal of Medicine, Lancet, Lancet Neurology, Neurology, Multiple Sclerosis, European Journal of Neurology, Journal of Neurology, Neurosurgery and Psychiatry). The search strategy was re-run in November 2012. All citations identified from the electronic databases and other sources were imported into the bibliographic software Endnote® (Thomas Reuters, CA, USA) for reference management.

7.3.3 Study Selection

A Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) flowchart is presented in Figure 7.1. Selection of included studies was based on the inclusion and exclusion criteria. An initial screening of titles identified all citations

which could possibly meet the inclusion criteria. Following a review of the title and abstract of all possibly relevant citations, the full manuscripts of potentially eligible citations were retrieved and assessed for inclusion where possible. Results published only in abstract form were not included.

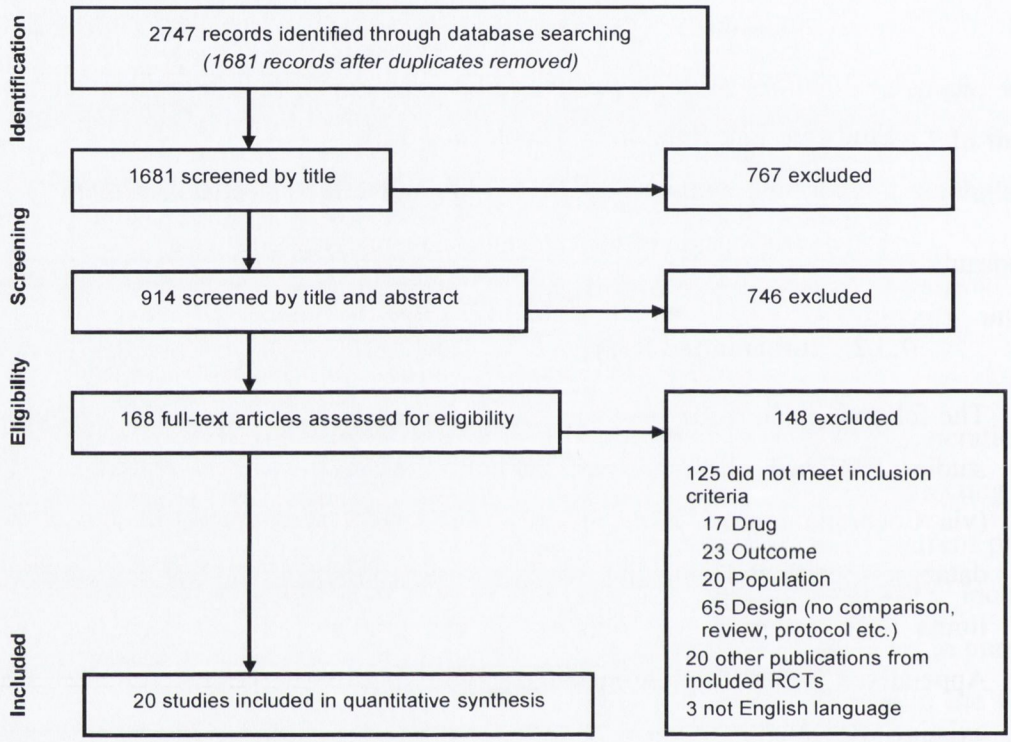


Figure 7.1: PRISMA flow diagram

7.3.4 Data Extraction

Data relating to study outcomes, participants, design and quality were extracted from all included studies and recorded on a data extraction form. Extracted data include:

- Outcomes: ARR (defined as the number of confirmed relapses per year) and proportion of patients free of short-term disability progression (confirmed at three months) at the end of the ITT follow-up period. Where ARR was not reported, results were derived from total number of patients recruited, total number of relapses, mean number of relapses per person and total patient years (TPY) of follow-up, where reported. Where TPY was not reported, it was calculated in a number of ways depending on the available data

- (median of patient)-(years of other outcomes within the same trial)
- (number of patients)*(mean follow-up duration of the trial)
- (number of patients not withdrawn)*(planned follow-up duration) + (number of patients withdrawn)*(planned follow-up duration/2)
- (number of patients)*(planned follow-up duration)

TPY calculation assumptions were tested in sensitivity analyses.

- Participants: age, gender distribution, mean baseline EDSS, mean duration of disease, mean number of relapses in the previous two years, proportion previously treated with DMT.
- General study information: study identifier, author, name, year of publication, design, inclusion and exclusion criteria, definitions of relapse and disease progression. Name and dose of interventions, number of participants per study arm.

7.3.5 Risk of bias in individual studies

The quality of included RCTs was assessed using the Cochrane Collaboration's Risk of bias tool focussing on sequence generation, allocation concealment, blinding of participants and personnel, blinding of outcome assessment, incomplete outcome data, selective outcome reporting and 'other issues'. Studies identified to be at high risk of bias were excluded in sensitivity analysis.[182]

7.3.6 Data Synthesis

A Bayesian NMA model was fitted in WinBUGS 1.4.3. [16] This approach allows the estimation of relative treatment-effects through the combination of evidence from across the network while preserving within-trial randomised treatment comparisons. [17] For all pairwise comparisons the model estimates relative hazard rates (HR) of 3-month confirmed disability progression (assuming progression-free survival follows an exponential distribution) and relative ARR (assuming a poisson distribution for the number of relapses within one study arm). The model assumes random effects to allow for variability between treatment-effects in different studies. A non-informative vague prior was used for means and a uniform prior on the standard deviation parameter was assumed for the baseline effects, as recommended by Gelman *et al.* [314]

The probability that each DMT was the most efficacious regimen (i.e. rank one), next most efficacious (rank two) and subsequent ranking was assessed by ranking each treatment according to the estimated effect size in each Markov chain Monte Carlo cycle. The proportion of iterations in which a given treatment ranks first, second etc. out of all comparators gives the probability that this treatment occupies that rank. [18]

Potential sources of treatment-effect modification from baseline population differences were investigated by extending the model to a meta-regression including age, gender, baseline EDSS, duration of disease, number of relapses in the previous two years, and proportion of patients previously treated with DMT.

Inconsistency between direct and indirect evidence for each mean treatment-effect was examined by comparing the NMA model to a model relaxing the consistency assumption, in terms of DIC (Deviance Information Criterion). Deviance contributions for each data point are used to locate potential inconsistencies.

7.3.7 Sensitivity Analysis

A sensitivity analysis (SA) was conducted in which trials at high risk of bias were excluded. A separate ranking analysis was also conducted based on this SA. A number of additional sensitivity analyses (SA) were conducted to explore the impact of disability progression definition and trial duration on the results for the disability progression outcome.

7.4 Results

7.4.1 Study Selection

A total of 2747 titles and abstracts were screened for inclusion, from which 20 RCTs met the inclusion criteria (Figure 7.1). [66-71 91 101 104 105 108-110 114 119 243-246 315] Reasons for exclusion of titles at the full-text stage are provided in Appendix 8. The inclusion/exclusion criteria and the relapse/progression definitions applied in the RCTs are summarised in Appendix 8.

7.4.2 Characteristics of included studies.

Included RCTs were published between 1993 and 2012, and comprised a total of 14,610 patients treated for an average 1.72 years, and considered ten DMTs and 14

treatment strategies (two dose regimens were included for four DMTs). DMTs were categorised as first generation (IFN β-1b SC 250mcg, IFN β-1a IM 30mcg, IFN β-1a SC 22mcg, IFN β-1a SC 44mcg and GA) based on existing treatment algorithms, or second-generation (natalizumab, alemtuzumab, fingolimod, teriflunomide, laquinimod, and BG-12) based on the new and emerging nature of these drugs. Both placebo-controlled and direct-comparative trials informed the analysis for six of ten DMTs. ARR outcomes were obtained from all 20 studies while short-term disability progression was reported in 13 studies. The evidence network is presented in Figure 7.2. All trials aimed to recruit patients with RRMS however 8.5% of the TEMSO study population (teriflunomide vs placebo) had a secondary progressive or relapsing progressive course. [114] This RCT was retained in the analysis as it is the only teriflunomide RCT contributing to the network and the proportion of progressive patients was small. Just one RCT (alemtuzumab 12mg vs IFN β-1a SC 44mcg) exclusively included patients with clinically active MS on an alternative DMT.[108] Direct trial outcome data are presented in Table 7.1.

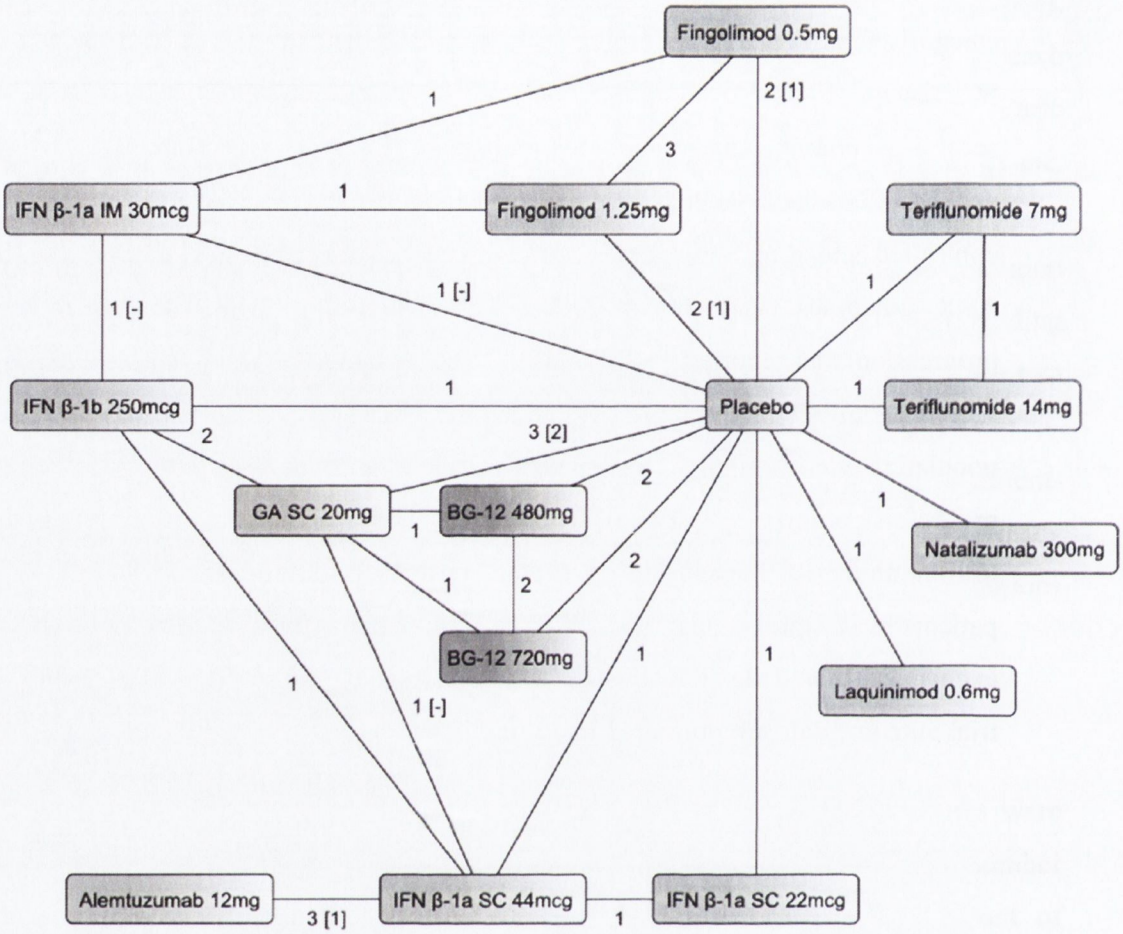


Figure 7.2: Network diagram of RCT evidence

Each node in the network represents a treatment strategy. Links between nodes represent pairwise treatment comparisons extracted from RCTs. Links are labelled with the number of trials for that link. Where included studies differ for relapse and disability progression outcomes, trial and patient numbers for the progression outcome are contained in square brackets and denoted with a [–] where progression outcome is not reported. Fingolimod 1.25mg forms a link between DMTs but is not itself a treatment strategy of interest.

Abbreviations: IFN B=interferon beta. GA=glatiramer acetate. SC=subcutaneous. IM=intramuscular

Table 7.1: Summary of RCT Outcome Data

Study Author (Study Acronym)	Year	Treatment	Number of Participants	Total Patient Years of follow-up*	Relapses*	ARR*	Proportion free of 3-month Confirmed Disability Progression
IFNβ MS Study Group [69 a]	1993	Placebo	123	209.45	266.00	1.27	0.73
		IFN β-1b SC	124	205.95	173.00	0.84	0.80
Johnson *et al* [68]	1995	Placebo	126	250.00	210.00	0.84	0.75
		GA	125	272.88	161.00	0.59	0.78
Jacobs *et al* (MSCRG) [67]	1996	Placebo	143	304.45	249.65	0.82	N/R
		IFN β-1a IM	158	327.38	219.34	0.67	N/R
PRISMS Study Group (PRISMS) [66]	1998	Placebo	187	363.00	477.41	1.32^	0.63¶
		IFN β-1a SC 22	189	365.00	343.04	0.94^	0.70¶
		IFN β-1a SC 44	184	362.01	317.45	0.88^	0.74¶
Comi *et al* [91]	2001	Placebo	120	75.37	91.20	1.21	N/R
		GA	119	74.93	60.69	0.81	N/R
Durelli *et al* (INCOMIN) [245]	2002	IFN β-1a IM	92	179.51	125.65	0.70	N/R
		IFN β-1b SC	96	188.48	94.24	0.50	N/R
Panitch *et al* (EVIDENCE) [244]	2002	IFN β-1a IM	338	304.24	216.46	0.71^	0.86
		IFN β-1a SC 44	339	305.62	183.18	0.60^	0.87
Polman *et al* (AFFIRM) [101]	2006	Placebo	315	738.00	538.74	0.73	0.71
		Natalizumab	627	1338.0	307.74	0.23	0.83
Mikol *et al* (REGARD) [246]	2008	GA	386	688.57	199.69	0.29	N/R
		IFN β-1a SC 44	378	689.49	206.85	0.30	N/R
CAMMS223 [110]	2008	IFN β-1a SC 44	111	247.22	89.00	0.36	0.67
		Alemtuzumab[b]	222	410.00	41.00	0.10	0.86
O'Connor *et al* (BEYOND) [243]	2009	GA	448	1126.1	382.88	0.34	0.20
		IFN β-1b SC	897	2299.0	827.64	0.36	0.21

Table 7.1: Summary of RCT Outcome Data Continued

Study Author (Study Acronym)	Year	Treatment	Number of Participants	Total Patient Years of follow-up*	Relapses*	ARR*	Proportion free of 3-month Confirmed Disability Progression
Kappos *et al* (FREEDOMS) [104]	**2010**	Placebo	418	515.00	206.00	0.40	0.76
		fingolimod 1·25mg[c]	429	537.50	86.00	0.16	0.83
		fingolimod 0·5mg	425	561.11	101.00	0.18	0.82
Cohen *et al* (TRANSFORMS) [105]	**2010**	IFN β-1a IM	431	542.42	179.00	0.33	0.92
		fingolimod 1·25mg[c]	426	525.00	105.00	0.20	0.93
		fingolimod 0·5mg	429	556.25	89.00	0.16	0.94
O'Connor *et al* (TEMSO)[114]	**2011**	Placebo	363	676.26	365.18	0.54	0.73
		teriflunomide 7	365	684.54	253.28	0.37	0.78
		teriflunomide 14	358	663.83	245.62	0.37	0.80
Saida *et al* [315]	**2012**	Placebo	57	27.02	26.75	0.99	N/R
		fingolimod 1·25mg[c]	57	25.52	10.46	0.41	N/R
		fingolimod 0·5mg	57	26.27	13.13	0.50	N/R
Comi *et al* (ALLEGRO) [71]	**2012**	Placebo	556	959.51	374.21	0.39	0.84
		Laquinimod	550	974.45	292.33	0.30	0.89
Gold *et al* (DEFINE) [70]	**2012**	Placebo	408	656.49	238.96	0.36	0.84
		BG-12 480	410	659.71	113.47	0.17	0.82
		BG-12 720	416	669.36	126.51	0.19	0.73
Fox *et al* (CONFIRM) [119]	**2012**	Placebo	363	599.40	239.76	0.40	0.87
		GA	350	594.04	172.27	0.29	0.83
		BG-12 480	359	581.09	127.84	0.22	0.87
		BG-12 720	345	556.44	111.29	0.20	0.84
Cohen *et al* (CAREMS1) [109]	**2012**	IFN β-1a SC 44	187	312.82	122.00	0.39	N/R
		Alemtuzumab	376	661.11	119.00	0.18	N/R

Table 7.1: Summary of RCT Outcome Data Continued

Study Author (Study Acronym)	Year	Treatment	Number of Participants	Total Patient Years of follow-up*	Relapses*	ARR*	Proportion free of 3-month Confirmed Disability Progression
Coles *et al* (CAREMS2) [108]	2012	IFN β-1a SC 44	202	386.54	201.00	0.52	N/R
		Alemtuzumab	426	907.69	236.00	0.26	N/R

DMT Doses: IFN β-1a IM 30mcg once weekly; IFN β-1a SC 22mcg three times weekly, IFN β-1a SC 44mcg three times weekly; IFN β-1b 250mcg every second day; GA SC 20mg once daily; BG-12 240mg oral twice daily (480mg), BG-12 240mg oral three times daily (720mg); fingolimod 0.5mg oral once daily; fingolimod 1.25mg oral once daily; teriflunomide 7mg oral once daily; teriflunomide 14mg oral once daily; natalizumab 300mg IV once monthly; Alemtuzumab 12mg IV once yearly; laquinimod 0.6mg oral once daily

Where ARR and/or total patient years of follow-up (TPY) were not reported, results were derived from total number of patients recruited, total number of relapses, mean number of relapses per person and total patient years of follow-up, where reported. Where TPY was not reported, it was calculated in a number of ways depending on the available data: median of patient-years of other outcomes within the same trial; (number of patients)(mean follow-up duration of the trial); (number of patients not withdrawn)*(planned follow-up duration)+(number of patients withdrawn)*(planned follow-up duration/2); (number of patients)*(planned follow-up duration).

[a] Interventions from IFNβ MS Study Group (IFN β-1b SC 50mcg) and BEYOND (IFN β-1b SC 500mcg) which were not among the treatment strategies of interest and which did not otherwise contribute to the network of evidence were excluded

[b] CAMMS223 Study found no significant differences between alemtuzumab 12mg and 24mg arms and reported pooled results which are used in this analysis and contribute to the efficacy estimate for alemtuzumab 12mg.

[c] Fingolimod 1.25mg forms a link between DMTs of interest but is not itself a treatment strategy of interest

^ ARR estimated from mean number of relapses per patient

¶ Proportion estimated from KM survival curve

Abbreviations: IFN β=interferon beta; ARR=annualised relapse rate; N/R = Not reported; SC=subcutaneous; IM=intramuscular

Baseline demographics and clinical characteristics are presented in Table 7.2. These were similar within trials although there were some differences between trials. The mean age ranged from 32.3 years to 38.7 years, 64.3% to 74.8% of the trial populations were female, the mean EDSS score ranged from 2.0 to 2.9 and the mean number of relapses in the previous two years ranged from 1.8 to 3.5. There were notable differences between trials in the duration of disease prior to recruitment (mean 6.01 years, SD 2.00, range 1.3 to 8.7 years), and in the proportion of patients who had received prior DMT treatment (0% for first-generation DMT pivotal trials, 8%-100% for second-generation DMT pivotal trials). Just one RCT (alemtuzumab 12mg vs IFN β-1a SC HD) exclusively included patients who were clinically active while on therapy with either IFN β or GA. [108]

Table 7.2: Baseline characteristics of RCT Participants

Study Author (Study Acronym)	Year	Treatment arm	Age (years)	Female (%)	Disease Duration (years)	Number of relapses in the past 2 years	EDSS score	Prior treatment (%)
IFNβ MS Study Group [69]	1993	placebo IFN β-1b SC	35.6	70.45%	4.3	3.5	2.9	0.00%
Johnson *et al* [68]	1995	placebo GA	34.45	73.31%	6.95	2.9	2.6	NR
Jacobs *et al* (MSCRG) [67]	1996	placebo IFN β-1a IM	36.8	73.57%	6.5	1.84*	2.35	NR
PRISMS Study Group (PRISMS) [66]	1998	placebo IFN β-1a SC LD IFN β-1a SC HD	35	69.34%	5.7	3	2.47	0.00%
Comi *et al* [81]	2001	placebo GA	34.05	NR	8.1	2.65	2.35	NR
Durelli *et al* (INCOMIN) [245]	2002	IFN β-1a IM IFN β-1b SC	36.89	65.57%	6.29	2.9	1.97	0.00%
Panitch *et al* (EVIDENCE) [244]	2002	IFN β-1a IM IFN β-1a SC HD	37.85	74.75%	6.6	2.6	2.3	NR
Polman *et al* (AFFIRM) [101]	2006	placebo natalizumab	35.97	70.33%	5.33	2.32*	2.3	8.39%
Mikol *et al* (REGARD) [246]	2008	GA IFN β-1a SC HD	36.75	70.52%	6.24§	1.95†	2.34	0.00%
International Campath-1H in Multiple Sclerosis trial Investigators (CAMMS223) [110]	2008	IFN β-1a SC HD alemtuzumab[b]	32.33	64.27%	1.33§	NR	1.97	0.00%
O'Connor *et al* (BEYOND) [243]	2009	GA IFN β-1b SC	35.6	69.33%	5.23	2.45*	2.33	0.00%

Table 7.2: Baseline characteristics of RCT Participants Continued

Study Author (Study Acronym)	Year	Treatment arm	Age (years)	Female (%)	Disease Duration (years)	Number of relapses in the past 2 years	EDSS score	Prior treatment (%)
Kappos *et al* (FREEDOMS) [104]	2010	placebo fingolimod 1·25mg[c] fingolimod 0·5mg	37.07	69.89%	8.17	2.13	2.4	40.87%
Cohen *et al* (TRANSFORMS) [105]	2010	IFN β-1a IM fingolimod 1·25mg[c] fingolimod 0·5mg	36.17	67.33%	7.4	2.27	2.21	56.66%
O'Connor *et al* (TEMSO) [114]	2011	placebo teriflunomide LD teriflunomide HD	37.87	72.17%	8.7	2.23	2.68	27.03%
Saida *et al* [315]	2012	placebo fingolimod 1·25mg[c] fingolimod 0·5mg	35.33	69.00%	7.83	2.43	2.07	NR
Comi *et al* (ALLEGRO) [71]	2012	placebo laquinimod	38.7	68.64%	8.7	1.9	2.6	38.95%
Gold *et al* (DEFINE) [70]	2012	placebo BG-12 LD BG-12 HD	38.47	73.67%	5.5	1.99	2.41	40.00%
Fox *et al* (CONFIRM) [119]	2012	placebo GA BG-12 LD BG-12 HD	37.3	69.97%	4.68	2.10*	2.58	29.26%
Cohen *et al* (CARE-MS1) [109]	2012	IFN β-1a SC HD Alemtuzumab	33.07	65.00%	2.07	2.50*	2	0.00%

Table 7.2: Baseline characteristics of RCT Participants Continued

Study Author (Study Acronym)	Year	Treatment arm	Age (years)	Female (%)	Disease Duration (years)	Number of relapses in the past 2 years	EDSS score	Prior treatment (%)
Coles *et al* (CARE-MS2) [108]	2012	IFN β-1a SC HD Alemtuzumab	35.12	65.68%	4.56	2.75*	2.7	100.00%
		Mean (SD)	36.02 (1.72)	69.62% (3.07%)	6.01	2.43	2.36 (0.26)	29.00% (35.00%)

DMT Doses: IFN β-1a IM=30mcg once weekly; IFN β-1a SC HD=22mcg (LD) three times weekly, HD=44mcg (HD) three times weekly; IFN β-1b SC=250mcg every second day; GA= SC 20mg once daily BG-12 LD=120mg twice daily, HD=120mg three times daily; fingolimod=oral once daily; teriflunomide LD=7mg oral once daily, HD=14mg oral once daily; natalizumab=300mg IV once monthly; Alemtuzumab=12mg IV once yearly ; laquinimod=0.6mg oral once daily

[a] Interventions from IFNβ MS Study Group (IFN β-1b SC 50mcg) and BEYOND (IFN β-1b SC 500mcg) which were not among the treatment strategies of interest and which did not otherwise contribute to the network of evidence were excluded

[b] CAMMS223 Study found no significant differences between alemtuzumab 12mg and 24mg arms and reported pooled results which are used in this analysis and contribute to the efficacy estimate for alemtuzumab 12mg.

[c] Fingolimod 1.25mg forms a link between DMTs of interest but is not itself a treatment strategy of interest

* Where not reported in RCTs the number of relapses in the previous two years was inferred using the relationship between the number of relapses in the previous year and the number of relapses in the previous two years from other studies where both were reported.

† Baseline mean number of relapses was not reported in REGARD study. Mean number of relapses in previous 2 years was estimated from Table 1 of REGARD study.

§ CAMMS223 and REGARD duration of disease is estimated from years since first relapse

Abbreviations: IFN β=interferon beta; ARR=annualised relapse rate; N/R = Not reported; SC=subcutaneous; IM=intramuscular

7.4.3 Risk of Bias Assessment

All but one study employed outcome-assessor blinding [245] but participants were not blinded to treatment allocation in a further seven RCTs (Figure 7.3). [108-110 119 243 244 246] In two further studies the integrity of participant blinding was questionable. [67 69] Eight trials did not report adequate information about allocation concealment but were reported to be randomised and blinded. [67 69 91 104 110 114 243 244] The significance of results from the pivotal placebo-controlled RCT of IFNβ-1a IM is compromised due to attrition bias as only 57% of the original ITT population completed two years of treatment, with subsequent analysis suggesting that those who enrolled early in the study did better than those who enrolled later. [316] Studies with high risk-of-bias due to poor/lack of blinding or significant attrition bias were excluded in sensitivity analysis. [67 69 108-110 119 243-246] As all studies including IFN β-1b were poorly blinded or single-blinded and all trials including alemtuzumab were single-blind, these DMTs were eliminated from the network in sensitivity analysis. [67 69 108-110 119 243-246]

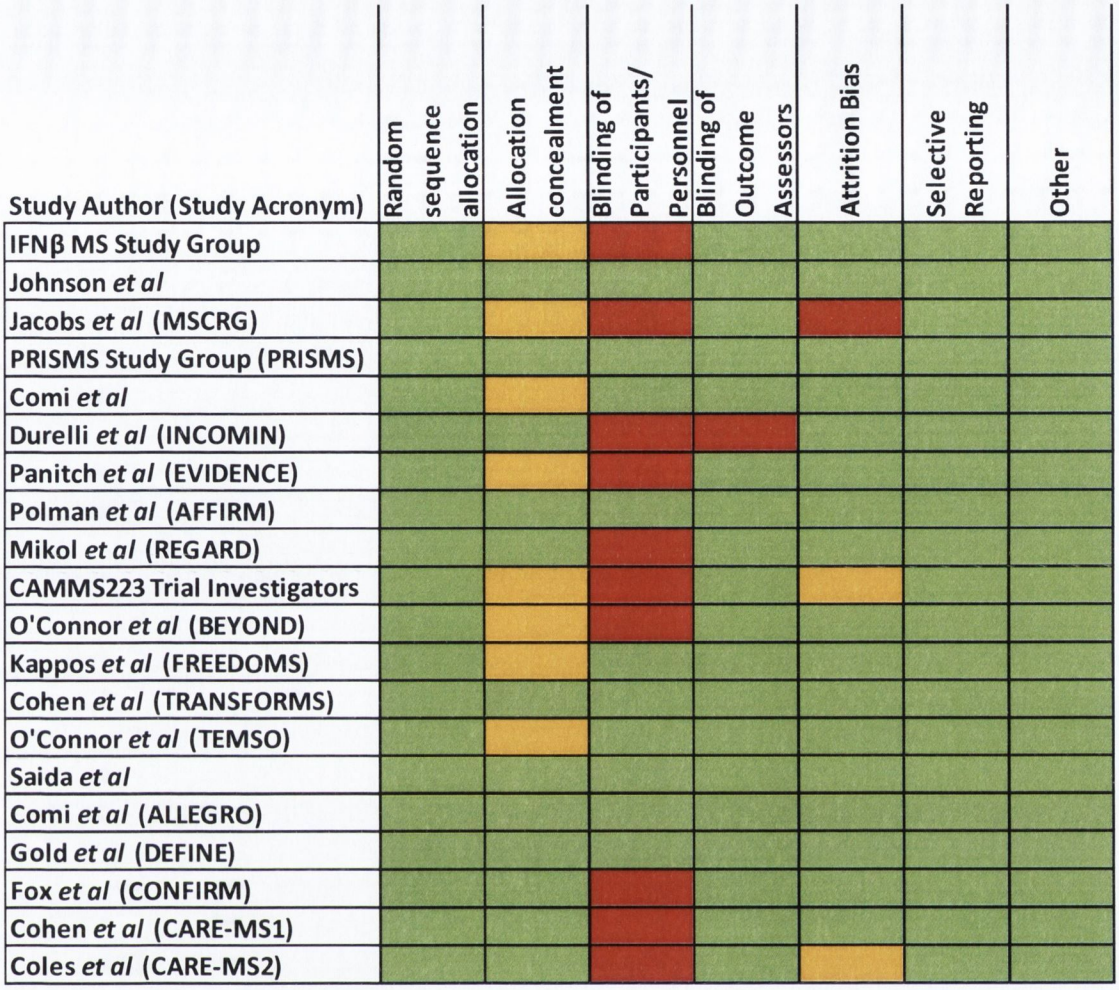


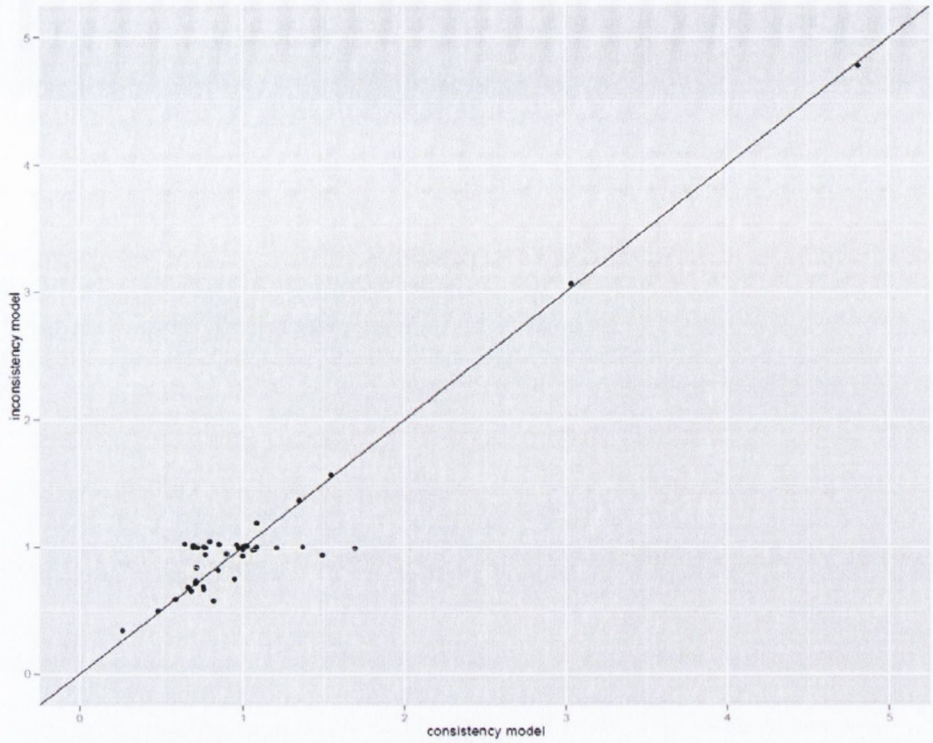
Figure 7.3: Risk of Bias Graph

Green = low risk of bias; Amber=unclear risk of bias; Red=high risk of bias

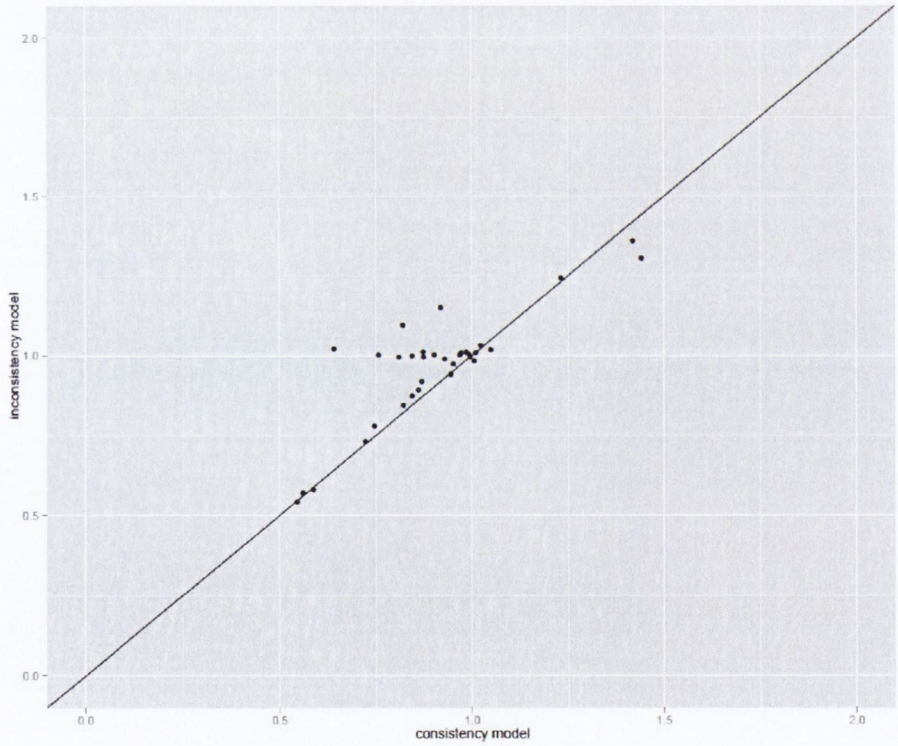
7.4.4 Consistency of the Evidence Network

Plots of the posterior mean deviance of the individual data points in the inconsistency model against those in the consistency model are presented in Figure 7.4. The plots indicate similar fit showing no evidence for statistical inconsistencies. The residual deviance of the ARR model was 49.57, and 29.92 for the Progression model. These values are close to the number of unconstrained data points of the model (49 ARR, 33 disability progression) demonstrating an overall good fit of the model to the data. Two points have higher than expected posterior mean deviance in the ARR model (the two arms of the CAMSS223 trial (alemtuzumab vs IFN β-1a SC HD)). The higher deviance is seen in both the consistency and inconsistency models and therefore is not a sign of

inconsistency per se, rather an indication of poor model fit for this trial. The CAMSS223 trial is excluded in sensitivity analysis.



a) Annualised Relapse Rate Outcome



b) Hazard ratio of disability progression Outcome

Figure 7.4: Plots of posterior mean deviance for individual data points and the line of equality

7.4.5 Heterogeneity

In a meta-regression analysis to assess potential treatment-effect modification, no covariate had a significant impact on the model.

7.4.6 Relative efficacy of DMTs in reducing ARR.

Mean relative relapse rates, for all treatments versus placebo, together with their 95% credible intervals are presented in Table 7.3.

Table 7.3: Efficacy of DMTs compared with placebo

Treatment	Mean	*95% confidence intervals*
	Relative Annualised Relapse Rate	
Alemtuzumab	0.31	0.23 - 0.36
Natalizumab	0.31	0.27 - 0.36
Fingolimod	0.44	0.37 - 0.53
BG12 480mg	0.50	0.43 - 0.58
BG-12 720mg	0.50	0.43 - 0.58
Glatiramer acetate	0.67	0.61 - 0.74
Teriflunomide 7mg	0.68	0.58 - 0.80
Teriflunomide 14mg	0.68	0.58 - 0.80
IFN β-1a SC 44mcg	0.69	0.62 - 0.76
IFN β-1b SC 250mcg	0.69	0.61 - 0.77
IFN β-1a SC 22mcg	0.73	0.63 - 0.83
Laquinimod	0.76	0.66 - 0.89
IFN β-1a IM 30mcg	0.83	0.74 - 0.94
	Hazard Ratio of short-term disability progression	
Alemtuzumab	0.27	0.15 - 0.49
Natalizumab	0.55	0.42 - 0.73
BG12 480mg	0.61	0.48 - 0.76
Laquinimod	0.65	0.46 - 0.90
Fingolimod	0.66	0.50 - 0.86
BG-12 720mg	0.66	0.53 - 0.83
Teriflunomide 14mg	0.72	0.54 - 0.97
IFN β-1a SC 44mcg	0.73	0.52 - 1.01
Teriflunomide 7mg	0.78	0.58 - 1.04
Glatiramer Acetate	0.81	0.63 - 1.03
IFN β-1a SC 22mcg	0.82	0.58 - 1.16
IFN β-1b SC 250mcg	0.82	0.61 - 1.11
IFN β-1a IM 30mcg	0.85	0.59 - 1.20

Mean values less than 1.0 indicate a reduction in relapse rate or progression relative to placebo, statistically significant at the 5% level if the upper end of the confidence interval is less than 1.0

IFN β=Interferon beta

Figure 7.5 displays the entire posterior distribution of the effect size for each treatment. All DMTs were associated with a statistically significant lower ARR compared with placebo (at the 0.05 level). The magnitude of ARR reduction varied between 16%-33% for first generation DMTs, and between 24%-69% for second-generation DMTs. Alemtuzumab, natalizumab, fingolimod, and BG-12 were significantly more efficacious than all other DMTs in reducing ARR. No significant differences were observed between first-generation DMTs, and the second-generation agents teriflunomide and laquinimod with the exception of IFN β-1a IM 30mcg which was significantly less efficacious than most other DMTs (Figure 7.6*)*. In sensitivity analysis excluding trials at high risk of bias, the efficacy of IFN β-1a IM 30mcg in reducing ARR improved slightly so that differences between it and other first-generation DMTs were no longer statistically significant.

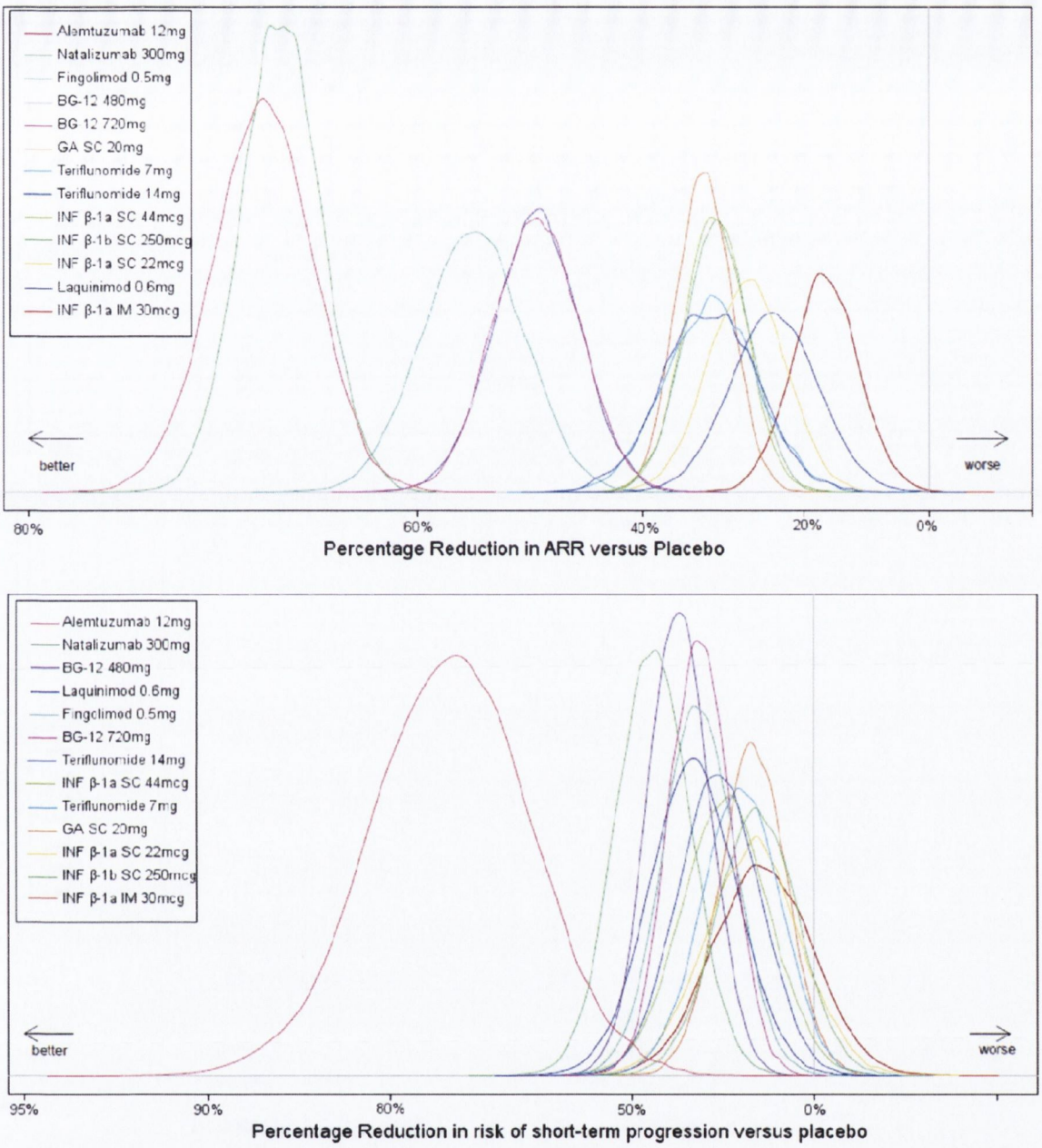


Figure 7.5: Efficacy of DMTs compared with placebo

Curves are posterior probability distributions which indicate likely values for the relative efficacy of DMTs compared with placebo, capturing the full uncertainty. The maximum of the curves can be used as point estimates, while the width of the curves indicates the uncertainty associated with each estimate. The higher the curve the less uncertainty associated with the estimate of relative efficacy. Vertical line at 0% indicates no difference between DMT and placebo. The x-axis is on the log-scale.

ARR=annualised relapse rate. IFN ß=interferon beta. GA=glatiramer acetate.

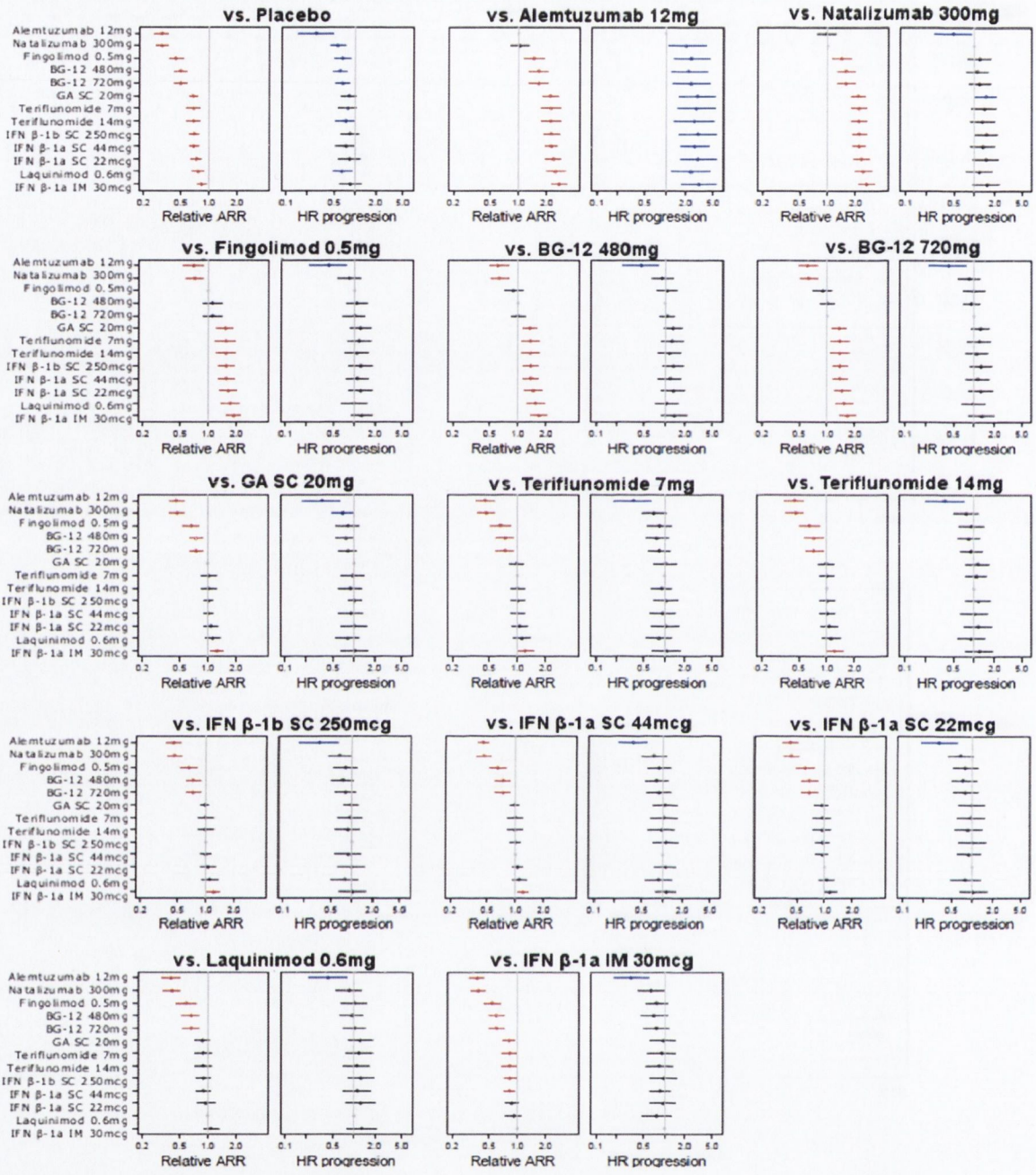


Figure 7.6: Relative efficacy of DMTs

95% CIs are presented by solid lines. Bars to the right of the central vertical line of no difference indicate superiority of the title DMT versus comparators. Coloured bars (red for ARR, blue for short-term disability progression) indicate statistically significant differences between DMTs.

Abbreviations: ARR=Annualised Relapse Rate; HR=hazard ratio; IFN ß=interferon beta; GA=glatiramer acetate; IM=intramuscular; SC=subcutaneous

The probabilities of each treatment occupying a particular rank from one (most efficacious) to 15 (least efficacious), according to the estimated effect size is

graphically illustrated in Figure 7.7. Alemtuzumab has the highest probability of being ranked as the most effective treatment strategy (60%). There is a 40% probability that natalizumab is the most effective strategy. IFN β-1a IM 30mcg has the greatest probability of being the least effective DMT.

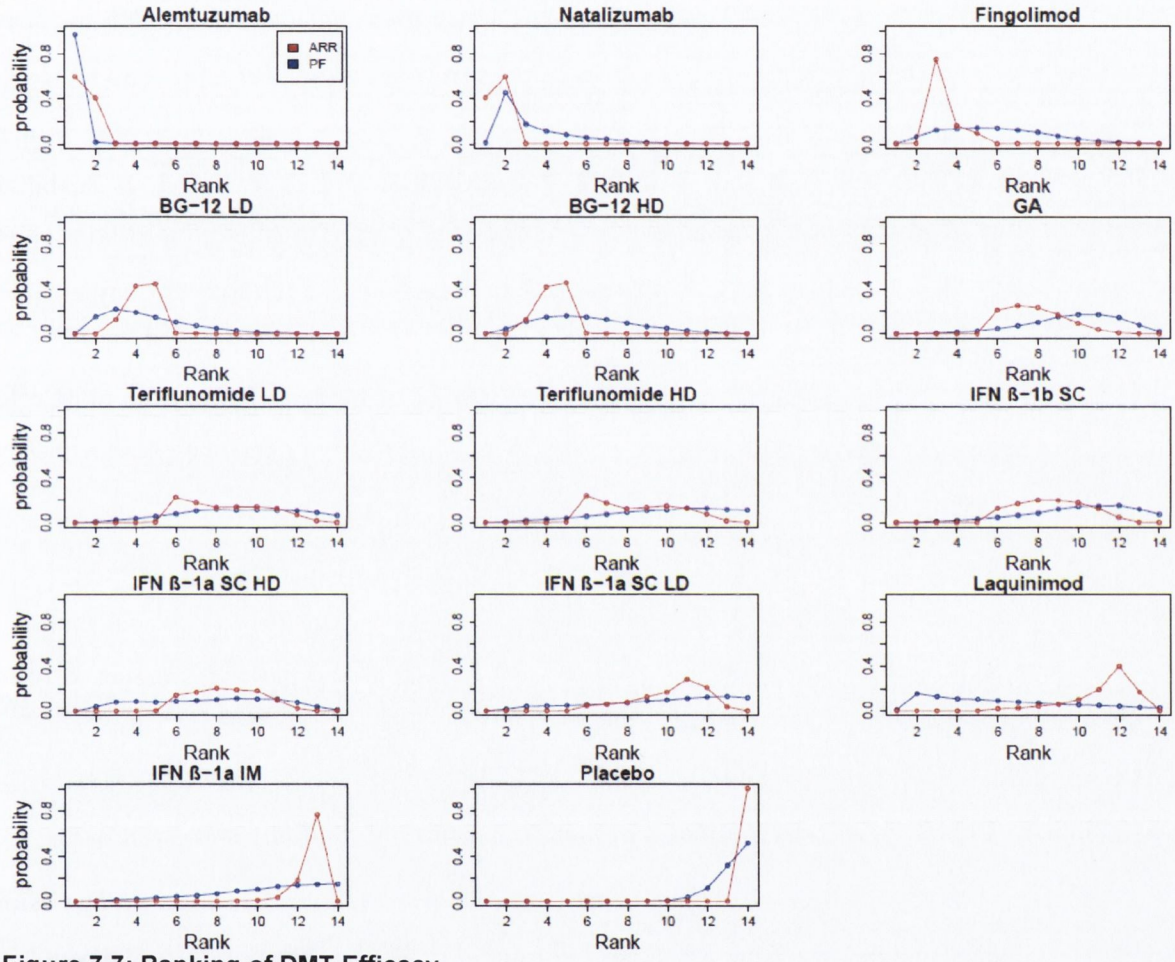


Figure 7.7: Ranking of DMT Efficacy

Lines show the distribution of probabilities for each DMT to be ranked as the best treatment (first), second best treatment (second), third best and so on among the 15 treatment strategies, for ARR outcome (red line) and progression outcome (blue line). Peaks indicate a higher probability of being at a particular rank for the relevant outcome.

Abbreviations: ARR=Annualised Relapse Rate; HR=hazard ratio; IFN ß=interferon beta; GA=glatiramer acetate; IM=intramuscular; SC=subcutaneous; LD=low dose; HD=high dose

7.4.7 Relative efficacy of DMTs in reducing short-term disability progression.

Mean hazard ratios of short-term disability progression, for all treatments versus placebo, together with their 95% credible intervals are presented in Table 7.3. Reductions in short-term disability progression were significantly greater for alemtuzumab, natalizumab, fingolimod, laquinimod, BG-12, and teriflunomide 14mg compared with placebo (HR 0.27-0.54). The relative efficacy of first-generation DMTs and teriflunomide 7mg versus placebo (HR 0.73-0.85) did not achieve statistical significance for this outcome. Alemtuzumab was significantly more efficacious than other DMTs in reducing short-term progression (HR 0.32-0.49), as was natalizumab versus GA (HR 0.68, 95% CI 0.48 to 0.98) (Figure 7.6). Excluding trials at high risk of bias in sensitivity analysis made negligible changes to the relative efficacy estimates of included DMTs.

Alemtuzumab has the highest probability of being ranked as the most effective treatment strategy (97%) (Figure 7.7). IFN β-1a IM 30mcg has the greatest probability of being the least effective DMT.

7.4.8 Sensitivity Analyses

The results of all sensitivity analyses are presented together with basecase results in Appendix 8.

7.4.8.1 SA1 (Included only trials confirming disability at 6-months)

Ten trials were included in this analysis. Five trials reported disability progression just on the basis of a 6-month confirmation [67 108 109 245 246] and five trials which report disability progression outcomes separately on the basis of a 6-month confirmation and 3-month confirmation. [66 101 104 110 244] Eight out of 14 treatment strategies are covered by these trials and therefore included in this sensitivity analysis. IFN β-1a SC 22mcg, laquinimod and both dose regimens for teriflunomide and BG-12 are omitted from this analysis. The efficacy of 1st generation DMTs IFN β-1a SC 44mcg, IFN β-1b SC 250mcg and GA is more pronounced in this analysis as these agents are now significantly more effective than placebo (HR 0.30-0.43). The efficacy of IFN β-1a IM 30mcg is also enhanced. Regarding the relative efficacy of DMTs, alemtuzumab is still significantly more effective than IFN β-1a IM 30mcg, IFN β-1a SC 44mcg and

fingolimod but statistical significance versus GA, IFN β-1b SC 250mcg and natalizumab is lost. IFN β-1b SC 250mcg is significantly more effective than IFN β-1a IM 30mcg (HR 2.33, 95% CI 1.21 to 4.68).

7.4.8.2 SA2 (Excluded trials less than two years duration)

Eleven trials were included in this analysis including 13 treatment strategies. [66 68-71 101 104 110 114 119 243] IFN β-1a IM 30mcg was omitted from this analysis as both trials which report 3-month confirmed disability progression for this treatment are just one year in duration. This analysis made negligible difference to basecase results on disability progression.

7.4.8.3 SA3 (Excluded trials at high risk of bias)

Ten trials (50%) were categorised as being at high risk of bias and were excluded in SA [67 69 108-110 119 243-246] This exclusion criteria eliminated IFNb-1b and alemtuzumab from the network as all studies including these treatments were either open-label or single/poorly blinded. The credible intervals surrounding point estimates widened for many comparisons. The efficacy point estimates of IFNβ-1a IM 30mcg in reducing ARR improved slightly, in addition to the uncertainty increasing, so that differences between it and other comparators including placebo, GA, IFN β-1a SC 44mcg and teriflunomide were no longer statistically significant. In the disability progression model, the difference between natalizumab and GA is no longer significant (HR 1.53, 95% CI 0.87 to 2.70). In the absence of alemtuzumab in this SA, the probability that natalizumab is most efficacious for reducing relapses was 99%. Natalizumab and BG-12 had similar probabilities of being ranked most efficacious for reducing short-term progression (33%-34%).

7.4.8.4 SA4 (Excluded CAMSS223 trial)

Higher than expected posterior mean deviance arose for the two arms of CAMSS223 trial (alemtuzumab vs IFNβ-1a SC HD) in the ARR model. [110] Repeated analysis excluding the CAMSS223 trial (alemtuzumab vs IFNβ-1a SC HD), on the basis of higher than expected posterior mean deviance, had negligible impact on results.

7.5 Discussion

7.5.1 Base case

Our study shows that second-generation, new and emerging DMTs are generally more efficacious than first-generation DMTs, with evidence of some dissociation between relapse-reduction and progression effects. Both relapses and progression are the clinical hallmarks of the MS disease process, but for many patients relapses are the initial defining feature of their disease. Relapses can have a significant physical, psychological and social impact on patients, and place a substantial cost burden on patients, their families and healthcare systems. All DMTs were significantly superior to placebo in reducing MS relapse rates with second-generation agents alemtuzumab, natalizumab, fingolimod, and BG-12 demonstrating significant improvements in efficacy compared with other DMTs.

Reducing the occurrence of relapses with DMT improves clinical outcomes for patients, and also has cost-saving implications in the short-term. However, the full cost-saving potential of these therapies cannot be realised in the absence of long-term effects on disability progression. Our study found little to distinguish the effects of different DMTs on short-term disability progression, with the exception of alemtuzumab which was superior to other comparators. This is not unexpected given the results of individual RCTs in which impressive reductions in ARR are accompanied by marginal changes in disability progression. Furthermore, evidence from natural history studies has shown the dissociation between relapses and disability progression pathologies. [317]

Alemtuzumab had the highest probability of being the most effective treatment for reducing relapse rates, followed by natalizumab. Alemtuzumab also ranked highest for efficacy in reducing short-term progression, followed by natalizumab and BG-12.

7.5.2 Sensitivity Analysis

Fifty per cent of trials in the network were categorised as being at high risk of bias, and as expected, the credible intervals surrounding point estimates widened for many comparisons when these trials were exlcluded. Almost all trial exclusions were due to the absence/failure of double-blinding. The only study categorised as being at high risk of bias for reasons other than blinding was the placebo-controlled study of IFN β-1a IM

30mcg vs placebo. [67] Unsurprisingly therefore, this SA had greatest impact on the comparisons for IFN β-1a IM 30mcg which were borderline significant in basecase ARR analysis and for which significance disappeared in SA. The potential for bias arising from single-blind study design cannot be excluded; however negligible changes to all other comparisons were found when only double-blind studies were analysed. Of interest upon elimination of alemtuzumab from the ranking analysis was the similar probability of both natalizumab and BG-12 being the most effective for the disability progression outcome.

The inclusion of just trials which defined disability progression on the basis of a 6-month confirmation interval had a substantial favourable impact on the efficacy versus placebo of the first-generation agents included in this SA, IFN β-1a SC 44mcg, IFN β-1a IM 30mcg and IFN β-1b SC 250mcg and a slight negative impact on alemtuzumab. It is difficult to predict the impact of the disability progression definition on trial outcomes as trials which report disability outcomes using both 3-month and 6-month definitions have not demonstrated a consistent trend as regards increasing/decreasing efficacy depending on the definition used. The inadequacy of progression outcomes confirmed at 3-6 month has been highlighted, as improvement in EDSS scores after relapses may continue beyond this timeframe.[318] A recent study by Ruddick *et al* demonstrated a strong relationship between 6-month confirmed EDSS worsening during the first two years of an RCT and the likelihood of clinically significant EDSS milestones eight years later. [319] Short-term disability progression, confirmed after three months, was chosen as a primary outcome in preference to 6-month confirmed disability progression as it is the most common definition used in RCTs and is accepted as clinically meaningful by both regulators and healthcare payers. However it is clear that inclusion of outcomes based on different definitions can have a significant impact on results. RCTs are increasingly incorporating adjunctive imaging outcomes and composite measures such as disease-activity-free-status. Further research on the comparative efficacy of all RRMS therapeutic options on these and other novel disability progression outcome measures is required.

7.5.3 Comparison with other NMAs

A comparison of our study findings with those of other NMAs reveals some notable differences, primarily due to the inclusion/exclusion of particular studies. Roskell *et al*

estimated the relative ARR of IFN β and GA products versus fingolimod 0.5mg. [252] Consistent with the findings of this study, statistically significant reductions in ARR were reported for fingolimod versus all comparators although the magnitude of the reduction was consistently greater in the Roskell analysis in all cases: GA (30% vs 19%), IFN β-1b (34% vs 20%), IFN β-1a SC 44mcg (36% vs10%), IFN β-1a SC 22mcg (40% vs 20%), IFN β-1a IM 30mcg (48% vs 23%) and placebo (57% vs 34%). Statistical analysis was similar between studies however Roskell did not include any trials of second-generation DMTs apart from fingolimod, and included three studies which didn't meet the inclusion criteria of our study (BECOME study, Saida *et al* and Bornstein *et al*, reasons provided in Appendix 8). [315 320 321] The BECOME trial found comparable efficacy between GA with IFN β-1b (similar to the BEYOND study included in our analysis). [320]The Bornstein *et al* study, conducted in 1987, found GA to be highly effective compared with placebo (relative ARR 0.25). [321] A third study by Saida *et al* compared IFN β-1b with a lower, unlicensed dose of the same product. [322] The discrepancy in study findings is likely due to the inclusion of the Bornstein trial in the Roskell analysis and the exclusion of more recent trials. In particular, the CONFIRM trial which included BG-12, placebo and GA and confirmed the ~30% reduction in ARR with GA versus placebo demonstrated in other studies. [119] The Roskell study was funded by the manufacturer of fingolimod. [252]

Tappenden *et al* compared first generation agents with placebo using an NMA and reported relative ARRs and relative hazards of progression. [236] Relative ARRs in the Tappenden study are very similar to the results presented here. HRs of disability progression versus placebo were broadly similar between first-generation agents in our analysis, with the possible exception of IFN β-1a SC 44mcg, but within the Tappenden NMA there is much greater variation in treatment efficacy estimates. There are also differences in the HR of disability progression between studies. In particular the HR of progression for both IFN β-1b SC 250mcg, IFN β-1a SC 44mcg and IFN β-1a IM 30mcg versus placebo are lower in the Tappenden study; 0.52 (SE 0.09) vs 0.82 (95% CI 0.58-1.16) for IFN β-1b SC 250mcg; 0.72 (SE 0.19) vs 0.82 (95% CI 0.61-1.11) for IFN β-1a SC 44mcg; and 0.79 (SE 0.12) vs 0.85 (95% CI 0.59-1.20) for IFN β-1a IM 30mcg. The Tappenden study included trials which confirmed disability progression at *six* months in addition to those confirming progression at *three* months, thereby including additional data from the MSCRG (IFN β-1a IM 30mcg vs placebo) and the INCOMIN (IFN β-1b SC 250mcg vs IFN β-1a IM 30mcg) trial. [67 245] The relative

efficacy of IFN β-1a IM 30mcg vs placebo is enhanced by the inclusion of MSCRG data. [67 245] In addition, the relative efficacy of IFN β-1b SC 250mcg vs IFN β-1a IM 30mcg is greatly enhanced by the inclusion of INCOMIN data (INCOMIN IFN β-1b SC 250mcg vs IFN β-1a IM 30mcg HR 0.40, p=0.01). [245] The inclusion of these trials may partly explain the superior outcomes with these agents. Inclusion of just *six* month confirmed progression outcomes in SA1 greatly enhanced the efficacy of IFN β-1b SC 250mcg versus placebo in sensitivity analysis (SA1) in this study also. A number of trials comparing first-generation agents were published subsequent to the Tappenden NMA, and were available for inclusion in our study in addition to trials of second-generation agents.

Disability progression odds ratios (OR) and treatment-ranking using the SUCRA method are reported in an NMA by Filippini *et al* for the Cochrane collaboration. [250] The Filippini NMA looked at recurrence of relapse but did not include relapse rate among their outcomes, stating that there is a consensus that immunotherapies reduce the frequency of relapses in MS but that their relative effectiveness in the prevention of new relapses remains unclear. First-generation agents and natalizumab are included in this study, in addition to some unlicensed treatments which are not the focus of our study. Similar to the Tappenden study, this NMA also combined disability progression results from all trials regardless of 3-month or 6-month definition. [236] Of the licensed agents, GA was found to be the most effective treatment for disability progression followed by natalizumab and IFN β-1b SC 250mcg. Similar to the Roskell study, the Filippini NMA included the Bornstein trial which enhances the overall efficacy of GA, and the INCOMIN trial which enhances the efficacy of IFN β-1b SC 250mcg. [320 321] Filippini *et al* concluded that IFN β-1a IM 30mcg has an unfavourable benefit-risk balance in RRMS (OR 1.1, 95% CI 0.64 to 2.16). The discrepancy in the IFN β-1a IM 30mcg results may be partly explained by the way in which the authors of the Filippini NMA analysed the disability progression outcomes of the MSCRG trial. [67] As a result of the significant attrition bias associated with the MSCRG study, discussed above, the authors make assumptions on the basis of a "likely scenario" wherein both IFN β-1a IM 30mcg and placebo dropouts were assumed to have worsened. This approach is not outlined in the Filippini NMA report but a comparison of the data with a traditional pairwise meta-analysis conducted by the same authors in 2003 suggests that the same "likely scenario" approach was taken, giving much less favourable results. [94]

7.6 Limitations

7.6.1 Changing RCT Populations

The trials included in the analysis were conducted over a period of 20 years and changes in patient populations were evident in duration of disease, proportion of trial populations who had received prior DMT, and also in the downward trend in relapse rates over time, a phenomenon which has been highlighted in recent reviews. Potential sources of variation from several known covariates were explored to adjust for baseline imbalance in underlying risk across studies. No significant confounding of treatment-effect was identified. It must be acknowledged however that treatment-effect modification from baseline covariates can be difficult to identify using aggregate study-level data. [187]

7.6.2 Duration of RCTs

The maximum duration of any RCT included in this analysis was two years. As a chronic, progressive disease, RRMS may require treatment with DMT for many years, but there is little evidence on the long-term efficacy of these agents. The development of neutralising antibodies can complicate prolonged IFN β therapy. Results from the US Glatiramer Acetate Trial suggest maintained efficacy on relapse rate over extended periods of ongoing use of GA.[122] Conflicting results have been reported for the long-term efficacy of first-generation DMT on reducing disability progression.[123 124] Longer-term studies are required to provide evidence that efficacy on short-term progression translates into meaningful, long-term effects on disability progression and the development of secondary-progressive disease. Given the chronic nature of MS and the complications associated with individual DMTs, it is likely that these agents will be used in sequence. In Europe, natalizumab and fingolimod are restricted for use in highly active RRMS either following failure of first-line therapy or in rapidly evolving severe MS. While many of the studies included in this analysis included a proportion of patients who had received prior DMT, just one study was specifically designed to address the efficacy of treatment in the second-line setting. [108] Further research must therefore reliably establish the relative benefits and risks of sequential therapy in order

to enable patients and clinicians to make evidence-based therapeutic decisions in this setting.

7.6.3 Exclusion of Observational Studies

This analysis included peer-reviewed publications of RCTs. While RCTs provide the foundation for evaluating comparative efficacy of DMTs, post-marketing observational studies can contribute complementary evidence. Observational studies could potentially be included in a network meta-analysis model which allows for bias adjustment while also accounting for heterogeneity between trial designs.

7.6.4 Safety of DMTs

The safety or tolerability of DMTs was not assessed in this analysis. The safety profile of first-generation DMTs has been demonstrated by long-term use, and they are generally regarded as safe treatments notwithstanding flu-like symptoms and injection-site reactions which may be distressing for some patients. PML, a rare, potentially fatal opportunistic brain infection is associated with natalizumab treatment, and while early experience with other second-generation DMTs is encouraging with regard to the absence of PML, other potentially serious complications have emerged from RCTs of alemtuzumab (infection and autoimmune disorders) and fingolimod (cardiotoxicity) which require careful monitoring. [104] [109] At this stage evidence suggests that laquinimod, BG-12, and teriflunomide appear to be safer and are not associated with these serious risks.[71] [114] [119] Given the growing choice of therapies available for RRMS, therapeutic decisions will be based on the relative risks as well as the relative efficacy of treatments.

7.7 Conclusion

The last decade has seen major breakthroughs in the development of new therapeutic strategies for RRMS. However, the extent to which they present efficacy advantages compared to established treatments with a proven safety record has been unclear, as many trials are placebo-controlled, or don't include all comparators of interest. The NMA described in this chapter has combined a wealth of evidence on DMT efficacy in order to estimate the relative efficacy of treatments which have not been directly

compared in RCTs. This analysis finds that the growing number of innovative second-generation DMTs for RRMS offers the potential of therapeutic advances in reducing relapse rates, with less certain benefits on short-term disability progression. Notwithstanding the potential bias which may be introduced by the single-blind design of Alemtuzumab RCTs, there appears to be strong evidence that this DMT in particular, offers significant advances compared to other therapies. Despite the potential advantages of second-generation agents, their relative position on the RRMS treatment landscape remains to be defined, due to potentially serious side effects and limited long-term safety data. This analysis provides estimates of the relative efficacy of DMTs which may be applied in CEA or clinical practice, allowing coherent, evidence based decisions to be made. These relative efficacy estimates will be applied in the decision-analytic model of DMT in RRMS, developed for this thesis and described in Chapter 8

CHAPTER 8 –ECONOMIC EVALUATION OF DMT IN RRMS IN IRELAND

CHAPTER 8 –ECONOMIC EVALUATION OF DMT FOR RRMS IN IRELAND

Chapter 8 describes the development of a decision-analytic model for the economic evaluation of DMT for RRMS in Ireland. The decision-analytic model integrates various aspects of other chapters in the thesis including costs (Chapter 5), HRQoL (Chapter 6), and DMT efficacy (Chapter 7). Synthesis of data on the natural history of disability progression and relapses was conducted in collaboration with Professor Cathal Walsh, Department of Statistics, Trinity College Dublin.

8.1 Introduction

Economic evaluation has become an integral part of HTA and health care decision-making in Ireland and around the world. While the cost effectiveness of DMTs for RRMS has been the subject of extensive research internationally, the results of analyses conducted in different settings and under different assumptions are not readily transferable to other settings. Furthermore, all treatments and comparators of current interest have not been included in any published economic evaluation to date. Economic evaluations of DMTs for RRMS in Ireland include NCPE assessments of natalizumab and fingolimod, conducted in 2006 and 2011 respectively. [49 50] For these evaluations, the evidence review group in the NCPE assessed dossiers of evidence and decision-analytic models submitted by the manufacturers. The cost effectiveness of IFN β or GA has not been established in Ireland, nor has an independent decision-analytic model been developed for the assessment of DMTs in Ireland. A decision-analytic model of DMT in RRMS has been developed for this thesis which includes all comparators of interest, in an Irish patient population, using base case assumptions and methods as recommended in national HTA guidelines. [7] Sensitivity analyses are also conducted to test the robustness of results to variation and uncertainty in model inputs and assumptions.

8.2 Aims

The aims of the work described in this chapter are to conduct an economic evaluation of available DMTs for RRMS in Ireland, and to estimate the price at which new DMTs to the Irish market may be considered cost-effective compared with current standard of care. Objectives include:

- synthesising data on the natural history of MS relapses and disability progression
- developing a baseline decision-analytic model (or simply "model", as it will be termed throughout the rest of the chapter) which represents the natural history of RRMS
- applying cost and utility evidence obtained from a cohort of Irish patients
- applying relative treatment-effects estimated by NMA methods
- evaluating the cost effectiveness of available DMTs
- identifying a price at which new DMTs (for which relative efficacy data is available) may be cost-effective at a threshold of €45,000 per QALY

8.3 Methods

8.3.1 Description of the baseline natural history model

The natural history of MS was modelled using a state-transition (Markov) cohort approach, similar to that which has been previously employed in the modelling of MS.[231 232 265 267] Markov modelling is well-suited to MS and the complexity of combining multiple health states and recurrent events. The model consists of 21 health states in total, including ten "on-treatment" states representing different levels of disability on the EDSS scale (half-points on the EDSS scale were combined to give 10 levels from 0 to 9), ten "off-treatment" states also based on the EDSS scale, and "dead".(Figure 8.1) In all EDSS states, patients receive BSC (assumed to include standard non-DMT based management such as symptom control, physiotherapy etc.). Patients "on-treatment" are assumed to receive a DMT in addition to BSC. The baseline, untreated cohort comprises patients with RRMS and is initially distributed between "off-treatment" EDSS states. At the end of each model cycle the cohort is redistributed between these EDSS states, on the basis of natural history of progression transition probabilities, and the "dead" state on the basis of MS standardised mortality rates. Patients who are "on-

treatment" are initially distributed between "on-treatment" EDSS states and at the end of each model cycle the cohort is redistributed between both "on-treatment" EDSS states (on the basis of DMT-specific hazard ratios of progression which are applied to baseline progression hazards) and "off-treatment" EDSS states (on the basis of a cycle-specific risk of treatment discontinuation) and "dead". Each cycle is associated with a risk of conversion from RRMS to SPMS. Patients "on-treatment" have an annual risk of conversion from RRMS to SPMS. Once conversion occurs, patients discontinue DMT and are redistributed between "off-treatment" EDSS states. Each EDSS state is associated with a baseline risk of MS relapse. Those "on-treatment" also benefit from a DMT-specific relative risk of relapse which is applied to the baseline relapse risk. Costs and utilities are applied in the model to each EDSS state and to relapses. The model is implemented in Microsoft Excel®, chosen because of its wide accessibility, ease of use, and capacity to handle the assumptions of the model.

8.3.1.1 Structural Assumptions

The model is based on the following structural assumptions:

- Progression through the model is unidirectional i.e. backward transitions to lower EDSS levels (improvement in disability) are not allowed.
- Patients who progress to EDSS ≥7 or who convert to SPMS automatically discontinue DMT. Once patients convert to SPMS or discontinue DMT they are redistributed into the "off-treatment" EDSS states progress on the basis of DMT-specific hazard ratios of progression and thereafter are assumed to progress according to natural history progression rates. [85]
- Costs and utilities for BSC are equivalent between RRMS and SPMS EDSS states, and between patients who are on- and of-treatment.
- The natural history of disease progression is dependent on EDSS state and does not differ between RRMS and SPMS.
- Treatment-effects are constant over time while patients remain on treatment.
- The influence of relapses on disability progression or vice versa are not directly incorporated in the model. However, given that relapse rates are EDSS state-specific, the differential effects of DMTs on progression between EDSS states will indirectly influence the effect of DMT on relapses.

- All-cause mortality rates based on the general population are adjusted with MS disability-specific standardised mortality ratio (SMR). [81] Different SMRs are applied to mild (EDSS 0-3), moderate (EDSS 4-6) and severe (EDSS 7-9) EDSS states. An effect of DMT on mortality has not been directly incorporated into the model. However, similar to MS relapses, an indirect effect on mortality arises from the efficacy of DMT on disability progression.

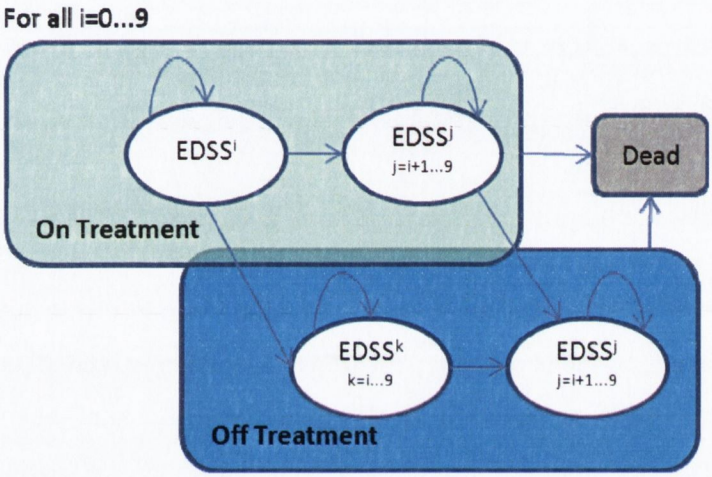


Figure 8.1: Simplified Model Structure

EDSS=Expanded Disability Status Scale

8.3.2 Application of the model for the economic evaluation of DMT in RRMS in Ireland

8.3.2.1 Target population

The target population includes adults with RRMS, eligible for treatment with a DMT. The initial cohort distribution was based on the EDSS distribution of patients with RRMS in the Cost and Quality of Life in MS study undertaken as part of this research (described in Chapter 5 and 6). [163] Alternative assumptions on the initial cohort distribution are applied in scenario-analyses including starting all patients in EDSS 0, 1, 2 etc. and using the distributions applied in IFN B/GA and fingolimod submissions to NICE. [51] [255] Patient age and gender distribution was based on the demographics of patients who received a DMT in Ireland in 2012, based on analysis of HSE-PCRS

prescribing records. [125] Patients enter the model at 45 years of age. 70% of the cohort are female. [125] The age of the cohort is varied +/- five years in DSA.

8.3.2.2 Setting and location

The setting for this evaluation is the Irish healthcare setting. In Ireland, the entire cost of treating patients with DMT in the community is covered by the HSE, as MS is classified as a "long-term illness". Natalizumab, as a hospital-only drug, is also reimbursed by the HSE, with the exception of a small proportion of patients whose costs may be borne by private health insurers.

8.3.2.3 Study perspective

The primary perspective of this study is that of the healthcare payer in Ireland, in line with national HTA guidelines. [7] All costs borne by the healthcare payer are included in this perspective including direct medical and direct non-medical costs. In a secondary scenario analysis, the societal perspective is adopted in which all costs, regardless of the payer, are considered including direct costs to patients, family and friends, and indirect costs to society in the form of productivity losses,

8.3.2.4 Treatments

Treatments of interest include potential first-line DMTs approved for use in RRMS in Ireland, including:

- fingolimod 0.5mg oral
- IFN β/GA weighted average, based on market share (%).
    - IFN β-1b 250mcg SC (*Betaferon®)* (25.70%)
    - IFN β-1a 30mcg IM *(Avonex®)* (25.05%)
    - IFN β-1a 22mcg SC *(Rebif 22®)* (8.99%)
    - IFN β-1a 44mcg SC *(Rebif 44®)* (17.54%)
    - GA 20 mg SC *(Copaxone ®)* (22.70%)

Other potential first-line treatments of interest include those which are currently under evaluation by US or European regulatory agencies for the treatment of RRMS, including teriflunomide 14mg oral, laquinimod 0.6mg oral, BG-12 480mg oral, alemtuzumab 12mg IV.

As drug costs are not available for these DMTs, analysis is restricted to the estimation of the cost at which these DMTs would be considered cost-effective versus standard of care at the current cost effectiveness threshold in Ireland of €45,000 per QALY

Treatments of interest for highly-active RRMS include:

- fingolimod 0.5mg once daily oral *(Gilenya®)*
- natalizumab 600mg IV once monthly *(Tysabri®)*
- IFN β/GA weighted average

8.3.2.5 Comparators

The cost effectiveness of fingolimod is compared with IFN β/GA and BSC alone. In the highly-active RRMS treatment setting, natalizumab is compared with fingolimod, IFN β/GA and BSC alone.

8.3.2.6 Rationale for Treatments and Comparisons

The preferred comparator for HTAs in Ireland is the technology or technologies most widely used in clinical practice in Ireland. [7] All IFN β and GA products are approved for general use in adults with RRMS, are widely used as first-line therapies in Ireland, and are therefore chosen as comparators. A weighted average of these products was based on their market share in 2012. [125] IFN β/GA is included as a comparator in the highly-active RRMS setting as in cases where first-line therapy with an IFN β or GA product has failed, it is common to switch between other IFN β or GA products. Despite fingolimod's restricted approval for use in highly active RRMS, prescribing analysis reveals that a substantial number of treatment-naive patients were initiated on fingolimod since its introduction in September 2012 (previously discussed in Chapter 2) and it is considered appropriate to include as a potential first-line DMT. [125] Like fingolimod, natalizumab is also approved for use in highly active RRMS. However, natalizumab is not considered a first-line treatment due to the serious safety concerns associated with its use, and also because it is administered in hospital according to strict protocols. [6 102] A separate scenario compares these agents in the highly-active RRMS treatment setting. BSC is also included as a comparator in secondary analysis as the cost effectiveness of IFN β/GA products has not been previously assessed in Ireland.

8.3.2.7 DMT Discontinuation and Duration of treatment

An annual risk of treatment discontinuation during the first two years of the model is based on discontinuations reported in pivotal Phase III RCTs for the second-generation agents and on previous CEA modelling assumptions for IFN β/GA which estimated a 10% risk of discontinuation in the first year. [236] The risk of long-term discontinuation in subsequent years is assumed to be the same for all agents, and is based on an Irish study which analysed stopping patterns among 394 patients prescribed IFN β over five years. [323] Aside from this annual risk of treatment discontinuation, the model assumes that all DMTs are given until conversion to SPMS or progression to EDSS ≥7. The alemtuzumab treatment pathway beyond the first two years is very uncertain. A two-dose restriction was imposed following the phase II RCT in 2005 but lifted in 2008. [112] An extension-study for all patients who participated in alemtuzumab phase II or III RCTs is ongoing. The extension-study protocol allows annual retreatment beyond two years "as needed", but not within the same 12-month period. [324] In light of this uncertainty, the assumption of continuous use which is applied to other DMTs, is also applied to alemtuzumab.

8.3.2.8 Time horizon and Discount Rate

Costs and consequences are evaluated over a 50-year time horizon, assumed to approximate patient lifetime. This is considered appropriate given the chronic, incurable nature of the illness. A standard discount rate of 4% is applied to both costs and outcomes in accordance with national HTA guidelines. [7] The time horizon was reduced to 20 years and the discount rate was varied between 0% and 6% in DSA.

8.3.2.9 Choice of health outcomes

The QALY is the chosen outcome for this CUA, as this has become the gold standard method for evaluating the cost effectiveness of healthcare choices. [7]

8.3.2.10 Measurement of efficacy

Relapses and progression of disability are the clinical hallmarks of the MS disease process. Therefore the clinical efficacy outcomes included in the analysis are reductions in disability progression and/or relapses. A systematic review was

undertaken to identify all RCTs which report disability progression and/or relapse outcomes for any of DMTs of interest to this analysis. Evidence was combined using NMA methods within a Bayesian framework. The outcomes of this review and analysis have been described in Chapter 7 in line with the PRISMA statement. [313] The relative effects estimated by the NMA are applied to fingolimod and natalizumab in the highly-active RRMS analysis due to lack of alternative evidence on efficacy in this setting. Treatment-effects were varied within the 95% CI in PSA and DSA. A long-term follow up of the pivotal IFN β-1b trial included 98.4% (366/372) of the original patient cohort and identified a significant reduction in the hazard-rate for all-cause mortality in patients originally assigned to receive IFN β-1b compared with those originally randomised to placebo. [82] The model allows a scenario analysis in which this survival advantage is applied to DMT treatment arms.

8.3.2.11 Measurement and valuation of preference based outcomes

The EQ-5D UK population tariff "crosswalk" was used to convert EQ-5D-5L responses from a cohort of Irish patients with MS to EDSS state utilities, as described in Chapter 6. A treatment disutility has previously been applied to IFN β/GA treatment (all administered by regular self-injection) in submissions to the NCPE and NICE. However, Orme *et al* performed a multivariate linear regression analysis to identify predictive variables associated with EQ-5D utility in a cross-sectional study of 2048 patients with MS in the UK. [238] The authors found no association between MS treatment and utility. A treatment-related disutility has not been applied in the base case however a disutility associated with IFN β/GA treatment of 0.05 is applied for the first six months of treatment in DSA. A relapse-related disutility of -0.22 was applied for a duration of 46 days. Treatment- and relapse-related disutilities and duration of relapse are based on a study by Prosser *et al* on the preferences for RRMS treatments and health states in the US. [325] Health state utilities were assumed to be dependent on EDSS state and do not differ between RRMS and SPMS patients. Health state utility values were varied within the 95% CI in PSA and DSA.

8.3.2.12 Estimating resources and costs

Health state costs were estimated from a cohort of Irish patients with MS as described in Chapter 5. Other costs in the model include the cost of a relapse and DMT costs.

DMT costs include the cost of the drug, monitoring and administration costs. Monitoring costs were based on prescribing information where available, the RCT safety profile and/or expert opinion. Drug costs are not known for the DMTs which have yet to come to the market. Hypothetical drug costs are therefore varied to investigate the impact on cost effectiveness versus standard of care. The cost of adverse events is not included as they are expected to be very low for frequent adverse events such as flushing, injection-site reactions for IFN β/GA, hypo- or hyperthyroidism for alemtuzumab, or very low frequency for serious adverse events such as PML for natalizumab (2.1 cases per 1000), or ITP for alemtuzumab (1 case per 100). Health state costs were assumed to be dependent on EDSS state and do not differ between RRMS and SPMS patients. All costs are reported in €2012. Where costs were not available for 2012, earlier costs were converted to €2012 using the CPI for health. [285] Where Irish costs were unavailable, costs from other settings were converted to euros using the purchasing power parity and inflated using the CPI where necessary. [7] Costs were varied within the 95% CI in PSA and DSA, with the exception of DMT costs which were varied +/-20% in DSA.

8.3.2.13 Mortality

In each cycle patients are at risk of death. The probability of dying in the general population was obtained from Irish life tables available from the CSO. [326] Three separate SMRs related to mild (1.60), moderate (1.84) and severe (4.44) MS were applied to the general population mortality risk. These SMRs were obtained from a study by Pokorski *et al* based on a population study of the Danish MS Registry [81] In deterministic scenario analysis, a single MS SMR of 2.89 (i.e. non disability related) is applied. [80]

8.3.2.14 Analytical Methods

8.3.2.14.1 Analysis of natural history of progression data

Transition probabilities of moving between EDSS health states in the model are calculated on the basis of median time from disease onset to DSS 3, 6, 8 and 10 reported for a longitudinal dataset of patients from the LO MS clinic in Canada. [29] This cohort was chosen because of its proven utility in previous CEAs, the extended length of follow-up, the continuous publication of additional analyses of interest and the

availability of relevant data. Observations on this cohort began in 1972. Patient accrual ended in 1984, and the observation period was extended for 28 years to 2000. The shortest follow-up was 16 years. Patients underwent annual or semi-annual evaluation and no patient received DMT. [57] Disability was scored using the DSS, which are analogous to EDSS scores in this model.[31] Median times from MS onset to DSS 3, 6 and 8 were first published in 1989 and formed the basis for the transition probabilities first used by Prosser *et al* in their CEA in 2004, and subsequently reproduced in many other CEAs. [52 54 56 265 327] In 2010, Scalfari *et al* published further analysis of the LO dataset including median times from MS onset to DSS 3, 6, 8, 10 and SPMS for 806 patients with relapsing-remitting onset disease. [29] At the end of the follow-up period, 657 patients (81.5%) had reached DSS 3, 543 patients (67.4%) DSS 6, 390 patients (48.4%) DSS 8 and 132 patients (16.4%) had reached DSS 10; the estimated median survival times were 10, 18, 28 and 63 years, respectively. Sixty six per cent of patients with RRMS had converted to SPMS. The estimated median time to secondary progressive onset was 15 years. [29] In the absence of a current dataset which may be more representative of our cohort, the LO dataset was considered appropriate for this analysis as it contains the longest follow-up of untreated patients with RRMS for disability endpoints of published registries, and no patients were treated with DMT. The model assumes disease onset to have occurred at EDSS 0.

Given median time (t) of progression from onset to a specified disability endpoint, assuming an exponential model, the mean time to progression (μ) was calculated as:

$$\mu = -(\ln(0.5)/t)^{-1}$$

In this way, the mean time from EDSS 0 to EDSS 3, 6, 8 and 10 was calculated. The median time from EDSS 3 to 6 was assumed to be equal to the difference between the median times from EDSS 0 to 3 and from EDSS 0 to 6, and so on for the median time between EDSS 6 and 8, and EDSS 8 and 10. The mean time to progression between these states was calculated in the same way as above. The mean time to progress *at least one step* within the EDSS grouping 0, 1, 2, 3 is assumed to be a third of the mean time to progress from EDSS 0 to 3.

The annual rate of progression (r) was given by $1/\mu$. The probability of making *at least one step* transition ($p(k \geq 1)$) within the EDSS grouping 0, 1, 2, 3 in one year is given by:

$p(k \geq 1) = 1-\exp(-r)$, where k=number of steps

The probability of making at least (K) step transitions is given by the poisson distribution, as follows:

$$p(k \geq K) = 1 - \exp(-r) - \sum_{j=1}^{K=1} \frac{rt^j \exp(-rt)}{j!}$$

The parameters of interest are probabilities of making exactly one step transition such as EDSS 0 to 1, or two step transitions such as EDSS 0 to 3 etc. The probability of exactly (k) step transitions is given by:

$p(k=K) = p(\geq k) - p(\geq k+1)$

It is assumed that transitions involving the same number of steps within each grouping were equivalent i.e. within the EDSS grouping 0, 1, 2, 3 the probability of progressing from EDSS 0 to 1 is equivalent to the probability of progressing from EDSS 1 to 2 etc. Steps between groupings e.g. from EDSS 0 to 4 are based on combinations of transition probabilities within groupings, as follows:

$p(EDSS_{0\text{-}4}) = p(EDSS_{0\text{-}3}) * p(EDSS_{3\text{-}4})$

A state transition matrix was constructed such that each cell contains the probability of moving from the Row-EDSS state to the column-EDSS state in one each model cycle (one year) (Table 8.1). The probability of remaining in a particular EDSS state is 1 – the probability of progressing.

Table 8.1: EDSS state transition matrix structure

EDSS	0	1	2	3	4	5	6	7	8	9
0	1-pp	$pEDSS_{0-1}$	$pEDSS_{0-2}$	$pEDSS_{0-3}$	$pEDSS_{0-4}$	$pEDSS_{0-5}$	$pEDSS_{0-6}$	$pEDSS_{0-7}$	$pEDSS_{0-8}$	$pEDSS_{0-9}$
1		1-pp	$pEDSS_{1-2}$	$pEDSS_{1-3}$	$pEDSS_{1-4}$	$pEDSS_{1-5}$	$pEDSS_{1-6}$	$pEDSS_{1-7}$	$pEDSS_{1-8}$	$pEDSS_{1-9}$
2			1-pp	$pEDSS_{2-3}$	$pEDSS_{2-4}$	$pEDSS_{2-5}$	$pEDSS_{2-6}$	$pEDSS_{2-7}$	$pEDSS_{2-8}$	$pEDSS_{2-9}$
3				1-pp	$pEDSS_{3-4}$	$pEDSS_{3-5}$	$pEDSS_{3-6}$	$pEDSS_{3-7}$	$pEDSS_{3-8}$	$pEDSS_{3-9}$
4					1-pp	$pEDSS_{4-5}$	$pEDSS_{4-6}$	$pEDSS_{4-7}$	$pEDSS_{4-8}$	$pEDSS_{4-9}$
5						1-pp	$pEDSS_{5-6}$	$pEDSS_{5-7}$	$pEDSS_{5-8}$	$pEDSS_{5-9}$
6							1-pp	$pEDSS_{6-7}$	$pEDSS_{6-8}$	$pEDSS_{6-9}$
7								1-pp	$pEDSS_{7-8}$	$pEDSS_{7-9}$
8									1-pp	$pEDSS_{8-9}$
9										1.0000

Each cell of the matrix contains the probability of moving from the Row-EDSS state to the column-EDSS state in one each model cycle (one year). The probability of remaining in a particular EDSS state is 1 – the probability of progressing (pp). Backward transitions to lower EDSS states (i.e. improvement) e.g. from EDSS 4 to EDSS 3, are not allowed
EDSS=Expanded disability status scale

Scalfari *et al* reported a median time of 15 years from onset of RRMS to onset of SPMS for the 806 patients in the LO dataset described above. [29]. The rate of change from a relapsing-remitting to a progressive course is accepted as being fairly constant over time, with a gradual rise in the total percentage of progressive cases as the disease advances. [26] In the model patients are at constant risk of conversion to SPMS during each model cycle, based on the estimated median time to SPMS of 15 years (t), which was used to define an annual probability of converting:

$$p(\text{conversion}) = 1 - \exp(-(-\ln(0.5) / t))$$

Baseline rates of disability progression were adjusted with 95% CI in DSA. The median time to SPMS is adjusted within the range 12 years (recently reported by Skoog *et* al from the Gothenberg MS cohort) to 19 years (reported from the Lyon database and other studies). [26 47] Upper and lower estimates of the median time to DSS endpoints were not applied in scenario analysis as an alternative source of natural history data compatible with the model structure was not found i.e. reporting time to DSS 3, 6, 8 and 10. Other longitudinal natural history cohorts have variously reported median time to DSS 6 and 8, or DSS 4, 6 and 7 and not DSS 3. The natural history cohorts are described in more detail in Chapter 2.

8.3.2.14.2 Analysis of natural history of relapses data

Relapse rates based on EDSS levels or based on time since diagnosis have not been reported from the LO dataset. A study by Patzold *et al*, published in 1982, has been used by numerous previous CEAs including submissions to the NCPE and NICE. The Patzold *et al* study reported relapse rates over 19 years for 102 patients with MS. [61] The baseline (untreated) relapse rates in the present study are based on a recent retrospective study by Tremlett *et al* because of its more representative patient population. The Tremlett *et al* study followed up 2477 patients with RRMS in British Colombia for a mean time of 20.6 years from onset, reporting ARR every five years between years five to 30 post-onset (Figure 2.7). [62] Single ARRs were calculated based on the expected MS gender distribution (66% female, 33% male). The ARR for every year since disease onset up to 50 years was imputed by an exponential regression (Table 8.2). The EDSS state transition matrix was used to simulate a cohort of 10,000 patients over 50 years to determine the average duration with disease for patients in each EDSS state. The resulting EDSS matrix was combined with data on number of relapses per year to estimate the average number of relapses per EDSS state. This analysis was done in R, and the syntax is contained in Appendix 9. Alternative relapse probabilities are applied in DSA, using the Patzold *et al* figures and also assuming a constant value of 0.5 per year which was proposed by Confavreux *et al* as "reasonable estimate of the yearly relapse rate". [26 61]

Table 8.2: Calculation of baseline MS relapse rates

Year since onset	Male	Female	weighted ARR (based on 2:1 f:m ratio)	Predicted ARR
1	0.31	0.33	0.32	0.36
2	0.31	0.33	0.32	0.35
3	0.31	0.33	0.32	0.33
4	0.31	0.33	0.32	0.32
5	0.31	0.33	0.32	0.31
6	0.22	0.27	0.25	0.29
7	0.22	0.27	0.25	0.28
8	0.22	0.27	0.25	0.27
9	0.22	0.27	0.25	0.26
10	0.22	0.27	0.25	0.25
11	0.18	0.23	0.22	0.24

Table 8.2: Calculation of baseline MS relapse rates

Year since onset	Male	Female	weighted ARR (based on 2:1 f:m ratio)	Predicted ARR
12	0.18	0.23	0.22	0.23
13	0.18	0.23	0.22	0.22
14	0.18	0.23	0.22	0.21
15	0.18	0.23	0.22	0.20
16	0.17	0.21	0.19	0.19
17	0.17	0.21	0.19	0.18
18	0.17	0.21	0.19	0.17
19	0.17	0.21	0.19	0.17
20	0.17	0.21	0.19	0.16
21	0.12	0.16	0.14	0.15
22	0.12	0.16	0.14	0.15
23	0.12	0.16	0.14	0.14
24	0.12	0.16	0.14	0.13
25	0.12	0.16	0.14	0.13
26	0.09	0.13	0.12	0.12
27	0.09	0.13	0.12	0.12
28	0.09	0.13	0.12	0.11
29	0.09	0.13	0.12	0.11
30	0.09	0.13	0.12	0.10
31	0.10	0.09	0.09	0.10
32	-	-	-	0.10
33	-	-	-	0.09
34	-	-	-	0.09
35	-	-	-	0.08
36	-	-	-	0.08
37	-	-	-	0.08
38	-	-	-	0.07
39	-	-	-	0.07
40	-	-	-	0.07
41	-	-	-	0.06
42	-	-	-	0.06
43	-	-	-	0.06
44	-	-	-	0.06
45	-	-	-	0.05
46	-	-	-	0.05
47	-	-	-	0.05
48	-	-	-	0.05
49	-	-	-	0.05
50	-	-	-	0.04

ARR=annualised relapse rate

8.3.2.14.3 Analysis of CEA results and model validation

Each treatment cohort is modelled to estimate mean expected lifetime costs and QALYs. Deterministic results were obtained using the mean point estimates for each input parameter. The model was also run probabilistically by assigning probability distributions to model inputs. Distributions were chosen for each parameter to reflect the nature of the data including gamma distribution for costs to represent uncertainty in skewed cost parameters, log-normal distribution for hazard ratios and relative risks associated with DMT treatment to reflect the ratio nature of these parameters, and beta distribution for probabilities as it is similarly defined on the interval zero to one. Due to the presence of negative utilities, a transformation of utility to utility decrement (disutility) was used and a gamma distribution applied. The probabilistic analysis was run over 1000 iterations. This was repeated over three successive runs to ensure that the results did not change appreciably.

Treatments are compared by using ICERs and the decision uncertainty is presented using a CEAC which plots the probability that each treatment is the most cost-effective for a given cost effectiveness threshold. Standard decision rules were used to identify the most cost-effective treatment. Strategies are ranked in order of increasing total expected costs and sequentially removed on the basis of dominance or extended dominance. ICERs are presented for each remaining options compared with the next most effective option. Results are presented using ICERs arising from the PSA to account for the uncertainty in the model. Deterministic ICERs are also presented and compared with probabilistic ICERs.

Tornado plots were constructed to illustrate the impact on the deterministic ICER of changing individual parameters and assumptions within a plausible range in DSA. In separate scenario analyses, model assumptions regarding time horizon, mortality, treatment disutility and the initial cohort distribution are tested.

The structural integrity of the model was validated by assessing the model response to predictable manipulations e.g. setting parameters to zero in the case of health-state specific parameters such as costs, utilities, progression rates etc. or equivalence in the case of treatment-specific parameters such as drug costs and treatment-effects.

8.4 Results

Table 8.3 summarises all model parameter inputs, distributions applied for PSA, plausible ranges applied in DSA and scenario analyses, and data sources. Table 8.4 summarises the total drug costs applied in the model. Drug costs include ingredient cost, pharmacist fees, monitoring and administration costs. Administration costs are applied to alemtuzumab and natalizumab (hospital drugs) and fingolimod to account for cardiovascular monitoring following the first dose, and an ophthalmological consultation recommended at 3-4 months after treatment initiation. No administration cost is applied to self-injected or orally administered DMTs. Monitoring costs include neurologist consultations, biochemistry and imaging costs in line with SPC recommendations or current best practice. Ingredient costs for IFN β/GA (weighted average based on market share), fingolimod and natalizumab are based on public list prices. The actual price of fingolimod is likely to be lower as a patient access scheme (PAS) is in place involving a confidential price reduction. The price of alemtuzumab, BG-12, laquinimod and teriflunomide is unknown as these drugs have yet to be marketed in Ireland.

Table 8.4: Annual drug costs

	Ingredient Cost*	High-tech scheme fee	Monitoring Cost**	Administration Cost	Total Cost
Alemtuzumab	unknown	€0	€378	€3,651 yr 1, €2,424 yr ≥2	unknown
Natalizumab	€21,352	€0	€1,302	€1,614	€24,268
BG-12	unknown	€744	€164	€0	unknown
Laquinimod	unknown	€744	€166	€0	unknown
Fingolimod*	€23,809	€744	€205	€739 (year 1)	€24,614
Teriflunomide	unknown	€744	€205	€0	unknown
IFN β/GA average	€12,684	€744	€227	€0	€13,510

Costs are in €2012. IFN ß/GA=weighted average of interferon beta and glatiramer acetate products.
**Unit costs of individual tests included in monitoring costs are listed in Appendix 4.
Monitoring cost assumptions: Alemtuzumab - three-monthly FBC, TSH, T3, T4, annual neurologist consultation [328] ; Natalizumab - 3-monthly FBC, LFT, U+E, annual JCV, 4-monthly neurologist consultation, annual MRI [328]; BG-12– annual FBC, annual neurologist consultation [329]; Laquinimod – six-monthly LFT, annual neurologist consultation [329]; Fingolimod – six-monthly FBC, annual neurologist consultation [329], LFT; teriflunomide – six-monthly FBC, LFT, annual neurologist consultation [329]; IFN β/GA average - 3-monthly FBC, LFT, U+E, , annual neurologist consultation [329]
Administration cost assumptions: Alemtuzumab – six day hospital admission. [142 328] ; natalizumab – 2.5 hours clinical nurse specialist time[328]; fingolimod – ophthalmological evaluation in year 1, six hours cardiac monitoring post first dose, 0.5% overnight admission post first dose[106 142].
FBC:full blood count, LFT:liver function tests, TSH:thyroid stimulating hormone, U+E:urea and electrolytes, T3, T4:thyroid hormones, JCV: John Cunningham virus, MRI:Magnetic resonance imaging.

Table 8.3: Model parameter inputs, distributions and data-sources

Parameter	Mean value (plausible range)	Source	Distribution for PSA/DSA/Comment
Costs *(mean annual)*	**Mean (95% CI)**		
Health State Costs (Healthcare payer perspective)			
EDSS 0 healthcare Cost	€871 (€446 - €1399)	Chapter 5 – Table 5.5	Gamma
EDSS 1 healthcare Cost	€1352 (€928 - €1843)		
EDSS 2 healthcare Cost	€1385 (€502 - €2536)		
EDSS 3 healthcare Cost	€5043 (€2439 - €8302)		
EDSS 4 healthcare Cost	€2144 (€1331 - €3142)		
EDSS 5 healthcare Cost	€1070 (€54 - €2882)		
EDSS 6 healthcare Cost	€7010 (€4286 - €10371)		
EDSS 7 healthcare Cost	€17694 (€8081 - €28637)		
EDSS 8 healthcare Cost	€53143 (€32185 - €74764)		
EDSS 9 healthcare Cost	€105091 (€68162 - €171024)		
Health state costs (Societal perspective)			
EDSS 0 societal Cost	€5950 (€952 - €12596)	Chapter 5 - Table 5.5	Gamma
EDSS 1 societal Cost	€7244 (€3940 - €11163)		
EDSS 2 societal Cost	€10426 (€3729 - €18225)		
EDSS 3 societal Cost	€30008 (€20801 - €38673)		
EDSS 4 societal Cost	€22518 (€13221 - €31915)		
EDSS 5 societal Cost	€47183 (€8096 - €96679)		
EDSS 6 societal Cost	€45698 (€37658 - €54090)		
EDSS 7 societal Cost	€70813 (€51032 - €91186)		
EDSS 8 societal Cost	€99674 (€78312 - €118434)		
EDSS 9 societal Cost	€148268 (€106669 - €221119)		
Relapse Cost	€2535(€865 - €4204)	Tyas *et al* [229]	Gamma
Drug Cost	See Table 8.4		Varied in DSA +/-20%

Table 8.3 Model parameter inputs, distributions and data-sources Continued

Parameter	Mean value (plausible range)	Source	Distribution for PSA/Comment
Utilities	**Mean (95% CI)**		
Health State Utilities			
EDSS 0 Utility	0.88 (0.8 - 0.96)	Chapter 6 – Table 6.2	
EDSS 1 Utility	0.8 (0.75 - 0.85)		
EDSS 2 Utility	0.75 (0.68 - 0.81)		
EDSS 3 Utility	0.67 (0.6 - 0.74)		Transformed to disutility (1-utilty) and Gamma distribution applied
EDSS 4 Utility	0.61 (0.53 - 0.69)		
EDSS 5 Utility	0.54 (0.45 - 0.64)		
EDSS 6 Utility	0.46 (0.41 - 0.52)		
EDSS 7 Utility	0.31 (0.18 - 0.43)		
EDSS 8 Utility	-0.09 (-0.2 - 0.01)		Relapse disutility plausible range for PSA and DSA calculated from high and low values of mean +/-10%
EDSS 9 Utility	-0.22 (-0.42 - -0.06)		
Relapse disutility	0.22 (0.198-0.242)	Orme *et al* [238]	
Natural History	**Mean (range)**		
Median time from onset to disability endpoint			
EDSS 3	10 years	Scalfari *et al* [29]	
EDSS-6	18 years		
EDSS 8	28 years		
EDSS 10	63 years	Scalfari *et al* [29], Skoog *et al*, Confavreux *et al* [26 47]	High and low levels of median time to SPMS applied in scenario analyses.
Median time from onset to SPMS conversion	15 years (12-19 years)		
Annual disability progression rates	**Mean (95% CI)**		
EDSS 0-3	0.208 (0.192 - 0.224)	Calculated from median time from onset to disability endpoints	Gamma
EDSS 3-6	0.260 (0.238 - 0.282)		
EDSS 6-8	0.139 (0.125 - 0.152)		
EDSS 8-10	0.040 (0.033 - 0.046)		
Risk of SPMS conversion	0.045 (0.041 - 0.049)		calculated from median time to conversion Log-normal

Table 8.3 Model parameter inputs, distributions and data-sources Continued

Parameter	Mean value (plausible range)	Source	Distribution for PSA/Comment
Natural History	**Mean (95% CI)**		
ARR			
EDSS 0	0.31 (0.30 - 0.32)	Synthesised from ARR data from Tremlett *et al* and EDSS transition matrix based on data from Scalfari *et al* [29 62] (Appendix 9)	Beta
EDSS 1	0.26 (0.25 - 0.27)		
EDSS 2	0.22 (0.21 - 0.23)		
EDSS 3	0.19 (0.18 - 0.20)		
EDSS 4	0.17 (0.16 - 0.17)		
EDSS 5	0.15 (0.14 - 0.15)	Alternative soucres for DSA scenarios include Patzold *et al* and Confavreux *et al*, [26]	DSA scenarios use relapse risks synthesised from ARRs from Patzold *et al* (Table 2.2) and a constant ARR of 0.5 per year from Confavreux *et al*, [26 61]
EDSS 6	0.10 (0.09 - 0.10)		
EDSS 7	0.08 (0.07 - 0.08)		
EDSS 8	0.07 (0.06 - 0.07)		
EDSS 9	0.06 (0.06 - 0.06)		
DMT treatment-effects	Mean (95% CI)		
Hazard ratio of disability progression			
Alemtuzumab	0.27 (0.15 - 0.49)	Chapter 7 – Table 7.3	Log-normal
Natalizumab	0.55 (0.42 - 0.73)		
BG12 480mg	0.61 (0.48 - 0.76)		Treatment-effect waning by 50% after five years is applied in scenario analysis.
Laquinimod	0.65 (0.46 - 0.9)		
Fingolimod	0.66 (0.50 - 0.86)		
Teriflunomide 14mg	0.72 (0.54 - 0.97)		
IFN β / GA	0.81 (0.59 - 1.10)		
Relative ARR			
Alemtuzumab	0.31 (0.23 - 0.36)	Chapter 7 - Table 7.3	Log-normal
Natalizumab	0.31 (0.27 - 0.36)		
BG12 480mg	0.50 (0.43 - 0.58)		Treatment-effect waning by 50% after five years is applied in scenario analysis.
Laquinimod	0.76 (0.66 - 0.89)		
Fingolimod	0.44 (0.37 - 0.53)		

Table 8.3 Model parameter inputs, distributions and data-sources Continued

Parameter	Mean value (plausible range)			Source	Distribution for PSA/Comment
DMT treatment-effects	Mean (95% CI)				
Relative risk of relapse					
Teriflunomide 14mg	0.68 (0.58 - 0.80)			Chapter 7 - NMA	Log-normal
IFN β / GA	0.72 (0.64 - 0.85)				
Risk of DMT Discontinuation	**Mean (+/-10%)**				
Year 0 and 1				RCTs:	
Alemtuzumab	0.029 (0.026 - 0.031)			Coles *et al*, Cohen *et al* [108 109]	Beta
Natalizumab	0.116 (0.105 - 0.128)			Polman *et al* RCT [101]	
BG12 480mg	0.110 (0.199 - 0.121)			Fox *et al*, Gold *et al* RCTs [70 119]	
Laquinimod	0.103 (0.092 - 0.113)			Comi *et al* [71]	Risk of discontinuation plausible range for PSA and DSA calculated from high and low values of mean +/-10%
Fingolimod	0.098 (0.089 - 0.108)			Cohen *et al*, Kappos *et al* [104 105]	
Teriflunomide 14mg	0.133 (0.119 - 0.146)			O'Connor *et al* [114]	
IFN β / GA	0.100 (0.090 - 0.110)			Tappenden *et al* [236]	
Year 2	0.066 (0.059 - 0.072)			O'Rourke *et al* [323]	
Mortality settings					
Disabiltiy-related SMR					
EDSS 0-3 SMR	1.60			Pokorski *et al* [81]	Mortality set to Disability-related SMR in base-case.
EDSS 4-6 SMR	1.84				
EDSS 7-9 SMR	4.44				Single, non-disability related SMR applied to all patients in DSA
Non-disability related SMR	2.89 *(scenario analysis)*			Bronnum-Hansen *et al* [80]	
Initial Cohort Distribution					
	Base	*Alt. 1*	*Alt. 2*		
EDSS 0	18.58%	32.94%	8%	Base case from Fogarty *et al.* Alternative distributions from NICE IFN B/GA assessment 2002, NICE fingolimod assessment 2011[51] NICE 2011 distributions estimated from graph in manufacturer submssion	DSA scanario analyses include: starting all patients in EDSS 0, 1, 2, 3, 4, 5 and 6; using distribution from NICE assessments in 2002 and 2006
EDSS 1	42.48%	29.45%	30%		
EDSS 2	15.93%	25.07%	28.50%		
EDSS 3	15.04%	8.75%	18.50%		
EDSS 4	5.31%	1.17%	10.50%		

Table 8.3 Model parameter inputs, distributions and data-sources Continued

Parameter	Mean value (plausible range)			Source	Distribution for PSA/Comment
Initial Cohort Distribution					
	Base	*Alt. 1*	*Alt. 2*		
EDSS 5	0.00%	1.17%	0.00%		
EDSS 5	0.00%	1.17%	0.00%		
EDSS 6	2.65%	1.46%	0.00%		
EDSS 7	0.00%	0.00%	0.00%		
EDSS 8	0.00%	0.00%	0.00%		
EDSS 9	0.00%	0.00%	0.00%		

Abbreviations: Alt=alternative; EDSS=Expanded disability status scale; SMR=standardised mortality ratio; IFN ß=interferon beta. GA=glatiramer acetate.CI=confidence interval. NICE=National Institute for Clinical Excellence; PSA=probabilistic sensitivity analysis. SMT=disease-modifying therapy. RCT=Randomised Controlled Trial; DSA=Deterministic Sensitivity Analysis; HRQoL= Health related quality of life ; ARR= Annualised relapse rate

The natural history of disability progression transition probability matrix is summarised in Table 8.5.

Table 8.5: EDSS state transition matrix

EDSS	0	1	2	3	4	5	6	7	8	9
0	0.8120	0.1689	0.0176	0.0012	0.0002	0.0000	0.0000	0.0000	0.0000	0.0000
1		0.8095	0.1689	0.0176	0.0035	0.0005	0.0000	0.0000	0.0000	0.0000
2			0.7924	0.1689	0.0339	0.0044	0.0004	0.0000	0.0000	0.0000
3				0.7710	0.2004	0.0260	0.0023	0.0003	0.0000	0.0000
4					0.7701	0.2004	0.0260	0.0031	0.0002	0.0000
5						0.7736	0.2004	0.0242	0.0017	0.0001
6							0.8706	0.1207	0.0084	0.0003
7								0.8747	0.1207	0.0046
8									0.9619	0.0381
9										1.0000

Each cell of the matrix contains the probability of moving from the Row-EDSS state to the column-EDSS state in one each model cycle (one year). The probability of remaining in a particular EDSS state is 1 – the probability of progressing. The probability of moving five or more steps in one year is negligible and is rounded to zero in the printed matrix. Backward transitions to lower EDSS states (i.e. improvement) e.g. from EDSS 4 to EDSS 3, are not allowed

EDSS: Expanded disability status scale

The total expected costs and QALYs for BSC (no treatment), IFN β / GA, fingolimod and natalizumab, from the healthcare perspective, are presented on a scatter-plot in Figure 8.2. Mean expected costs and QALYs are presented from both the healthcare and societal perspective in Table 8.6 a) and 8.6 b). IFN β / GA, Fingolimod and natalizumab accounted for 18.46%, 31.70% and 31.89% of lifetime healthcare costs for the cohort, respectively. Total lifetime healthcare costs per patient on BSC were €192,605, compared with €661,483 if societal costs are included.

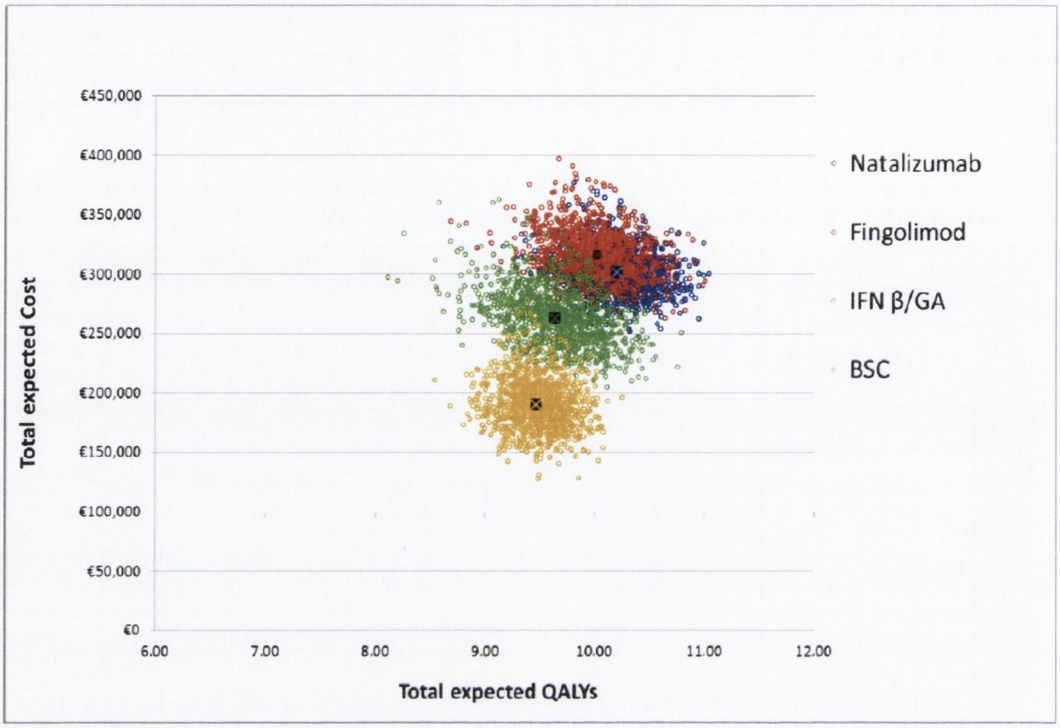


Figure 8.2: Scatterplot of Total Expected Costs and QALYs (Healthcare payer perspective)

Costs are in €2012. Each dot represents the costs and QALYs estimated by each of 1000 iterations of the analysis. The black markers on the scatters indicate the mean cost per QALY.
Abbreviations: BSC=best supportive care. QALY=quality adjusted life year.

8.4.1 Comparison of potential first-line DMTs

In the comparison of potential first-line DMTs (IFN β/GA and fingolimod), IFN β/GA is the least costly and least effective strategy. Fingolimod is expected to result in a gain of 0.35 QALYs compared with IFN β/GA at an additional cost of €54,061. The ICER of fingolimod is €155,000 per QALY. At low threshold values, IFN β/GA has the highest probability of being cost-effective. At a cost effectiveness threshold of €45,000 per QALY, the probability that fingolimod is the most cost-effective strategy is 10%, rising to above 50% only when the threshold increases to €150,000 per QALY. (Figure 8.3) If BSC (i.e. no treatment) is included in the analysis as a comparator, IFN β/GA is ruled out by extended dominance and the ICER for fingolimod is €238,000. The probability that fingolimod is the most cost-effective strategy in this scenario at a €45,000 per QALY threshold is 0% (Figure 8.4). From the societal perspective, the ICER for fingolimod reduces to €105,000 per QALY versus IFN β/GA and to €198,000 per QALY versus BSC.

Table 8.6 a): Results of base-case analysis (healthcare payer perspective)

	Mean Costs*	Mean QALYs*	ICER vs BSC	ICER vs IFN β/GA	Comparison of 1st line DMTs (including BSC)	Comparison of 1st line DMTs (not including BSC)	Comparison of 2nd line DMTs (including BSC)	Comparison of 2nd line DMTs (not including BSC)
					ICER	ICER	ICER	ICER
BSC alone	€192,605	9.45	-	-	-	NA	-	NA
IFN β/GA	€264,241	9.63	**€397,000**	-	ED	-	ED	-
Natalizumab	€303,748	10.18	**€152,000**	**€72,000**	NA	NA	**€152,000**	**€72,000**
Fingolimod	€318,301	9.98	**€238,000**	**€155,000**	€238,**000**	€155,**000**	D	D

Table 8.6 b): Results of base-case analysis (societal perspective)

	Mean Costs*	Mean QALYs*	ICER vs BSC	ICER vs IFN β/GA	Comparison of 1st line DMTs (including BSC)	Comparison of 1st line DMTs (not including BSC)	Comparison of 2nd line DMTs (including BSC)	Comparison of 2nd line DMTs (not including BSC)
					ICER	ICER	ICER	ICER
BSC alone	€661,483	9.46	-	-	-	NA	-	NA
IFN β/GA	€724,604	9.65	€340,**000**	-	ED	-	ED	-
Natalizumab	€738,004	10.19	€105,**000**	€25,**000**	NA	NA	€105,**000**	€25,**000**
Fingolimod	€763,769	9.98	€198,**000**	€118,**000**	€198,**000**	€118,**000**	D	D

Costs in €2012. Probabilistic results are presented (equivalent deterministic ICERs vs BSC from healthcare payer perspective are **€373,000**, **€232,000**and **€149,000**for IFN β/GA, fingolimod and natalizumab respectively; equivalent deterministic ICERs vs BSC from societal perspective are €330,**000**, €186,**000**and €102,**000**for IFN β/GA, fingolimod and natalizumab respectively.)

The DMTs included in each comparison are indicated by the bold border. BSC is included in some comparisons because although IFN β/GA is standard-of-care, its cost effectiveness hasn't been established. IFN β/GA is eliminated from the first line comparison containing BSC through extended dominance (it has a higher ICER than fingolimod). IFN β/GA is also eliminated from the comparison of highly-active RRMS DMTs by extended dominance. Fingolimod is eliminated from the comparison of highly-active RRMS DMTs as it is dominated by natalizumab (fingolimod is more costly and less effective). Natalizumab is not included in any comparison of 1st line DMTs as it is only used in highly-active RRMS

Abbreviations: IFN ß/GA=weighted average of interferon beta and glatiramer acetate products.. ICER=incremental cost-effectiveness ratio (euros per QALY). D=Dominated. ED=Extended dominated. NA=not applicable. DMT=disease-modifying therapy. BSC=best supportive care. QALY=quality adjusted life year

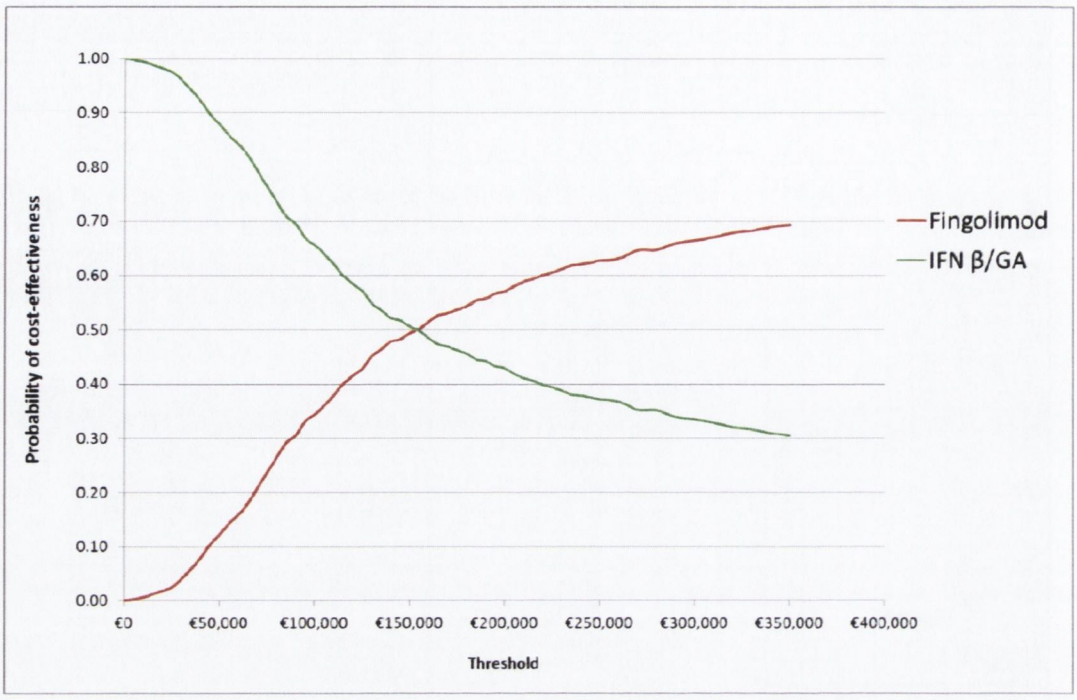


Figure 8.3: CEAC of potential first-line DMTs IFN β/GA and fingolimod

Costs are in €2012.IFN ß/GA=weighted average of interferon beta and glatiramer acetate products.

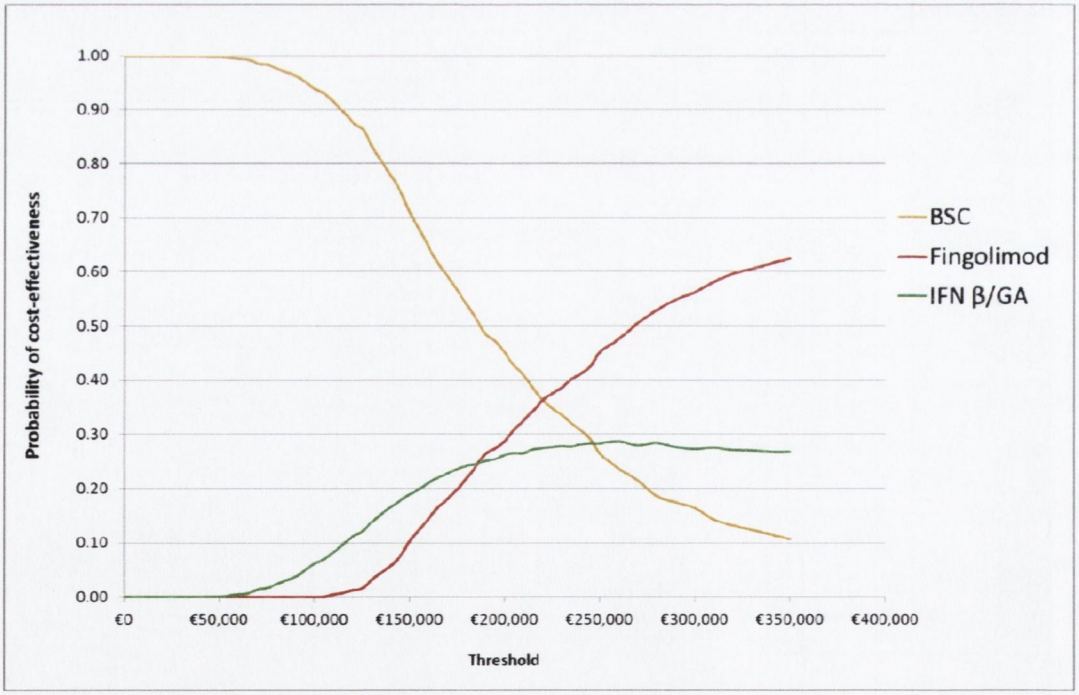


Figure 8.4: CEAC of potential first-line DMTs IFN β/GA and fingolimod (including BSC alone)

Costs are in €2012. IFN ß/GA=weighted average of interferon beta and glatiramer acetate products. BSC=best supportive care.

8.4.2 Comparison of potential highly-active RRMS DMTs

In the comparison of DMTs for highly-active RRMS (IFN β / GA, fingolimod and natalizumab), fingolimod is dominated by natalizumab as it is less effective and more costly. Compared with IFN β / GA, natalizumab is expected to result in a gain of 0.55 QALYs at an additional cost of €39,508. The ICER of natalizumab is €72,000 per QALY. At a cost effectiveness threshold of €45,000 per QALY, the probability that natalizumab is the most cost-effective strategy is 27%, rising to above 50% when the threshold increases to €85,000 per QALY. (Figure 8.5) If BSC is included in the comparison, both IFN β/GA and Fingolimod are eliminated by extended dominance and the ICER for natalizumab versus BSC is €152,000. The probability that natalizumab is the most cost-effective strategy at a €45,000 per QALY threshold is 0% (Figure 8.6). From the societal perspective, the ICER for natalizumab reduces to €23,000 versus IFN β/GA and to €107,000 per QALY versus BSC.

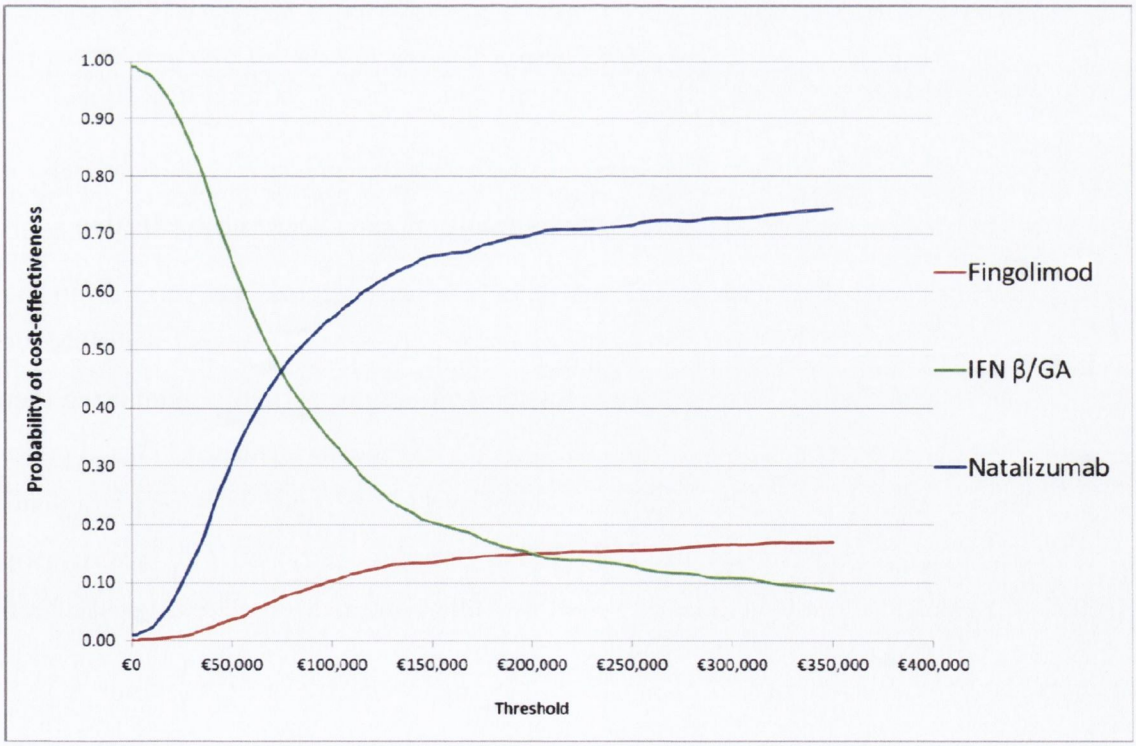


Figure 8.5: CEAC of potential DMTs for highly-active RRMS IFN β/GA, fingolimod and natalizumab

Costs are in €2012. IFN ß/GA=weighted average of interferon beta and glatiramer acetate products.

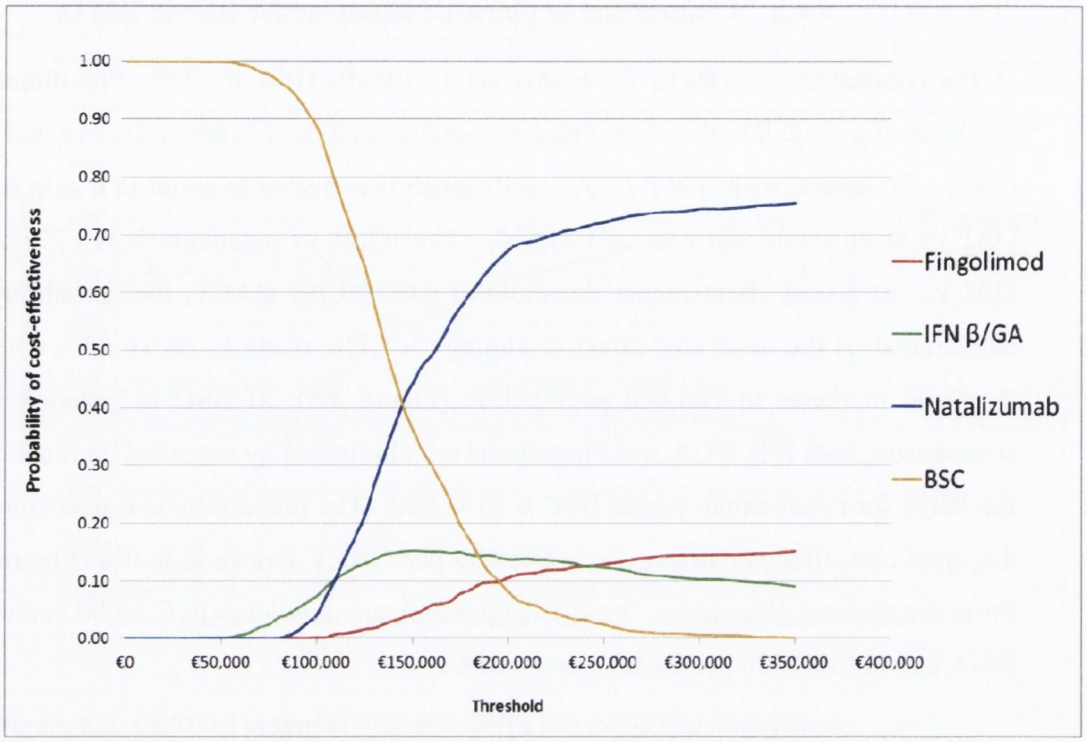


Figure 8.6: CEAC of DMTs for highly-active RRMS IFN β/GA, fingolimod, natalizumab (including BSC alone)

Costs are in €2012. IFN ß/GA=weighted average of interferon beta and glatiramer acetate products. BSC=best supportive care.

8.4.3 Cost at which new DMTs would be considered cost-effective

The price at which new DMTs would be considered cost-effective at a threshold of €45,000 per QALY from the healthcare payer perspective compared with IFN β/GA is outlined in Table 8.7. The price reduction required for currently reimbursed therapies in order achieve an ICER of €45,000 per QALY is also presented. Based on current model assumptions, price estimates range from €16,012 per year for teriflunomide to €24,984 per year for alemtuzumab. Reductions of 11.62% and 26.63% were estimated for fingolimod and natalizumab respectively, in order to be considered cost-effective at this threshold.

Table 8.7: Estimated price at which DMTs would be considered cost-effective

DMT	Cost-effective Annual Price*	Incremental cost over IFN β / GA	Price reduction required
Alemtuzumab	€24,984	93.97%	-
Natalizumab	€18,872	47.00%	11.62%
BG-12	€19,142	48.21%	-
Laquinimod	€17,514	37.71%	-
Fingolimod	€17,469	35.33%	26.63%
Teriflunomide	€16,012	24.31%	-

*Cost-effective versus IFN β/GA at a threshold of €45,000 per QALY from the healthcare payer perspective on the basis of current model assumptions. IFN ß/GA=weighted average of interferon beta and glatiramer acetate products

8.4.4 Deterministic Sensitivity Analysis

Figure 8.7 and 8.8 illustrate the impact of varying parameters in one-way SA on the results of the natalizumab and fingolimod comparisons versus IFN β / GA, from the healthcare payer perspective. The results of all deterministic one-way and scenario analyses are presented in Table 8.8. The HR of disability progression has the greatest impact on results. Variation within plausible ranges resulted in an ICER of €62,000 per QALY versus IFN β/GA using the most favourable HR for fingolimod, and at the other extreme, fingolimod being dominated by IFN β/GA using the least favourable HR for fingolimod. Similar extremes were observed when HR of disability progression of natalizumab and IFN β/GA were varied. Of the remaining parameters, drug cost, discount rate, health state costs, starting age, durability of treatment-effects and the baseline rates of disability progression had the greatest influence on the results. Low drug costs, zero discount rate, high health state costs, low starting age and high baseline rates of disability progression favour natalizumab and fingolimod over IFN β/GA. The cost-effectiveness of natalizumab and fingolimod versus IFN β/GA was greatly reduced if treatment efficacy is reduced by 50% after five years. Relapse-related parameters have very little impact on the results, by comparison. The impact of starting the cohort at various levels of disability and of applying health-state distributions used in other CEAs is illustrated in Figure 8.9. The results are sensitive to the initial distribution of the cohort across EDSS states. ICERs versus IFN β/GA were lowest if the entire cohort starts in EDSS 5 (€27,000 natalizumab, €105,000 fingolimod) and highest if the cohort starts in EDSS 0 (€92,000 natalizumab, €181,000 fingolimod). Applying cohort distributions used in previous NICE assessments resulted in ICER ranges from €64,000 to €75,000 for natalizumab and from €146,000 to €159,000 for fingolimod.

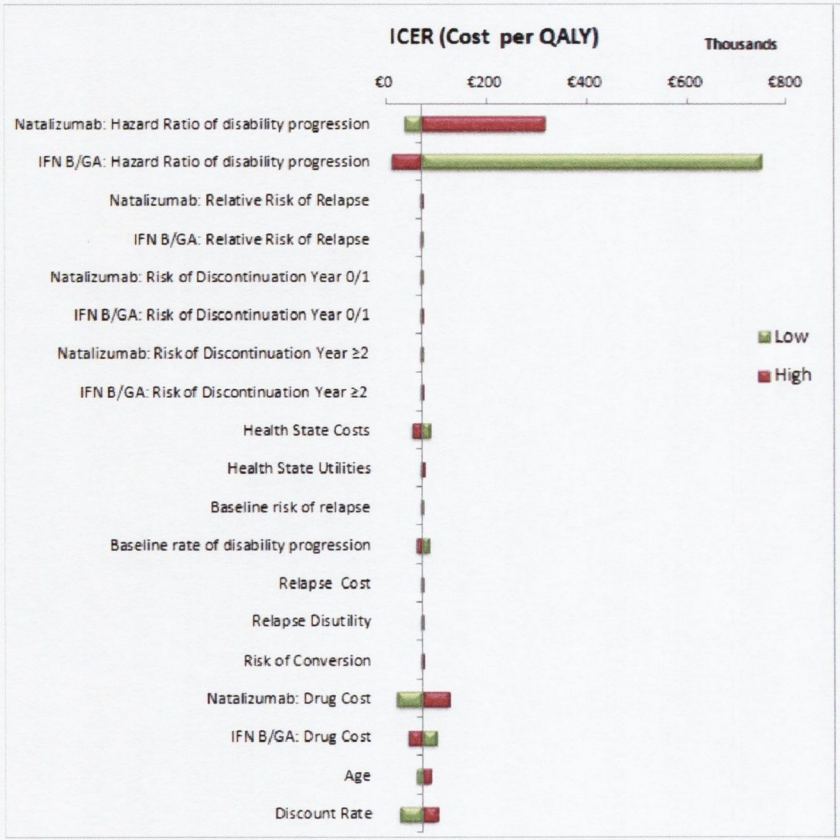


Figure 8.7: Tornado diagram of one-way SA (natalizumab vs IFN β/GA)

Mean deterministic ICER is €72,000 per QALY.

IFN ß/GA=weighted average of interferon beta and glatiramer acetate products

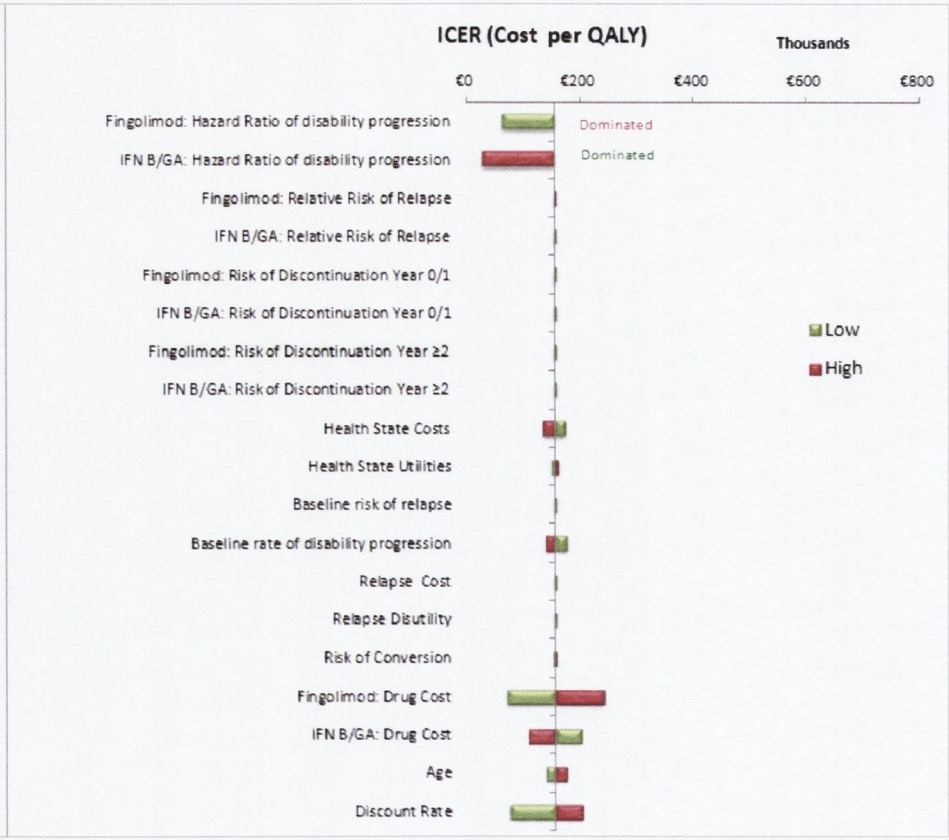


Figure 8.8: Tornado diagram of one-way SA (fingolimod vs IFN β/GA)

Mean deterministic ICER is €155,000 per QALY.

IFN ß/GA=weighted average of interferon beta and glatiramer acetate products

Table 8.8: Deterministic Sensitivity Analysis Results (treatments versus IFN β/GA from the healthcare payer perspective)

	Natalizumab Mean ICER	**€71,595**	**Natalizumab**		**Fingolimod**	
	Fingolimod Mean ICER	**€154,985**				
	Parameter	**Mean/Basecase assumption (range/alternative assumption)**	**Low**	**High**	**Low**	**High**
Hazard Ratio of disability progression	Natalizumab	0.55 (0.42 - 0.73)	€37,549	€316,365	NA	NA
	Fingolimod	0.66 (0.50 - 0.86)	NA	NA	€62,012	Dominated
	IFN B/GA	0.81 (0.59 - 1.10)	€748,325	€9,921	Dominated	€26,742
Relative Risk of Relapse	Natalizumab	0.31 (0.27 - 0.36)	€71,154	€72,102	NA	NA
	Fingolimod	0.44 (0.37 - 0.53)	NA	NA	€153,107	€157,261
	IFN B/GA	0.72 (0.64 - 0.85)	€72,401	€70,707	€156,918	€152,870
Risk of Discontinuation Year 0/1	Natalizumab	0.116 (0.110 - 0.122)	€73,056	€70,047	NA	NA
	Fingolimod	0.098 (0.093 - 0.103)	NA	NA	€155,016	€154,953
	IFN B/GA	0.1 (0.095 - 0.105)	€70,696	€72,457	€155,606	€154,397
Risk of Discontinuation Year ≥2	Natalizumab	0.058 (0.055 - 0.060)	€73,832	€69,368	NA	NA
	Fingolimod	0.058 (0.055 - 0.060)	NA	NA	€155,610	€154,393
	IFN B/GA	0.058 (0.055 - 0.060)	€70,317	€72,733	€155,865	€154,198
Other Parameters	Health State Costs	10 parameters changed (see Table 8.3)	€88,216	€50,076	€172,028	€132,896
	Health State Utilities	10 parameters changed (see Table 8.3)	€68,367	€74,806	€147,909	€161,891
	Baseline risk of relapse	10 parameters changed (see Table 8.3)	€71,720	€71,469	€155,204	€154,766
	Baseline rate of disability progression	4 parameters changed (see Table 8.3)	€85,116	€60,085	€176,277	€137,159
	Relapse Cost	€2535(€865 - €4204)	€72,770	€70,419	€156,345	€153,624
	Relapse Disutility	0.22 (0.198-0.242)	€71,735	€71,455	€155,335	€154,636
	Risk of Conversion	0.045 (0.041 - 0.049)	€69,410	€73,609	€151,847	€157,840
Drug Cost	Natalizumab	+/- 20%	€19,550	€123,639	NA	NA
	Fingolimod	+/- 20%	NA	NA	€69,092	€240,878
	IFN B/GA	+/- 20%	€100,000	€41,654	€199,914	€107,628
Other Parameters	Age	42 years (37-47 years)	€59,784	€86,147	€138,146	€176,420
	Discount Rate	4% (0%-6%)	€24,468	€100,242	€74,778	€203,354

Table 8.8: Deterministic Sensitivity Analysis Results (treatments versus IFN β/GA from the healthcare payer perspective)

	Natalizumab Mean ICER	**€71,595**	**Natalizumab**		**Fingolimod**	
	Fingolimod Mean ICER	**€154,985**				
	Parameter	**Mean/Basecase assumption (range/alternative assumption)**	**Low**	**High**	**Low**	**High**
			Alt.1	**Alt.2**	**Alt.1**	**Alt.2**
	Time horizon*	50 years (10 years - 20 years)	€321,091	€133,185	€573,691	€255,473
	Standardised mortality ratio*	Disabilty related, 1.60-4.44 (non-disability related, 2.89)	€68,569	-	€157,551	-
	IFN B/GA Disutility*	none (0.05 for first 6 months)	€68,507	-	€144,672	-
	Duration of treatment efficacy*	indefinite (50% reduction after 5 years)	€103,273	-	€215,539	-
	Source of baseline relapse data*	Tremlett et al (Patzold *et al* - Confavreux *et al*)	€63,427	€65,653	€141,051	€144,960

*Parameters denoted with an asterisk (*) are changed to reflect alternative scenarios/assumptions and are not necessarily representative of "low" or "high" alternatives.
Dominated=more costly and less effective. Dominant=less costly and more effective.
Abbreviations: Alt=alternative; IFN ß/GA=weighted average of interferon beta and glatiramer acetate products; ICER=incremental cost-effectiveness ratio (euros per QALY)

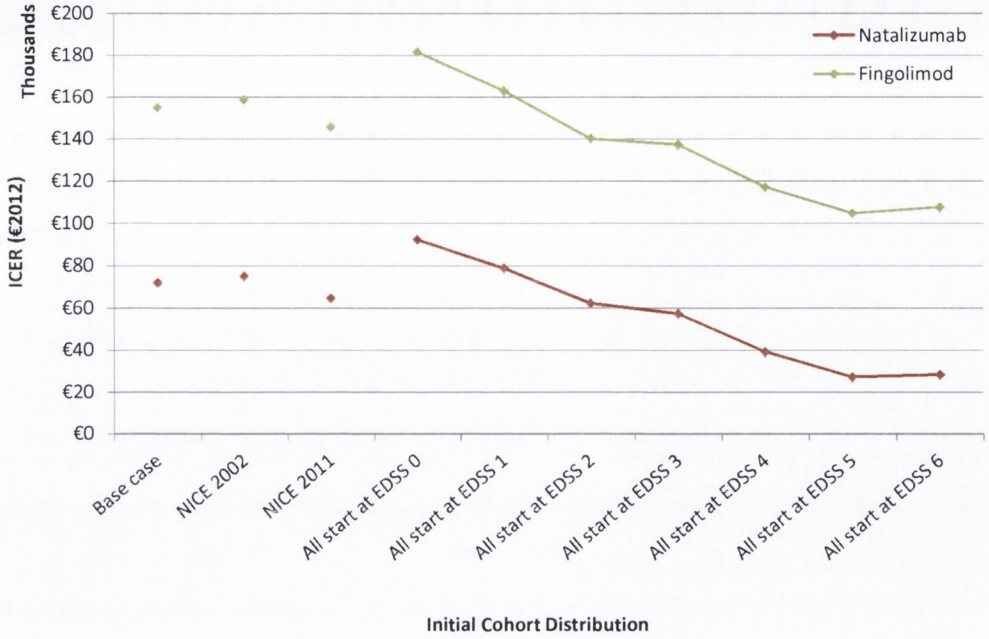


Figure 8.9: Impact of initial cohort distribution on results

8.5 Discussion

A model of DMT in RRMS was developed for the purposes of assessing the cost effectiveness of DMTs in Ireland and to provide a framework within which the cost effectiveness of future therapies may be assessed. Cost and utility parameter inputs were derived from a cohort of Irish patients, natural history of MS was based on data reported in the literature, and relative efficacy data was estimated by NMA methods following a systematic review of RCTs. DMT accounted for a substantial proportion of lifetime healthcare costs, while yielding less than one additional QALY compared with no treatment. Based on the available data and associated assumptions, the analysis shows that neither fingolimod nor natalizumab are cost-effective versus IFN β/GA from the healthcare payer perspective, at the current cost effectiveness threshold of €45,000 per QALY and have a very low probability of cost effectiveness at any threshold below €85,000 to €150,000 per QALY. It is likely that the ICER of fingolimod versus IFN β/GA is lower than that presented in the base-case analysis as a result of the confidential patient-access scheme which is currently in place. However when the cost is reduced by 20% the ICER remains well above the current cost effectiveness threshold

(€69,000 per QALY). In the highly-active RRMS population, a scenario may arise where IFN/GA options have been exhausted and the choice is between natalizumab and fingolimod, both of which are currently reimbursed in Ireland. Greater health gain is achievable with natalizumab compared with fingolimod, and at a lower cost. However, fingolimod represents a potentially useful treatment option, particularly for those patients for whom Natalizumab is considered unsuitable due to the risks of serious side-effects.

From the societal perspective, the ICERs are more favourable, falling below the current threshold for natalizumab (€23,000 per QALY), however it is questionable whether the same threshold, which is applied to ICERs generated from the healthcare payer perspectives, should be applied to ICERs from the societal perspective. Claxton *et al* argue that applying the existing threshold to ICERs from the societal perspective treats the wider cost savings as if they accrue to the healthcare system and can be used to generate health at the threshold rate. The importance of these savings is therefore overestimated and there is a positive bias in favour of the technology which may be approved when it should be rejected. [330] The societal perspective is presented here in order to reflect the full potential opportunity cost associated with the decision to reimburse DMTs, however the relevant perspective for the purposes of making the most efficient use of HSE resources is that of the healthcare payer. An improvement in cost effectiveness is expected following the incorporation of societal costs as this perspective takes account of the economic losses associated with the provision of care in advanced stages of the disease, and with withdrawal from the work force, which are avoided if progression is delayed.

The findings of this economic evaluation are consistent with those of previous independent assessments of the cost effectiveness of IFN β/GA products. [52 235 265 267] Among previous CEAs, Prosser *et al* estimated the highest ICERs, up to $US 2 million per QALY. [265] A ten-year time horizon was used in the base case in that study. When the time horizon was extended to 40 years, ICERs decreased to ~$250,000 per QALY. [265] The results of the AHRQ CEA by Tappenden *et al* were more favourable than those presented here (ICERs of $104,000 to £332,000 per QALY). Treatment-effects were calculated directly from placebo-controlled RCTs of IFN β and GA products resulting in much lower HRs of disability progression compared with the HRs obtained from the NMA conducted as part of this thesis. Much higher health state costs were also used. [236] Submissions to the NCPE and NICE presented more favourable ICERs for fingolimod

and natalizumab compared with the results presented here. [48-51] The natural history progression rates used in those models were higher than those applied here, as patient-level data from a highly-active MS cohort were available to the manufacturers. The NICE fingolimod model was found to be "very sensitive" to progression rates. [233] A 50% reduction in rates increased the ICER for fingolimod compared with IFN β-1a IM 30mcg from £56,000per QALY to £252,000 per QALY.

A similar pattern of influential parameters was observed in DSA compared with previously reported CEAs, in that results were most sensitive to the effect of treatment on disability progression, time horizon, discount rate, and the cost of DMT. The HR of disability progression has a considerable impact on the cost effectiveness of these agents. Variation within plausible ranges resulted in an ICER of €62,000 per QALY versus IFN β/GA using the most favourable HR for fingolimod, and at the other extreme, fingolimod being dominated by IFN β/GA using the least favourable HR for fingolimod. Similar extremes were observed when HR of disability progression of natalizumab and IFN β/GA were varied. The assumption of unwaning DMT efficacy while on treatment was tested by reducing efficacy by 50% after five years. Under this alternative assumption, the cost-effectiveness of natalizumab and fingolimod compared with IFN β/GA is greatly reduced. In the absence of long-term studies on the durability of treatment efficacy, there is little to inform either the base-case or alternative assumptions with regard to the durability of treatment-effects. Shorter time horizons were associated with less favourable ICERs, as high treatment costs in early years result in benefits accruing over time. The impact of varying the discount rate between 0% and 6% is also expected given the duration of the time horizon over which both costs and benefits are continuously accrued. The influence of the initial health state distribution of the cohort on results has been inconsistent in previous CEAs. Prosser *et al* found that starting treatment in patients with moderate disability was more cost-effective than if all patients start when disability is mild. [265] Conversely, Noyes *et al,* Pan *et al,* and Kobelt *et al* found that initiating DMT earlier improved the cost-effectiveness of all DMTs compared to waiting to start DMT after patients reach noticeable disability or compared to the base case, that is, initiating treatment at any health state. [235 269 277] This may be explained by the underlying natural history progression rates applied in these studies. Higher transition probabilities were associated with moderate disability states in the Prosser *et al* study compared with mild disability states whereas the opposite is the case for the Pan *et al* study. [265 277] Progression rates for the other two studies were

not reported. [235 269] In the study described here, transition probabilities are highest for patients leaving EDSS states 3, 4 and 5 so targeting treatment to these patients is most cost-effective. The insensitivity of the model results to changes in relapse-related parameters is an indication of the discrepancy between the immediate impact of relapses in the early stages of RRMS, and the long-term economic consequences of continuous disease progression and associated functional disability. This finding has been reported in previous CEAs. [236 262] For many patients relapses are the initial defining feature of their disease and the most immediate concern. However, the relapsing-remitting phase of the disease is often short relative to the entire disease duration and relapse rates decrease over time. The long-term clinical and economic benefit of treatment arises from delaying progression of disability.

The cost of DMTs represented a substantial proportion of total healthcare costs for the cohort, ranging from 18% to 32% for IFN β/GA and natalizumab, respectively. Cost effectiveness results were strongly influenced by drug price. Different pricing mechanisms therefore have the potential to significantly increase the cost effectiveness of these agents. It was estimated that current (list) prices would have to decrease by 27% and 12% for fingolimod and natalizumab respectively in order to be considered cost-effective at a threshold of €45,000 per QALY from the healthcare payer perspective. In line with their relative ranking in terms of efficacy, the estimated cost-effective price of new DMTs was highest for alemtuzumab, followed by BG-12. Teriflunomide pricing would be expected to be similar to the upper price range of the first line IFN β/GA products in order to be considered cost-effective. The introduction of newer first line agents, with apparently favourable safety profiles may provide the opportunity to rationalise use of less cost-effective options such as IFN β/GA. This will of course depend on the price of the new products, which as this analysis shows is required to be less than the most recent entrants to the market.

This is the first study to explicitly evaluate the cost effectiveness of IFN β/GA compared with BSC (no treatment) in Ireland. When a fully incremental analysis is conducted including all DMTs and BSC (with regard to standard decision rules of dominance and extended dominance), IFN β/GA is eliminated by extended dominance (ICER for IFN β/GA versus BSC is €398,000 per QALY), indicating that BSC is the most appropriate comparator. IFN β/GA products are among a large number, perhaps the majority, of medicines reimbursed on the CDS in Ireland, the cost effectiveness of which is either unknown or unfavourable. In the setting of a serious disease and in the

absence of any alternative treatments, an argument may be made for funding such therapies in certain patient groups. A problem arises, however, when new products enter the market, such as fingolimod and natalizumab. It is conventional to structure pricing on current standard-of-care, and indeed to request a price premium for incremental benefits. In the case of DMTs for RRMS, it is clear that the continued use of IFN β/GA as a comparator, while in compliance with guidelines on choice of comparator, will lead to reimbursement of drugs at prices which are not cost-effective.

8.6 Limitations

Models are useful as they allow projection of short-term data over prolonged durations, which is very important for a long-term disease such as MS. However models require many assumptions to be made about long-term effects of drugs, long-term costs and also the natural history of the disease. Given the influence of the efficacy of DMTs on disease progression on the results, the lack of evidence on long-term efficacy is a major limitation. In the model, it is assumed that efficacy estimates (based on RCTs of maximum two years duration) are applied as long as patients remain on therapy. The model also assumes that once patients discontinue, they retain the benefits accrued up to the point of discontinuation. Both of these assumptions introduce bias in favour of the treatment compared with the comparator.

The efficacy inputs incorporated in the model are subject to a great deal of uncertainty, which exerts a substantial influence on results Many of the comparators have not been directly compared in clinical trials and relative efficacy estimates were thus calculated using NMA methods. The 95% CI for the HR of disability progression for IFN β/GA extends beyond zero, implying worse outcomes compared with no treatment, and at the higher end of the 95% CI for fingolimod, efficacy is worse than the mean estimate for IFN β/GA resulting in fingolimod being dominated. Direct comparative studies are required in order to ascertain the relative efficacy of these agents with greater certainty. The disability progression results of the Cochrane NMA can not readily be applied in this model as odds ratios were included as the main outcome in the Cochrane analysis and the model in this thesis is structured around the hazard ratio. However, it is likely that the inclusion of the six-month confirmed disability progression definition in the Cochrane analysis would improve the cost-effectiveness of the IFN β/GA comparator, as the NMA sensitivity analysis conducted

as part of this thesis (chapter 7) showed an improvement in efficacy of first line DMTs when this outcome definition was included. The inclusion of a wider range of GA trials in the Cochrane analysis would also favour the IFN β/GA comparator, however the heterogeneity of these trials lead to a quality rating of "very low" in that analysis. Further research is needed on the most approporiate outcome to use both in clinical and cost-effectiveness studies of DMTs for RRMS.

Scenarios in which patients are initiated on one DMT and switch to an alternative treatment have not been considered in this model. In the setting of a progressive disease, where deterioration may be, for many, inevitable, the likelihood is that different treatments will be tried before the onset of the progressive phase at which DMT is eventually discontinued. [331] The occurrence or risk of adverse events are further reasons for switching therapies, particularly in the case of natalizumab, as the risk of PML has been shown to increase with duration of use. [102] It has been suggested that fingolimod is an appropriate choice for natalizumab after patients discontinue natalizumab, but the efficacy or safety of fingolimod in this setting is unknown.

The dearth of published natural history data on which to model the progression of a cohort on BSC is a further limitation. Other studies, particularly those developed with the support of pharmaceutical companies, have benefited from access to patient-level data from which to more accurately base transition probabilities, between EDSS health states, and within particular subgroups e.g. highly active RRMS. The baseline risk of relapse was derived from a longitudinal retrospective study and as such may underestimate the risk of relapse, however the risk of relapse applied in the model is consistent with rates observed in recent RCTs. [70 104 105 119]

The cost and utility inputs in the model were estimated from a sample of patients from just one centre and the extent to which our sample is representative of the general population of MS patients cannot be definitively assessed. However, as discussed in earlier chapter, the demographics of our sample are highly comparable with those of a cross-sectional epidemiological study that includes 632 patients with MS from three different regions of Ireland. [73]

8.7 Conclusions

Natalizumab and fingolimod represent an advance in the treatment of RRMS over IFN β/GA, in terms of efficacy and in terms of convenience in the case of fingolimod, the

first oral drug offering an alternative to regular self-injection. However, there is little evidence to suggest that the price at which DMTs are currently reimbursed in Ireland is cost-effective. The price reductions estimated by this study, at which available DMTs would be considered cost-effective, are unlikely to be achieved as there is no incentive for the manufacturers to reduce prices. It is essential that future therapies which may not offer incremental benefits in terms of efficacy or other measures of innovation, are reimbursed at a price which represents value for money.

CHAPTER 9 – CONCLUSIONS

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9.1 Introduction

This study aimed to evaluate the economic and HRQoL burden of MS in Ireland, and to develop a framework for the assessment of cost effectiveness of DMT. In publicly funded healthcare systems, decision-makers must make difficult choices in the allocation of limited resources in order to maximise health gain. For this reason, an understanding of the financial consequences of an illness and the HRQoL benefits provided by treatment is essential. Knowledge of the relative benefits provided by different treatments is also central to the assessment of cost effectiveness of competing alternatives. DMTs for MS are among the most costly pharmaceuticals reimbursed in Ireland. While the economics of MS and its treatment have been the subject of research in other countries, the results of analyses conducted in different settings and under different assumptions are not readily transferable to other settings, or relevant to the perspective of the local decision-maker. The objectives of the thesis included the estimation of direct and indirect costs of MS from the perspective of the Irish healthcare payer and of society, exploration of the relationship between MS disability and HRQoL, evaluation of the relative efficacy of DMT and development of a decision-analytic model to estimate the cost effectiveness of DMT in Ireland.

9.2 Main Findings

The CoI study described in Chapter 5 established MS as a high cost therapeutic area with significant economic implications for the Irish healthcare system, individual patients and society as a whole. The mean annual direct (indirect) costs per person were approximately €10,000 (€9,500), €13,000 (€32,000) and €56,500 (€39,500) in mild, moderate and severe MS respectively. Progression from mild or moderate MS to severe MS was associated with the greatest economic consequences for the healthcare payer, driven by the excess cost of episodic or permanent institutional care, and the provision of professional care in the home. Similarly, societal costs were shown to rise with increasing disability arising from loss of independence in the home and early withdrawal from the workforce. DMT costs dominated in early MS, while in moderate and severe MS the overall management approach changes from acute inpatient and

outpatient intervention to more supportive home-based management strategies, long-term multidisciplinary management and rehabilitation, in order to achieve the highest possible independence and HRQoL for patients.

Chapter 6 confirmed the detrimental impact of MS-related disability on utility which had previously been shown in other settings, showing an inverse relationship between EDSS score and utility. A linear decline in utility was observed as EDSS progresses from 0 to 6, followed by sharp declines in utility, falling below 0 at EDSS 8 and 9. In its first reported use in MS, the EQ-5D-5L in general displayed good discriminatory capacity in our MS cohort, albeit lower for the domains self-care and anxiety/depression than for the other three domains covered by the instrument.

The NMA described in chapter 7 combined a wealth of evidence on DMT efficacy in order to estimate the relative efficacy of treatments which have not been directly compared in RCTs. All DMTs were significantly superior to placebo in reducing MS relapse rates with many newer agents demonstrating significant improvements in efficacy compared with older DMTs. Significant benefits in reducing short-term disability progression compared with no treatment were limited to the newer DMTs. The analysis found little to distinguish the effects of different DMTs on short-term disability progression, with the exception of alemtuzumab which was superior to other comparators. Alemtuzumab had the highest probability of being the most effective treatment for reducing relapse rates, followed by natalizumab. Alemtuzumab also ranked highest for efficacy in reducing short-term progression, followed by natalizumab and BG-12. The chosen definition of disability progression had a significant impact on results when tested in sensitivity analysis. The inclusion of just trials which defined disability progression on the basis of a 6-month confirmation interval had a substantial favourable impact on the efficacy versus placebo of the first-generation agents and a slight negative impact on alemtuzumab.

Findings from Chapter 5, 6 and 7 were integrated into the decision-analytic model developed for the economic evaluation of DMTs in Ireland, described in Chapter 8. DMTs accounted for a substantial proportion of lifetime healthcare costs, while yielding less than one additional QALY. This analysis revealed that from the healthcare payer perspective, the probability that fingolimod or natalizumab are cost-effective compared with current standard of care at a threshold of €45,000 per QALY is very low (10% and 27%, respectively). A fully incremental analysis reveals that BSC is the appropriate comparator for new DMTs as the existing standard-of-care, represented by

IFN β/GA products is excluded by extended dominance. The primary economic benefit of DMT arose from delaying disability progression. As such, results were highly sensitive to treatment-effects on the natural history of progression, and less sensitive to relapse-related parameters indicating that while relapses are clinically relevant in the short-term, the long-term clinical and economic benefit of treatment arises from delaying progression of disability. An estimation of cost-effective prices for new entrants to the market found that the highest price could be set for alemtuzumab, in line with its efficacy ranking as outlined in Chapter 7, while the price of teriflunomide would be expected to be similar to IFN β/GA products.

9.3 Implications for Policy and Research

The findings of this study present numerous issues for consideration by decision-makers. Based on the inputs and assumptions applied in the decision model, reimbursed DMTs are not cost-effective at the prices currently paid i.e. do not make the most efficient use of the finite resources available. The implications of this finding as regards the poor value obtained from current spending are clear, however the implications extend to future spending on emerging DMTs. The price of current "standard-of-care" will dictate the price at which competitors will seek reimbursement and there is little incentive for manufacturers to reduce current prices. Recent policy initiatives have limited the funding of oral nutritional supplements and other products which were deemed to provide poor value for money, however there is little precedent for imposing price-reductions on existing products for serious conditions on the basis of retrospective economic evaluations such as this. It is essential that future therapies, which may not offer incremental benefits in terms of efficacy or other measures of innovation, are reimbursed at a price which represents value for money, at least over current "standard-of-care". National HTA guidelines currently allow for the inclusion of a range of comparators in addition to "routine care", including "where routine practice differs from what is considered best practice…or the most appropriate care". There is sufficient scope within the current guidelines to choose the most appropriate comparators, on clinical or economic grounds. [7]

The pattern of MS costs identified in this study show that interventions which aim to prevent or delay disease progression have the potential to reduce overall costs associated with the illness. However, the chronic, progressive nature of the disease also

necessitates consideration of non-pharmacological cost-saving interventions which may be used at more advanced levels of disability where DMT has proved ineffective. Such interventions would aim to support independent living at home and maintain workforce participation.

Further research is necessary to address areas of key uncertainty identified in this study. The relative efficacy of DMT on the progression of disability is principal among these areas of uncertainty. The lack of direct comparative studies and the short-duration of RCTs limits the reliability of RCT evidence in the modelling of long-term economic consequences of treatment. Longer-term studies are required to provide evidence that efficacy on short-term progression translates into meaningful, long-term effects on disability progression. Furthermore, the sequence of therapies following treatment failure has yet to be clearly elucidated. A model of sequential use of DMTs would more accurately reflect current practice and necessitates evidence on the efficacy of second-line DMT following failure on first-line agents. The limitations of using historical cohorts to derive natural history progression and relapse rates are difficult to overcome, in that a contemporary untreated cohort is unlikely to emerge. Nevertheless, access to patient-level-data rather than published aggregate data would further enhance the model developed in this study. The methodological limitations associated with HSUV estimation particularly for very severe health states should also be a priority. Application of the methods applied in Chapter 5 and 6 of this study, in the estimation of costs and the derivation of HSUVs, to a wider population of patients with MS in Ireland would further enhance the reliability of the findings.

9.4 Conclusion

In this study, the cost and HrQoL of MS have been evaluated and combined with a synthesis of evidence on the relative efficacy of DMT in a decision model from an Irish perspective. A framework has been developed whereby the existing evidence base can be used, supplemented with further evidence which may become available, to support the decision-making process and to estimate the price at which DMTs represent value for money.

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APPENDICES

APPENDICES

Appendix 1 – EuroQol-5D

Three level EQ-5D (EQ-5D-3L) Descriptive System

Please indicate which statements best describe your own health state TODAY by placing a tick in ONE box in EACH group below

Mobility

- I have no problems in walking about ☐
- I have some problems in walking about ☐
- I am confined to bed ☐

Self-care

- I have no problems with self-care ☐
- I have some problems washing or dressing myself ☐
- I am unable to wash or dress myself ☐

Usual activities *(e.g. work, study, housework, family or leisure activities)*

- I have no problems with performing my usual activities ☐
- I have some problems with performing my usual activities ☐
- I am unable to perform my usual activities ☐

Pain/Discomfort

- I have no pain or discomfort ☐
- I have moderate pain or discomfort ☐
- I have extreme pain or discomfort ☐

Anxiety/Depression

- I am not anxious or depressed ☐
- I am moderately anxious or depressed ☐
- I am extremely anxious or depressed ☐

Five level EQ-5D (EQ-5D-5L) Descriptive System

MOBILITY

- I have no problems in walking about ☐
- I have slight problems in walking about ☐
- I have moderate problems in walking about ☐
- I have severe problems in walking about ☐
- I am unable to walk about ☐

SELF-CARE

- I have no problems in washing or dressing myself ☐
- I have slight problems in washing or dressing myself ☐
- I have moderate problems in washing or dressing myself ☐
- I have severe problems in washing or dressing myself ☐
- I am unable to wash or dress myself ☐

USUAL ACTIVITIES ***(e.g. work, study, housework, family or leisure activities)***

- I have no problems doing my usual activities ☐
- I have slight problems doing my usual activities ☐
- I have moderate problems doing my usual activities ☐
- I have severe problems doing my usual activities ☐
- I am unable to do my usual activities ☐

PAIN/DISCOMFORT

- I have no pain or discomfort ☐
- I have slight pain or discomfort ☐
- I have moderate pain or discomfort ☐
- I have severe pain or discomfort ☐
- I have extreme pain or discomfort ☐

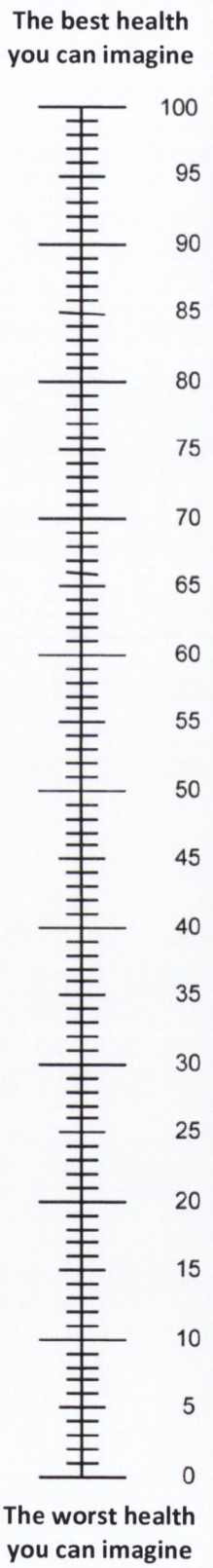
ANXIETY/DEPRESSION

- I am not anxious or depressed ☐
- I am slightly anxious or depressed ☐
- I am moderately anxious or depressed ☐
- I am severely anxious or depressed ☐
- I am extremely anxious or depressed ☐

EQ-5D Visual Analogue Scale

- **We would like to know how good or bad your health is TODAY**
- **This scale is numbered from 0 to 100**
- **100 means the <u>best</u> health you can imagine**
  0 means the <u>worst</u> health you can imagine
- **<u>Mark X on the scale</u> to indicate how your health is TODAY**
- **Now, please <u>write the number</u> you marked on the scale in the box below**

YOUR HEALTH TODAY = ☐



Appendix 2 – Patient Information Leaflet

St. Vincent's Healthcare GROUP LIMITED

EL

M PARK, DUBLIN 4

NEUROLOGY DEPARTMENT, ST. VINCENT'S UNIVERSITY HOSPITAL

PARTICIPANT INFORMATION AND CONSENT FORM

COSTS AND QUALITY OF LIFE OF MULTIPLE SCLEROSIS

WE ARE INVITING YOU TO TAKE PART IN A STUDY LOOKING AT THE COSTS AND QUALITY OF LIFE ASSOCIATED WITH MULTIPLE SCLEROSIS. THE STUDY WILL LOOK AT THE AMOUNT OF HEALTHCARE RESOURCES USED BY PEOPLE WITH MULTIPLE SCLEROSIS AND THE IMPACT THAT MULTIPLE SCLEROSIS HAS ON QUALITY OF LIFE.

PROFESSOR NIALL TUBRIDY:

You are being invited to participate in a research study. Thank you for taking time to read this.

WHAT IS THE PURPOSE OF THIS STUDY?

Multiple sclerosis can place a heavy financial burden on patients, their families and on the healthcare system. The costs of multiple sclerosis arise from treatment of MS symptoms and relapses, hospitalisation, rehabilitation, time off work etc. Quality of life can be affected by MS as a result of physical limitations and emotional strain. Very little is known about the costs and quality of life of MS in Ireland. The purpose of this study is to gather information on cost of illness and the impact illness has on quality of life, to help determine value for money from investment in MS treatments and resources.

WHY HAVE I BEEN CHOSEN?

All patients with MS who are seen in the MS clinic in SVUH during the study period are being asked to take part in this study. For this study to be successful, and produce reliable results, we need many different people with MS to agree to take part. This includes people with varying levels of disease severity, from very mild disease to very severe disease.

WHAT WILL HAPPEN IF I VOLUNTEER?

Your participation is entirely voluntary. If you initially decide to take part you can subsequently change your mind without difficulty. This will not affect your future treatment in any way. Furthermore your doctor may decide to withdraw you from this study if he feels it is in your best interest. If you agree to participate, you will be requested to complete an interview which should take about ten minutes:

1. A researcher will ask some basic questions about yourself and your MS and a series of questions about the healthcare services that you have used recently (e.g. hospitalisation, outpatient and GP visits, tests and medication etc.) and the impact MS has had on your employment
2. You will also be asked to fill out a very short form to describe your health state TODAY.
3. You will be asked to give us permission to collect details about your multiple sclerosis and your treatment from your medical records.

WHAT ARE THE POSSIBLE BENEFITS AND RISKS OF TAKING PART?

You will not benefit directly from taking part in this study but the information we will obtain may provide further knowledge of the costs associated with MS and the impact it has on quality of life.

WHAT HAPPENS IF I DO NOT AGREE TO PARTICIPATE?

If you decide not to participate in this study your treatment will not be affected in any way.

CONFIDENTIALITY

Your identity will remain confidential. A study number will identify you. Your name will not be published or disclosed to anyone.

COMPENSATION

Your doctors are adequately insured by virtue of their participation in the clinical indemnity scheme.

WHO IS ORGANISING AND FUNDING THIS RESEARCH?

This study is organised by the National Centre for Pharmacoeconomics, St. James's Hospital, and The Neurology Department, St. Vincent's University Hospital.

You will not be paid be paid for taking part in this study.

HAS THIS STUDY BEEN REVIEWED BY AN ETHICS COMMITTEE?

The St. Vincent's Healthcare Group, Ethics and Medical Research Committee have reviewed and approved this study.

CONTACT DETAILS

Emer Fogarty, Project Leader
Email: efogarty@stjames.ie Tel: 01 4284569
National Centre for Pharmacoeconomics
St. James's Hospital
Dublin 8

PLEASE TICK YOUR RESPONSE IN THE APPROPRIATE BOX

- I have read and understood the Participant Information YES ☐ NO ☐
- I have had the opportunity to ask questions and discuss the study YES ☐ NO ☐
- I have received satisfactory answers to all my questions YES ☐ NO ☐
- I have received enough information about this study YES ☐ NO ☐
- I understand that I am free to withdraw from the study at any time without giving a reason and without this affecting my future medical care YES ☐ NO ☐
- I agree to take part in the study YES ☐ NO ☐

Participant's Signature: _____ Date: _____

Participant's Name in print: _____

Investigator's Signature: _____ Date: _____

Investigator's Name in print: _____

Appendix 3 – Cost and HrQoL Study Protocol

TITLE

Costs and Quality of Life of Multiple Sclerosis – Stud Protocol

INTRODUCTION

Multiple sclerosis (MS) is the most common disabling neurological disease of young adults, with a prevalence in Ireland of between 180 and 290/100,000. Over 7000 people in the Republic of Ireland are estimated to be affected by this disease.[1] MS is associated with significant economic and Health-Related Quality-of-Life burden. [2,3] Healthcare utilisation patterns in MS have significant financial consequences for the healthcare system, patients and their families, where both pharmacological and non-pharmacological interventions are focussed on symptom management, relapse treatment and delaying disease progression. Neurological symptoms of varying severity can result in functional limitations which can severely impact patients' physical activity, employment capabilities and opportunities. MS can result in chronic disability, and potentially have a major impact on quality of life.

A number of cost-of-illness studies have been performed in MS, including a large European study in nine European countries in 2005. [2] This study also looked at utilities (quality of life) of MS patients. The economic findings of this study were extrapolated to the rest of Europe, estimating the overall economic burden of MS in Europe at €13 billion per year. [4] This study contributed to the understanding of the economic impact of MS, however Ireland was not included in the study. Economic data is generally not considered to be transferable between countries because of differences in the prices or tariffs of the resources used and differences in resource consumption due to differing healthcare management methods. [5] Similarly for quality of life valuations or health state preferences, population values may differ by demographical area.

This study will evaluate the economic impact of MS in an Irish cohort. In addition, the impact of MS on quality of life will also be assessed. Knowledge of the magnitude and distribution of healthcare costs is important for policy-makers, to inform decisions on resource-allocation. Information on costs and quality of life of MS patients will

provide a basis on which the economic benefit of disease modifying treatments can be estimated. This is of particular benefit in a resource-constrained system.

AIMS AND OBJECTIVES

The aims of this study are:

- to describe service utilisation patterns and quality of life of MS patients at different levels of disease severity
- to calculate the associated costs of MS to provide a basis on which the economic benefit of disease modifying treatments can be estimated.

The objectives of this study are:

- to collect detailed data on all costs related to MS in a representative sample of patients in SVUH, by means of:
  - a structured interview with completion of a detailed questionnaire for each patient
  - medical notes review
- to estimate the quality of life of patients with MS using a self-completed quality of life instrument

METHODS

Overview

This is an interview-based study in which patients are guided through a structured interview comprising a series of questions on MS-related healthcare resource utilisation and quality of life. Data on resource utilisation for a defined time-period will be combined with unit costs to estimate the annual cost of MS for patients attending SVUH. A cross-section of patients from all levels of disease severity will be included to facilitate evaluation of the impact of disease progression on costs and quality of life.

Patients

Inclusion Criteria

- All patients with a diagnosis of MS will be eligible for inclusion.
- Carers of patients with MS are also eligible for inclusion as a proxy for the patient.

Recruitment

- Consecutive patients with MS attending in the SVUH MS clinic during the study period will be invited to participate in the study
- When patients check in at the MS clinic reception, they will be provided with a patient information leaflet
- Following their neurology review, the consultant neurologist will discuss the study with the patient
- Patients will be informed that participation is voluntary. If patients decide to take part, they will be informed that they are free to withdraw from the study at any time, and that the decision to/not to participate or to withdraw from the study, will not affect the care they receive in any way. If they decide to withdraw at any time after the interview has been conducted, all identifiable data will be destroyed
- If consent to participate is given, a consent form will be signed by the patient

Data collection

- The recruiting neurologist will record each patient's EDSS score and type of MS
- The patients will be interviewed individually by the project leader. A carer may be present to assist in answering questions if the patient has recall difficulty or is unable to answer certain questions
- Patients will be asked a series of questions including basic questions about themselves and their MS, and their level of resource utilisation. Responses will be recorded for each patient, by the interviewer
- Patients will be asked to complete the EQ-5D descriptive system and visual analogue scale. This may be completed before the interview while/if patients are waiting
- Patients' medical notes will be reviewed to obtain information on their disease course and co-morbidity

- The medical notes of a random sample of patients will be reviewed in order to validate responses on resource utilisation

Resource use Questionnaire

The resource use questionnaire to be used in this study includes questions on the following:

- Basic sociodemographic details e.g. ethnicity, marital status, living arrangements, education
- History of MS diagnosis and symptoms
- Healthcare services used/received recently e.g. hospitalisations, consultant visits, GP visits and consultations with other health professionals, tests, medications
- Informal care from family and friends
- Aids and home adaptations
- Impact of MS on employment status

All resources commonly associated with MS are included in the questionnaire. The recall time period for use of different resources will be different for types of resource e.g. hospitalisation during the previous 12 months, outpatient consultations or GP visits during the previous 6 months, medication use during the previous month etc. Patients can also elaborate on MS-related costs not specified in the questionnaire. This questionnaire was developed following a review of the literature on the management of MS and MS costing studies.

Costing

Following data collection on resource utilisation, each resource unit will be multiplied by its unit cost to estimate overall costs, average costs per patient, and average cost per patient at different levels of disability. A variety of sources will be used for valuing services e.g. National Casemix Programme, Health Service Executive, Primary Care Reimbursement Service, Central Statistics Office, laboratory and radiology departments of SVUH and SJH. Costs for patients' own expenses and investments will be based on patients' estimates. Costs will be presented from different viewpoints e.g. that of the payer, including only resources covered by payers (i.e. HSE), and that of

society e.g. including resources paid for by patients themselves, lost work productivity etc.

Quality of Life

The EuroQoL 5-Domain (EQ-5D) self-report questionnaire will be used to assess MS patients' quality of life. The EQ5D has become one of the most widely used instruments of its type, since it was first developed in the 1980s. The EQ5D is a generic preference-based instrument which consists of 2 elements.

1. EQ-5D descriptive system: comprises 5 dimensions (mobility, self-care, usual activities, pain/discomfort, anxiety/depression). Each dimension has 3 levels: no problems, some problems, severe problems. Patients describe the health state in which they perceive themselves to be, and then valuations derived from the general public are placed on these health states.[6] In the absence of Irish valuations, valuations derived from the UK population will be used.
2. EQ-5D VAS: records the self-rated health on a vertical, visual analogue scale where the endpoints are labelled 'Best imaginable health state' and 'Worst imaginable health state'. This information can be used as a quantitative measure of health outcome as judged by the individual respondents.[6]

ANALYSIS

A linear regression model will be fitted linking EDSS level to log(cost) and to utility values as measured by EQ-5D. Study endpoints include:

- Direct and indirect annual costs of MS for 11 levels of disability as defined by the Expanded Disability Status Scale (EDSS) 0,1,2,3,4,5,6,6.5,7,8,9, from the perspective of the Health Service Executive and from the societal perspective
- Utility value (measure of preference) for each EDSS level as measured by EQ-5D

This will be also a descriptive study in which levels of utilisation of particular resources, overall costs and utilities may be linked to patient characteristics e.g. age, gender, disease status and other sociodemographic variables.

Data will be managed using Microsoft Access and analysed using SAS statistical software package version 9.1 (SAS Institute Inc. Cary, NC, USA).

Sample Size

With an f^2 of 0.05, 80% power and a significance level of α=5%, a sample size of 156 would be required (using pwr.f2.test in R version 2.12). It is planned to recruit 20 patients at each EDSS level.

STUDY TIMETABLE

- Submission of documentation to St. Vincent's Healthcare Group Ethics and Medical Research Committee: June 15th 2011
- St. Vincent's Healthcare Group Ethics and Medical Research Committee Meeting Date: July 6th 2011
- Commence patient recruitment and data collection: 18th July 2011
- Finish patient recruitment and data collection on recruitment of 210 patients
- Estimated duration of study: 10 weeks

ETHICS

This study will be submitted for ethical review by St. Vincent's Healthcare Group Ethics and Medical Research Committee.

REFERENCES

1. Lonergan R, Jordan S, Hagan R, Kinsella K, Fitzpatrick P, Duggan M, et al. Multiple sclerosis in Ireland: regional variation in prevalence and vitamin D status. J Neurol Neurosurg Psychiatry 2011;82:317–322.
2. Kobelt G, Berg J, Lindgren P, Jonsson B. Costs and quality of life in multiple sclerosis in Europe: method of assessment and analysis. Eur J Health Econ 2006;7:S5–S13
3. Naci H, Fleurence R, Birt J, Duhig A. The impact of increasing neurological disability of multiple sclerosis on health utilities: A systematic review of the literature. Journal of Medical Economics 2010 13:1 (78-89)
4. Sobocki P, Pugliatti M, Lauer K, Kobelt G. Estimation of the cost of MS in Europe: Extrapolations from a multinational cost study. Multiple Sclerosis 2007;13:1054–1064

5. Health Information and Quality Authority. Guidelines for the Economic Evaluation of Health Technologies in Ireland. 2010
6. Cheung K, Oemar M, Oppe M, Rabin R on behalf of the EuroQol Group. EQ-5D User Guide. Version 2.0 March 2009. www.euroqol.org

Appendix 4 – Ethical Approval

St. Vincent's Healthcare GROUP LIMITED

UCD DUBLIN

Ethics and Medical Research Committee
ELM PARK, DUBLIN 4
Tel. (01) 2214117 Fax (01) 2214428
email: joan.mcdonnell@ucd.ie or jacinta.mcmanus@ucd.ie

21st July, 2011

Professor Niall Tubridy,
Consultant Neurologist,
St. Vincent's University Hospital,
Elm Park,
D. 4.

Re: Costs and Quality of Life of Multiple Sclerosis. Covering Letter and Standard Application Form vs 1.2. PIL/Consent Form Version 1 dated 15/6/2011. Study Protocol. Questionnaire vs 1.2 21/7/11

Dear Professor Tubridy,

Ms Fogarty has forwarded the clarifications and revised documents that were requested at the Ethics and Medical Research Committee meeting held on Wednesday 6th July, 2011 at which the above study was reviewed.

Following review of the revised documents and clarifications this study is now granted full ethical approval.

Yours sincerely,

Dr. B. Kirby,
Chairman,
Ethics & Medical Research Committee

cc Ms Emer Fogarty, Research Pharmacist, National Centre for Pharmacoeconomics.

Appendix 5 – Study Questionnaire

Date _____ **Study ID** _____

1. Study Participant Details

Date of birth *(Day/Month/Year)* _____ Type of MS *RRMS* ☐ *SPMS* ☐ *PPMS* ☐

Gender Male ☐ Female ☐ EDSS score _____

Is respondent is a carer? Yes ☐ No ☐ *If yes, what relation?* _____

2. In this part of the questionnaire we will ask you about yourself and your MS diagnosis

What age were you when you had your first symptoms of MS? _____

What age were you when you were diagnosed with MS? _____

Have you had a relapse in the past 6 months? Yes ☐ No ☐ NA ☐

If yes: when and how long did it last? _____

How would you describe your ethnicity?

(e.g white, black/black Irish, asian/asian irish, other) _____

What is your marital status? *(please tick)*

- Married/Cohabiting ☐
- Single ☐
- Divorced or Separated ☐
- Widowed ☐

How many children under 18 do you have? _____

Who do you live with? *(please tick)*

- Live Alone ☐
- With parents ☐
- With children but *no* partner spouse ☐
- With children *and* partner spouse ☐
- With partner/spouse ☐
- With friends ☐
- Live in a care home ☐
- Other (please specify) ☐

What was your highest level of education? *(please tick)*

- National School ☐
- Inter-Cert/Junior Cert ☐
- Leaving Cert ☐
- Diploma/Certificate ☐
- Degree ☐
- Higher degree ☐

What age were you when you finished full time education? _____

3. Here we would like to know about the healthcare services that you have used during the past year

Have you been admitted to a hospital during the past <u>12 months</u> <u>because of your MS</u>? Yes ☐ No ☐

If yes, please tick box and indicate the number of times you were admitted and the total number of days spent in hospital

		no. of times	*no. of days in total*
General hospital	☐		
Days in ICU?	☐		

Date _____ **Study ID** _____

		no. of times	*no. of days in total*
Day hospital	☐		
Nursing home/rehabilitation hospital	☐		
Other (please specify) _____	☐		

Have you attended an OPD appointment with a consultant during the past 6 months because of your MS? Yes ☐ No ☐

If yes, please tick box and indicate how many times during the past 6 months, and if you had to pay part of the cost yourself

		no. of times	*Amount paid*
Consultant neurologist	☐		
Other e.g. urologist, ophthalmologist, psychiatrist etc.			
Other (please specify) _____	☐		
Other (please specify) _____	☐		

During the past 6 months, did you use any other services from health professionals for your MS? Yes ☐ No ☐

If yes, please tick box and indicate the number of sessions during the past 6 months, and if you had to pay part of the cost yourself

		no. of sessions	*Amount paid*
GP (General Practitioner/Family Doctor)	☐		
MS specialist nurse	☐		
Physiotherapist	☐		
Public Health Nurse	☐		
Rehabilitation centre	☐		
Home Help	☐		
Social worker	☐		
Occupational Therapist	☐		
Speech Therapist	☐		
Other e.g. acupuncture, chiropractor, reflexologist	☐		
Other (please specify) _____	☐		

4. In this section, we will ask you about tests you have received over the last 6 months

Have you had any of the following tests/investigations over the last 6 months? Yes ☐ No ☐

If yes, please tick box:		*no. of tests*	*Reason for test*	*Amount paid*
MRI	☐			
CT	☐			
EEG	☐			
Blood Test	☐			
Other (please specify) _____	☐			
Other (please specify) _____	☐			

5. In this section, we will ask you about any medication you have taken in the last month

Have you taken any medication for MS (prescription and over-the-counter) during the last month? Yes ☐ No ☐

If yes, please tick box and indicate the name, dose, frequency and duration/no. of days on medication, and if you had to pay yourself

		Name	*Dose/Frequency/no. of days*	*Amount paid*
Disease modifying therapy (Avonex, Rebif Betaferon, Copaxone, Tysabri, CT drug)	☐			

Date _____ Study ID _____

		Name	Dose/Frequency/no. of days	Amount paid
Other (please specify)	☐			
Other (please specify)	☐			
Other (please specify)	☐			
Other (please specify)	☐			
Other (please specify)	☐			

Do you get ALL of your medicines free of charge under the Long Term Illness Scheme? Yes ☐ No ☐ NA ☐

If NO, why not? _____

6. In this section, we will ask you about any help you have received from friends or family members, or home-help/personal assistants in the last month, as a result of your MS

Have you had help with personal care (e.g. bathing, dressing), help inside the home (e.g. cooking, cleaning), help outside the home (e.g. shopping) or other help in the last month? Yes ☐ No ☐

If yes, please tick box and indicate the average number of hours of help received per week, and the cost if you paid for the service

		No. of hrs per week	Cost per week
From friends/family	☐		
From home-help/personal assistant	☐		

7. In this section, we will ask you about any aids you required because of your MS or any adaptations you made to your home because of your MS, in the last 6 months

Do you use any of the following aids? Yes ☐ No ☐

If yes, please tick box and indicate if you received it in the last 6 months and if it was funded by you/family/friends or the HSE

		Last 6 months (yes/no)	Funding source	Cost estimate
Crutches/sticks	☐			
Wheelchair	☐			
Zimmerframe	☐			
Commode	☐			
Bath board	☐			
Pressure relieving cushions/mattress	☐			
Adapted eating utensils	☐			
Other (specify)	☐			

Have you made any of the following adaptations to your home? Yes ☐ No ☐

		In last 6 months	Funding source	Cost estimate
Stairlift	☐			
Handrails	☐			
Ramps	☐			
Shower / bath relocation	☐			
Toilet relocation	☐			
Redesign kitchen	☐			
Chair raises / Special chair	☐			
Bed moved downstairs	☐			
Medicalised bed	☐			
Other (specify)	☐			

Date _____ Study ID _____

8. This section is about the impact MS has had on your employment

How would you describe your current employment status? *(tick)*

Employed full-time	☐	Employed part-time	☐	Self employed	☐
Unemployed	☐	Retired (because of MS related ill health)	☐	Retired (because of age)	☐
Student	☐	Housewife/husband	☐	Other	☐

If you are currently employed, what is your occupation? _____

Have you had to stop or reduce work due to MS related ill-health? Yes ☐ No ☐ NA ☐

If yes: how many days in the last 6 months have you been off work because of MS? _____

Or how many fewer hours per week have you worked because of MS? _____

If you are not working, are you receiving disability allowance? Yes ☐ No ☐ NA ☐

If yes: for how long have you been receiving this allowance? _____

If you are unemployed/retired

Do you intend to return to work? Yes ☐ No ☐ NA ☐

How long have you been unemployed/retired? _____

9. Transport, and any other costs incurred due to your MS that you feel are significant?

How do you travel to outpatient appointments? _____

How much have you spent on transport in the last 6 months due to your MS (est.)? _____

Other costs (please specify) _____

Comments

Appendix 6 – Table of Unit Costs and Data Sources

Table A6.1 Unit Costs and Data Sources

Resource	Cost	Source
Hospital Inpatient DRG costs	**Cost per day**	**Source of unit cost**
B68 - Mlt sclrosis & cerebrl ataxia	€620.75	HSE-Casemix (Inpatient DRG)
L06 - Minor bladder procedures	€991.72	
I78 - Fracture neck femur	€332.48	
I78 - Fracture of neck femur	€242.76	*Specific DRGs selected depending on MS-related reason for hospital admission, cost per-diem applied based on reported length of stay*
Y61 - Severe burns	€663.96	
Z61 - Signs and symptoms	€416.30	
B72 - Nrvs sys inf ex vrl mngts	€665.61	
E62 - Respiratry infectn/inflamm	€611.11	
C61 - Neurological&vasclr eye dis	€842.59	
Z60 - Rehabilitation	€437.39	
Z60 - Rehabilitation	€592.13	
B07 - Prphl & cranl nerv & oth pr	€337.20	
B71 - Cranial & periphl nerv dsrd	€738.11	
Nursing Home costs	**Cost per week**	**Source of unit cost**
Villa Marie Nursing Home	€711.54	HSE Nursing Home Support Scheme
Marymount Nursing Home	€1,220	
San Remo Nursing Home	€1,105	*Institution-specific costs used where reported, cost per-diem applied based on reported length of stay*
Millrace Nursing Home	€714	
Eyrefield Manor Nursing Home	€1,075	
Greystones Nursing Home	€935	
Cheshire home	€1,081.73	
Respite costs	**Cost per day**	**Source of unit cost**
MS Care Respite	€136.69	MS Ireland
Healthcare Professional	**Cost per 30 minute consultation**	**Source of unit cost**
Chiropodist	€25.94	HSE Salary Scales
Counsellor	€32.20	
Dietician	€27.97	*Median point on relevant salary scale plus overheads, consultation assumed to be of 30 minutes duration*
Occupational Therapist	€27.97	
Physiotherapist	€27.97	
Public Health Nurse	€26.19	
Social Worker	€26.37	
Specialist nurse	€26.90	
Speech therapist	€27.97	
Optician	€21.55	
Hospital outpatient consultation	€144.44	HSE-Casemix *Average cost per case for an OPD attendance*
GP visit	€35.25	HSE-PCRS Statistical Analysis of Claims and Payments 2011, and Madden et al. *Cost per GP visit calculated from GP capitation fee and national average number of GP visits per annum*
Test	**Unit cost**	**Source of unit cost**
MRI brain	€212.25	St. James's Hospital and St. Vincent's

Table A6.1 Unit Costs and Data Sources

Resource	Cost	Source
MRI brain+contrast	€244.73	Hospital Laboratory/Finance Departments
MRI Spine	€151.60	
MRI Spine+contrast	€184.09	
MRI Ankle	€151.60	
CT abdo	€128.86	
CT brain	€103.96	
CXR	€32.49	
XR foot/hip	€43.32	
ultrasound	€151.60	
VEP	€59.00	
EEG	€59.00	
ECG	€30.00	
bone scan	€223.07	
LFT	€10.83	
U+E	€10.83	
TSH	€12.99	
T3	€12.99	
T4	€12.99	
FBC	€19.49	
GGT	€5.41	
CRP	€12.99	
ESR	€6.88	
Coag Screen	€16.50	
Glucose	€3.25	
Electrophoresis	€14.08	
CSF (micro)	€27.07	
IFN NAB	€187.83	
sodium valproate level	€10.83	
colonoscopy	€572.58	
cystoscopy	€468.66	
OGD	€537.25	
LP	€202.92	
UCUL	€15.00	
ANA	€70.00	
Aquaporin 4 antibodies	€160.00	
ACE	€12.00	
Vit B12	€16.50	
VDRL	€10.00	
JCV	€130.70	
urinalysis	€0.43	
bladder scan	€151.60	
wound swab	€16.24	
DEXA	€90.00	
video flouroscopy	€490.62	

Table A6.1 Unit Costs and Data Sources

Resource	Cost	Source
catheter insertion	€9	
urodynamics	€504.62	
Medication	**Cost per dose**	**Source of unit cost**
Hospital medication		St. James's Hospital Pharmacy Department
Over-the-counter medication		Patient estimates
Prescription medication¶		HSE-PCRS *Where dose not reported, average of reported doses from other study-participants used*
Aid/home modification	**Cost**	**Source of unit cost**
Aphasia mug	€8.91	Patient estimates, public price-lists, national procurement expert opinion
Chair raise	€12.74	
Special chair	€24.11	
Chair raises for toilet	€13.06	
Commode	€63.09	*Costs of living aids and home modifications were annualised assuming a useful life of 5 years and 10 years respectively*
Commode (on wheels)	€59.53	
CPAP	€156.61	
Crutches/sticks	€1.63	
Eating utensils	€35.58	
Electric wheelchair	€467.74	
Exercise bike	€84.50	
grabber	€2.24	
Handrails (shower)	€4.81	
Handrails	€4.81	
hoist	€429.48	
Hoist (wall)	€429.48	
Medicalised bed	€223.50	
motomed	€1,797.02	
Paper lifter	€3.29	
Perch chair	€24.11	
Pressure Relieving Cushions	€32.36	
Pressure relieving cushions/mattress	€45.16	
Pressure relieving mattress	€57.95	
Recliner	€231.06	
Rollator	€32.35	
Scooter	€183.11	
Seat raise for toilet	€13.06	
shoe horn	€5.79	
shower chair	€28.91	
shower chair and perch chair	€53.02	
shower chair and toilet seat	€159.37	
sliding sheets	€6.46	
speech enabled phone	€22.46	

Table A6.1 Unit Costs and Data Sources

Resource	Cost	Source
Standing frame	€136.52	
standing hoist	€136.52	
Wheelchair	€80.68	
Zimmerframe	€10.34	
Bath board	€6.62	
Bath rail	€7.66	
Bed lever	€13.92	
Bed redesign/moved downstairs - extension	€2,301.43	
Doors widened	€634.95	
mobile hoist	€235.73	
overall renovation - bed/bath	€3,637.08	
Ramps	€36.99	
Redesign kitchen	€332.89	
Shower/Bath relocation	€332.89	
Toilet relocation	€332.89	
overall renovation - stairlift/ramp/disabled shower	€804.27	
stairlift	€585.63	
disabled shower	€181.65	
Productivity losses	**Mean labour Costs**	**Source of unit cost**
Male (annual)	€43,609.63	Central statistics office (CSO)
Female (annual)	€37,940.37	*Gross gender specific mean earnings*
Male (hourly)	€13.49	
Female (hourly)	€11.74	
HSE=Health Service Executive, DRG=Diagnosis Related Group, PCRS=Primary Care Reimbursement Service, OPD=outpatient department		

Appendix 7 – Multiple Sclerosis Journal Publication

Appendix 8 – Network Meta-Analysis Appendices

Appendix 8a – Literature search strategy

Embase Search Terms

#1

'beta interferon'/exp OR 'rebif'/exp OR 'interferon beta'/exp OR 'betaferon'/exp OR 'betaseron'/exp OR 'extavia'/exp OR 'avonex'/exp OR 'copolymer 1'/exp OR 'cop-1'/exp OR 'glatiramer acetate'/exp OR 'copolymer'/exp OR 'copaxone'/exp OR 'natalizumab'/exp OR 'antegren'/exp OR 'tysabri'/exp OR 'fingolimod'/exp OR 'gilenya'/exp OR 'teriflunomide'/exp OR 'laquinimod'/exp OR 'alemtuzumab'/exp OR 'campath'/exp OR 'mabcampath'/exp OR 'aubagio'/exp OR 'BG-12'/exp OR 'ferrous fumarate'/exp OR 'fumaric acid dimethyl ester'/exp

#2

'encephalomyelitis'/exp OR 'demyelinating disease'/exp OR 'multiple sclerosis'/exp OR 'myelooptic neuropathy'/exp OR 'multiple sclerosis':ab,ti OR 'neuromyelitis optica':ab,ti OR encephalomyelitis:ab,ti OR devic:ab,ti

#3

'double blind procedure'/exp OR 'single blind procedure'/exp OR 'randomized controlled trial'/exp OR random*:ab,ti OR 'double blind':ab,ti OR 'single blind':ab,ti OR assign*:ab,ti OR allocat*:ab,ti

#1 AND #2 AND #3

Appendix 8b – Reasons for exclusion of titles at the full-text stage of the systematic review of RCTs of DMTs in RRMS

Reasons for exclusion of titles at the full-text stage are based on the PICOS (Population/ Intervention/ Comparator/ Outcome/ Study Design) criteria. Intervention/Comparator exclusions are classified as "Drug", study Design exclusions are classified as "Design". "Language" denotes trials excluded as they were not available in the English Language. Non original-research studies are denoted by "Review".

Table A8.1 Reasons for Exclusion of titles at the full-text stage of the systematic review

First Author	Year	Title	Journal	Reason
Bornstein, M. B.	1987	A pilot trial of Cop 1 in exacerbating-remitting multiple sclerosis	New England Journal of Medicine	Outcome
Knobler, R. L.	1993	Systemic recombinant human interferon-beta treatment of relapsing-remitting multiple sclerosis: pilot study analysis and six-year follow-up	J Interferon Res	Design
Hellema, H.	1994	Copolymer-1 diminished exacerbations in MS-patients	TGO	Language
Connelly, J. F.	1994	Interferon beta for multiple sclerosis	Annals of Pharmacotherapy	Review
Fieschi, C.	1995	Human recombinant interferon beta in the treatment of relapsing-remitting multiple sclerosis: preliminary observations	Multiple Sclerosis	Drug
Sibley, W. A.	1995	Interferon beta-1b in the treatment of multiple sclerosis: Final outcome of the randomized controlled trial	Neurology	Design
Bates, D.	1995	New therapies in multiple sclerosis	Pharmaceutical Journal	Review
Jacobs, L. D.	1995	A phase III trial of intramuscular recombinant interferon beta as treatment for exacerbating-remitting multiple sclerosis: design and conduct of study and baseline characteristics of patients. Multiple Sclerosis Collaborative Research Group (MSCRG)	Multiple Sclerosis	Review
Comi, G.	1996	Interferon beta treatment in multiple sclerosis: the European clinical trials	Multiple sclerosis	Review
Sibley, W. A.	1996	Clinical efficacy of interferon beta-1b in multiple sclerosis: The US/Canadian multicentre trial evidence	Clinical Immunotherapeutics	Review
Rudick, R. A.	1997	Impact of interferon beta-1a on neurologic disability in relapsing multiple sclerosis. The Multiple Sclerosis Collaborative Research Group (MSCRG)	Neurology	Design
Abdul-Ahad, A. K.	1997	Incidence of antibodies to interferon-beta in patients treated with recombinant human interferon-beta 1a from mammalian cells	Cytokines Cell Mol Ther	Outcome
Abdul-Ahad, A.	1997	Treatment of multiple sclerosis with interferon beta-1 b	Neurology	Review

Table A8.1 Reasons for Exclusion of titles at the full-text stage of the systematic review

First Author	Year	Title	Journal	Reason
Abramowicz, M.	1997	Glatiramer acetate for relapsing multiple sclerosis	Medical Letter on Drugs and Therapeutics	Review
Johnson, K. P.	1998	Extended use of glatiramer acetate (Copaxone) is well tolerated and maintains its clinical effect on multiple sclerosis relapse rate and degree of disability. Copolymer 1 Multiple Sclerosis Study Group	Neurology	Design
	1998	Placebo-controlled multicentre randomised trial of interferon beta-1b in treatment of secondary progressive multiple sclerosis. European Study Group on interferon beta-1b in secondary progressive MS	Lancet	Population
	1998	Interferon beta-1b in secondary progressive multiple sclerosis	Deutsche Apotheker Zeitung	Population
Kappos, L.	1998	Placebo-controlled multicentre randomised trial of interferon (beta)-1b in treatment of secondary progressive multiple sclerosis	Lancet	Population
Dixon, C.	1998	PRISMS trial [4]	Pharmaceutical Journal	Review
Fernandez, O.	1999	[Natural interferon-beta in the treatment of relapsing-remitting multiple sclerosis: a multicenter, randomized, MRI-based, phase II clinical trial]	Rev Neurol	Drug
Freedman, M. S.	1999	Evidence of interferon (beta)-1a dose response in relapsing-remitting MS: The OWIMS study	Neurology	Drug
Liu, C.	1999	Randomised, double blind, placebo controlled study of interferon (beta)-1a in relapsing-remitting multiple sclerosis analysed by area under disability/time curves	Journal of Neurology Neurosurgery and Psychiatry	Design
	1999	MS Therapy Consensus Group. Immunomodulating staged therapy of multiple sclerosis	Der Nervenarzt	Review
Bencsik, K.	1999	Treatment of relapsing-remitting multiple sclerosis with interferon beta type 1-b	Orv Hetil	Review
Galazka, A.	1999	Interferon beta treatment for multiple sclerosis	Lancet	Review
Goodin, D. S.	1999	Interferon beta treatment for multiple sclerosis	Lancet	Review
O'Connor, P.	1999	Interferon beta treatment for multiple sclerosis	Lancet	Review
Jacobs, L.	2000	Extended observations on MS patients treated with IM interferon-beta1a (Avonex): implications for modern MS trials and therapeutics	J Neuroimmunol	Design
Johnson, K. P.	2000	Sustained clinical benefits of glatiramer acetate in relapsing multiple sclerosis patients observed for 6 years. Copolymer 1 Multiple Sclerosis Study Group	Multiple Sclerosis	Design
Balcer, L. J.	2000	Self-reported visual dysfunction in multiple sclerosis: results from the 25-Item National Eye Institute Visual Function Questionnaire (VFQ-25)	Multiple Sclerosis	Outcome
Liu, C.	2000	Benefits of glatiramer acetate on disability in relapsing-remitting multiple sclerosis: An analysis by area under disability/time curves	Journal of the Neurological Sciences	Design

Table A8.1 Reasons for Exclusion of titles at the full-text stage of the systematic review

First Author	Year	Title	Journal	Reason
Debelic, D.	2001	Twice weekly low dose interferon-(beta)-1a in relapsing-remitting multiple sclerosis	Acta Facultatis Medicae Fluminensis	Drug
Limmroth, V.	2001	[PRISMS study. Interferon beta-1a therapy in relapsing-remitting multiple sclerosis]	Internist (Berl)	Language
	2001	Interferon beta-1a for optic neuritis patients at high risk for multiple sclerosis	Am J Ophthalmol	Population
Beck, R. W.	2001	Interferon (beta)-1a for optic neuritis patients at high risk for multiple sclerosis	American Journal of Ophthalmology	Population
	2001	Early administration of interferon-(beta)-1a in multiple sclerosis	European Journal of Pediatrics	Population
Barkhof, F.	2001	T(1) hypointense lesions in secondary progressive multiple sclerosis: effect of interferon beta-1b treatment	Brain	Population
Galetta, S. L.	2001	The controlled high risk Avonex multiple sclerosis trial (CHAMPS Study)	J Neuroophthalmol	Population
Kappos, L.	2001	Final analysis of the European multicenter trial on IFN(beta)-1b in secondary-progressive MS	Neurology	Population
	2001	[Escalating immunomodulatory therapy of multiple sclerosis. 1st supplement: December 2000]	Nervenarzt	Review
Bayas, A.	2001	Beta interferons in multiple sclerosis	Internistische Praxis	Review
Durelli, L.	2001	Interferon-(beta) dose and efficacy: The OPTIMS study	Neurological Sciences	Review
Fuller, G. N.	2001	Disease modifying treatment in multiple sclerosis	J Neurol Neurosurg Psychiatry	Review
Khan, O. A.	2001	A prospective, open-label treatment trial to compare the effect of IFNbeta-1a (Avonex), IFNbeta-1b (Betaseron), and glatiramer acetate (Copaxone) on the relapse rate in relapsing--remitting multiple sclerosis: results after 18 months of therapy	Multiple Sclerosis	Review
Wolinsky, J. S.	2001	United States open-label glatiramer acetate extension trial for relapsing multiple sclerosis: MRI and clinical correlates. Multiple Sclerosis Study Group and the MRI Analysis Center	Multiple Sclerosis	Review
Clanet, M.	2002	A randomized, double-blind, dose-comparison study of weekly interferon beta-1a in relapsing MS	Neurology	Drug
Liu, C.	2002	Randomized, double-blind, placebo-controlled study of subcutaneous interferon beta-1a in relapsing-remitting multiple sclerosis: a categorical disability trend analysis	Multiple Sclerosis	Design
Balcer, L. J.	2002	Treatment of acute demyelinating optic neuritis	Seminars in Ophthalmology	Population
	2002	Baseline MRI characteristics of patients at high risk for multiple sclerosis: results from the CHAMPS trial. Controlled High-Risk Subjects Avonex Multiple Sclerosis Prevention Study	Multiple Sclerosis	Review
Khan, O.	2002	Comparative assessment of immunomodulating therapies for relapsing-remitting multiple sclerosis	CNS Drugs	Review
Zavalishin, I. A.	2002	[Results of open post-registration clinical trials of copaxone in patients with multiple sclerosis]	Zh Nevrol Psikhiatr Im S S Korsakova	Review

Table A8.1 Reasons for Exclusion of titles at the full-text stage of the systematic review

First Author	Year	Title	Journal	Reason
Zavalishin, I. A.	2002	Results of open post-registration clinical trials of copaxone in patients with multiple sclerosis	Zhurnal nevrologii i psikhiatrii	Review
Johnson, K. P.	2003	Glatiramer acetate (Copaxone): Comparison of continuous versus delayed therapy in a six-year organized multiple sclerosis trial	Multiple Sclerosis	Design
Barkhof, F.	2003	Validation of diagnostic magnetic resonance imaging criteria for multiple sclerosis and response to interferon (beta)1a	Annals of Neurology	Design
Siger-Zajdel, M.	2003	Open trial of the effectiveness of interferon beta 1a (Avonex) in the treatment of multiple sclerosis in Poland: MRI results	Neurologia i Neurochirurgia Polska	Design
Miller, D. H.	2003	A controlled trial of natalizumab for relapsing multiple sclerosis	New England Journal of Medicine	Population
Byrne, E.	2003	Randomized, comparative study of interferon beta-1a treatment regimens in MS: the EVIDENCE trial	Neurology	Review
Byrne, E.	2003	Randomized, comparative study of interferon beta-1a treatment regimens in MS: The EVIDENCE trial [5] (multiple letters)	Neurology	Review
Fernandez, O.	2003	Clinical benefits of interferon beta-1a in relapsing-remitting MS: A phase IV study	Acta Neurologica Scandinavica	Design
Kolar, O. J.	2003	Interferons in relapsing remitting multiple sclerosis	Lancet	Review
Liang-Kim, K. S.	2003	Interferon (beta)-Ia in the Treatment of Multiple Sclerosis	P and T	Review
Martinelli Boneschi, F.	2003	Effects of glatiramer acetate on relapse rate and accumulated disability in multiple sclerosis: meta-analysis of three double-blind, randomized, placebo-controlled clinical trials	Multiple Sclerosis	Review
Zavalishin, I. A.	2003	[Results of a multicenter study of Rebif-22 mcg administration in Russia]	Zh Nevrol Psikhiatr Im S S Korsakova	Review
Zavalishin, I. A.	2003	Results of a multicenter study of Rebif-22 mcg administration in Russia	Zhurnal nevrologii i psikhiatrii	Review
O'Connor, P. W.	2004	Randomized multicenter trial of natalizumab in acute MS relapses: Clinical and MRI effects	Neurology	Outcome
	2004	Glatiramer: new preparation. No place in multiple sclerosis	Prescrire International	Review
Munari, L.	2004	Therapy with glatiramer acetate for multiple sclerosis	Cochrane Database Syst Rev	Review
Freedman, M. S.	2005	Randomized study of once-weekly interferon beta-1Ia therapy in relapsing multiple sclerosis: three-year data from the OWIMS study	Multiple Sclerosis	Drug
Johnson, K. P.	2005	Neurologic consequence of delaying glatiramer acetate therapy for multiple sclerosis: 8-Year data	Acta Neurologica Scandinavica	Design
Oger, J.	2005	Prospective assessment of changing from placebo to IFN beta-1a in relapsing MS: The PRISMS study	Journal of the Neurological Sciences	Design

Table A8.1 Reasons for Exclusion of titles at the full-text stage of the systematic review

First Author	Year	Title	Journal	Reason
Panitch, H.	2005	Benefits of high-dose, high-frequency interferon beta-1a in relapsing-remitting multiple sclerosis are sustained to 16 months: Final comparative results of the EVIDENCE trial	Journal of the Neurological Sciences	Design
Schwid, S. R.	2005	Enhanced benefit of increasing interferon beta-1a dose and frequency in relapsing multiple sclerosis: The EVIDENCE study	Archives of neurology	Design
Berger, B. A.	2005	Evaluation of software-based telephone counseling to enhance medication persistency among patients with multiple sclerosis	Journal of the American Pharmacists Association	Outcome
Saida, T.	2005	Interferon beta-1b is effective in Japanese RRMS patients: A randomized, multicenter study	Neurology	Outcome
Cree, B. A.	2005	Response to interferon beta-1a treatment in African American multiple sclerosis patients	Arch Neurol	Population
O'Connor, P.	2005	Relapse rates and enhancing lesions in a phase II trial of natalizumab in multiple sclerosis	Multiple Sclerosis	Population
	2005	Natalizumab (Tysabri) for relapsing multiple sclerosis	Med Lett Drugs Ther	Review
	2005	Randomized, comparative study of Interferon beta1a treatment regimens in MS: The EVIDENCE trial - Commentary	Advances in Pharmacy	Review
Caramanos, Z.	2005	Evidence for use of glatiramer acetate in multiple sclerosis	Lancet Neurol	Review
Comi, G.	2005	Evidence for use of glatiramer acetate in multiple sclerosis	Lancet Neurology	Review
Rudick, R. A.	2005	Estimating long-term effects of disease-modifying drug therapy in multiple sclerosis patients	Multiple Sclerosis	Review
Koch-Henriksen, N.	2006	A randomized study of two interferon- beta treatments in relapsing-remitting multiple sclerosis	Neurology	Drug
Kappos, L.	2006	Long-term subcutaneous interferon beta-1a therapy in patients with relapsing-remitting MS	Neurology	Design
Baum, K.	2006	Safety and tolerability of a 'refrigeration-free' formulation of interferon beta-1b - Results of a double-blind, multicentre, comparative study in patients with relapsing-remitting or secondary progressive multiple sclerosis	Journal of International Medical Research	Outcome
Kappos, L.	2006	Oral fingolimod (FTY720) for relapsing multiple sclerosis	New England Journal of Medicine	Population
O'Connor, P. W.	2006	A Phase II study of the safety and efficacy of teriflunomide in multiple sclerosis with relapses	Neurology	Population
Ceballos-Baumann, A.	2006	Natalizumab alone and in combination with interferon in relapsing multiple sclerosis and the risk of developing a progressive multifocal leukoencephalopathy under natalizumab treatment: Comment	Nervenheilkunde	Review
Durelli, L.	2006	A randomized study of two interferon-beta treatments in relapsing-remitting multiple sclerosis	Neurology	Review
Ford, C. C.	2006	A prospective open-label study of glatiramer acetate: over a decade of continuous use in multiple sclerosis patients	Multiple Sclerosis	Design
Goodin, D. S.	2006	A randomized study of two interferon-beta treatments in relapsing-remitting multiple sclerosis	Neurology	Review

Table A8.1 Reasons for Exclusion of titles at the full-text stage of the systematic review

First Author	Year	Title	Journal	Reason
Goodin, D. S.	2006	Interferon beta in relapsing-remitting multiple sclerosis: an eight years experience in a specialist multiple sclerosis centre	J Neurol	Review
Cohen, J. A.	2007	Randomized, double-blind, dose-comparison study of glatiramer acetate in relapsing-remitting MS	Neurology	Drug
Rovaris, M.	2007	Long-term follow-up of patients treated with glatiramer acetate: a multicentre, multinational extension of the European/Canadian double-blind, placebo-controlled, MRI-monitored trial	Multiple Sclerosis	Design
Schwid, S. R.	2007	Full results of the Evidence of Interferon Dose-Response-European North American Comparative Efficacy (EVIDENCE) study: a multicenter, randomized, assessor-blinded comparison of low-dose weekly versus high-dose, high-frequency interferon beta-1a for relapsing multiple sclerosis	Clin Ther	Design
Balcer, L. J.	2007	Natalizumab reduces visual loss in patients with relapsing multiple sclerosis	Neurology	Outcome
Barkhof, F.	2007	Magnetic resonance imaging effects of interferon beta-1b in the BENEFIT study: Integrated 2-year results	Archives of neurology	Design
Beiske, A. G.	2007	Health-related quality of life in secondary progressive multiple sclerosis	Multiple Sclerosis	Outcome
Bell, C.	2007	Cost-effectiveness of four immunomodulatory therapies for relapsing-remitting multiple sclerosis: A Markov model based on long-term clinical data	Journal of Managed Care Pharmacy	Review
Buttmann, M.	2007	Interferon-(beta)1b in multiple sclerosis	Expert Review of Neurotherapeutics	Review
Clerico, M.	2007	Interferon-(beta)1a for the treatment of multiple sclerosis	Expert Opinion on Biological Therapy	Review
Durelli, L.	2008	The OPTimization of interferon for MS study: 375 microg interferon beta-1b in suboptimal responders	J Neurol	Drug
Durelli, L.	2008	The OPTimization of Interferon for MS study: 375 (mu)g interferon beta-1b in suboptimal responders	Journal of Neurology	Drug
Demina, T. L.	2008	[Clinical efficacy and safety of long-term immunomodulating therapy with interferon beta]	Zh Nevrol Psikhiatr Im S S Korsakova	Language
Melo, A.	2008	Beta interferons in clinically isolated syndromes: A meta-analysis	Arquivos de Neuro-Psiquiatria	Population
Polman, C.	2008	Subgroups of the BENEFIT study: risk of developing MS and treatment effect of interferon beta-1b	J Neurol	Population
Brochet, B.	2008	Long-term effects of glatiramer acetate in multiple sclerosis	Revue Neurologique	Review
Clar, C.	2008	Interferons and natalizumab for multiple sclerosis	GMS Health Technol Assess	Review
Goodin, D.	2008	Comparative studies of glatiramer acetate and interferon beta	International MS Journal	Review
Manova, M. G.	2008	A clinical study of multiple sclerosis patients treated with betaferon	Folia Med (Plovdiv)	Review

Table A8.1 Reasons for Exclusion of titles at the full-text stage of the systematic review

First Author	Year	Title	Journal	Reason
Miller, A.	2008	Long-term (up to 22 years), open-label, compassionate-use study of glatiramer acetate in relapsing-remitting multiple sclerosis	Multiple Sclerosis	Review
Bever Jr, C. T.	2009	Sustained-release fampridine for multiple sclerosis	Expert Opinion on Investigational Drugs	Drug
Goodman, A. D.	2009	Glance: Results of a phase 2, randomized, double-blind, placebo-controlled study	Neurology	Drug
Havrdova, E.	2009	Randomized study of interferon beta-1a, low-dose azathioprine, and low-dose corticosteroids in multiple sclerosis	Multiple Sclerosis	Drug
Oconnor, P.	2009	Oral fingolimod (FTY720) in multiple sclerosis: Two-year results of a phase II extension study	Neurology	Design
Achiron, A.	2009	Molecular profiling of glatiramer acetate early treatment effects in multiple sclerosis	Dis Markers	Design
Havrdova, E.	2009	Effect of natalizumab on clinical and radiological disease activity in multiple sclerosis: a retrospective analysis of the Natalizumab Safety and Efficacy in Relapsing-Remitting Multiple Sclerosis (AFFIRM) study	Lancet Neurol	Outcome
O'Connor, P.	2009	Oral fingolimod (FTY720) in multiple sclerosis: two-year results of a phase II extension study	Neurology	Population
Carroll, W. M.	2009	Clinical trials of multiple sclerosis therapies: Improvements to demonstrate long-term patient benefit	Multiple Sclerosis	Review
Demina, T. L.	2009	Efficacy and safety of prolonged immunomodulatory treatment with interferon beta	Neurosci Behav Physiol	Review
Sorensen, P. S.	2009	How effective is natalizumab as second-line treatment for multiple sclerosis in daily clinical praxis?	Eur J Neurol	Review
Cadavid, D.	2009	Efficacy of treatment of MS with IFNbeta-1b or glatiramer acetate by monthly brain MRI in the BECOME study	Neurology	Population
Comi, G.	2010	Oral laquinimod in patients with relapsing-remitting multiple sclerosis: 36-week double-blind active extension of the multi-centre, randomized, double-blind, parallel-group placebo-controlled study	Multiple Sclerosis	Design
Ebers, G. C.	2010	Analysis of clinical outcomes according to original treatment groups 16 years after the pivotal IFNB-1b trial	Journal of Neurology, Neurosurgery and Psychiatry	Design
De Stefano, N.	2010	Rapid benefits of a new formulation of subcutaneous interferon beta-1a in relapsing-remitting multiple sclerosis	Multiple Sclerosis	Outcome
	2010	Early treatment of clinical multiple sclerosis with glatiramer delays onset	Australian Journal of Pharmacy	Population
Comi, G.	2010	Phase II study of oral fingolimod (FTY720) in multiple sclerosis: 3-year results	Multiple Sclerosis	Population
Mazdeh, M.	2010	The therapeutic effect of avonex, rebif and betaferon on EDSS and relapse in multiple sclerosis: A comparative study	Acta Medica Iranica	Population
	2010	20th Meeting of the European Neurological Society - Symposia and Free Communications	Journal of Neurology	Review

Table A8.1 Reasons for Exclusion of titles at the full-text stage of the systematic review

First Author	Year	Title	Journal	Reason
Bar-Or, A.	2010	Abnormal B-cell cytokine responses a trigger of T-cell-mediated disease in MS?	Ann Neurol	Review
Ford, C.	2010	Continuous long-term immunomodulatory therapy in relapsing multiple sclerosis: Results from the 15-year analysis of the US prospective open-label study of glatiramer acetate	Multiple Sclerosis	Design
Hughes, J.	2010	Oral fingolimod was more effective than intramuscular interferon for relapsing-remitting multiple sclerosis	Annals of Internal Medicine	Review
La Mantia, L.	2010	Glatiramer acetate for multiple sclerosis	Cochrane Database Syst Rev	Review
Tselis, A.	2010	Laquinimod, a new oral autoimmune modulator for the treatment of relapsing-remitting multiple sclerosis	Current Opinion in Investigational Drugs	Review
Comi, G.	2011	Phase III dose-comparison study of glatiramer acetate for multiple sclerosis	Annals of Neurology	Drug
Khatri, B.	2011	Comparison of fingolimod with interferon beta-1a in relapsing-remitting multiple sclerosis: A randomised extension of the TRANSFORMS study	The Lancet Neurology	Design
Cree, B. A.	2011	Efficacy of natalizumab therapy in patients of African descent with relapsing multiple sclerosis: analysis of AFFIRM and SENTINEL data	Arch Neurol	Population
	2011	[The technology of treatment of multiple sclerosis with long-term immunomodulating drugs (disease modifying drugs--DMD)--beta-interferons and glatiramer-acetate]	Zh Nevrol Psikhiatr Im S S Korsakova	Review
Bar-Or, A.	2011	Targeting progressive neuroaxonal injury: lessons from multiple sclerosis	CNS Drugs	Review
Bejarano, B.	2011	Computational classifiers for predicting the short-term course of Multiple sclerosis	BMC Neurology	Review
Uitdehaag, B.	2011	Impact of exposure to interferon beta-1a on outcomes in patients with relapsing-remitting multiple sclerosis: Exploratory analyses from the PRISMS long-term follow-up study	Therapeutic Advances in Neurological Disorders	Review
De Stefano, N.	2012	Efficacy and safety of subcutaneous interferon beta-1a in relapsing-remitting multiple sclerosis: Further outcomes from the IMPROVE study	Journal of the Neurological Sciences	Drug
Freedman, M. S.	2012	Teriflunomide added to interferon-(beta) in relapsing multiple sclerosis: A randomized phase II trial	Neurology	Drug
Nafissi, S.	2012	Comparing efficacy and side effects of a weekly intramuscular biogeneric/biosimilar interferon beta-1a with Avonex in relapsing remitting multiple sclerosis: A double blind randomized clinical trial	Clinical Neurology and Neurosurgery	Drug
Balcer, L. J.	2012	Low-contrast acuity measures visual improvement in phase 3 trial of natalizumab in relapsing MS	Journal of the Neurological Sciences	Outcome
Campbell, J.	2012	New versus old: Long-term comparative effectiveness research projections for disease modifying therapies in relapse-remitting multiple sclerosis	Neurology	Review

Appendix 8c) Summary of Inclusion/Exclusion Criteria and Relapse/Progression Definitions of Studies included in the NMA described in Chapter 7

Table A8.2 Inclusion/Exclusion Criteria and Relapse/Progression Definitions of Included Studies

Study Name	Inclusion Criteria	Exclusion Criteria	Relapse definition	Progression Definition
IFNβ MS Study Group [51]	clinically definite or laboratory supported definite MS for more than 1 year; [327] Aged 18-50; ambulatory with EDSS scores of 5.5 or less; at least two acute exacerbations during the previous 2 years; clinically stable for at least 30 days before entry and had received no ACTH or prednisone during this period	prior treatment with azathioprine or cyclophosphamide excluded patients from the study	defined as the appearance of a new symptom or worsening of an old symptom, attributable to MS; accompanied by an appropriate new neurologic abnormality lasting at least 24 hours in the absence of fever; and preceded by stability or improvement for at least 30 days.	increase in EDSS of at least 1.0 p oint sustained over at least 3 months
Johnson *et al* [50]	clinically definite MS or laboratory supported definite MS; [327] aged 18-45 years; ambulatory with an EDSS score of 0-5.0, a history of at least two clearly identified and documented relapses in the 2 years prior to entry, onset of the first relapse at least 1 year before randomization, and a period of neurologic stability and freedom from corticosteroid therapy of at least 30 days prior to entry.	previous treatment with copolymer 1 or previous immunosuppressive therapy with cytotoxic chemotherapy (azathioprine, cyclophosphamide, or cyclosporine) or lymphoid irradiation; pregnancy or lactation, insulin-dependent diabetes mellitus, positive HIV or HTLV-I serology, evidence of Lyme disease, or required use of aspirin or chronic nonsteroidal anti-inflammatory drugs during the course of the trial	the appearance or reappearance of one or more neurologic abnormalities persisting for at least 48 hours and immediately preceded by a relatively stable or improving neurologic state of at least 30 days...consistent with an increase of at least a half a step on the EDSS, two points on one of the seven functional systems, or one point on two or more of the functional systems. Events associated with fever were excluded. A change in bowel, bladder or cognitive function could not be solely responsible for the changes in either the EDSS or the functional system scores	an increase of at least one full step on the EDSS that persisted for at least 3 months
Jacobs *et al* (MSCRG) [49]	definite multiple sclerosis [327] for at least 1 year, baseline EDSS of 1.0 - 3.5 inclusive, at	prior immunosuppressant or interferon therapy, adrenocorticotropic hormone or	the appearance of new neurological symptoms or worsening of pre-existing neurological symptoms lasting at least 48	deterioration from baseline by at least 1.0 point on the EDSS persisting for at least

Table A8.2 Inclusion/Exclusion Criteria and Relapse/Progression Definitions of Included Studies

Study Name	Inclusion Criteria	Exclusion Criteria	Relapse definition	Progression Definition
	least 2 documented exacerbations in the prior 3 years, no exacerbations for at least 2 months at study entry aged 18- 55 years. (including patients with complete and incomplete remissions)	corticosreroid treatment within 2 months of study entry, pregnancy or nursing, an unwillingness to practice contraception, chronic-progressive multiple sclerosis, or any disease other than MS compromising organ function.	hours in a patient who had been neurologically stable or improving for the previous 30 days accompanied by objective change on neurological examination (worsening of 0.5 point on the EDSS or a worsening by 1 .O point on the pyramidal, cerebellar, brainstem, or visual functional system scores)	6 months
PRISMS Study Group (PRISMS) [48]	adults with RRMS; [327] at least two relapses in the preceding 2 years and had EDSS scores of 0–5·0.	any previous systemic treatment with interferons, lymphoid irradiation, or cyclophospamide, or with other immunomodulatory or immunosuppressive treatments in the preceding 12 months.	the appearance of a new symptom or worsening of an old symptom, attributable to MS, accompanied by an appropriate new neurologic abnormality or focal neurological dysfunction lasting at least 24 hours in the absence of fever, and proceeded by stability or improvement for at least 30 days.	an increase in EDSS of 1.0 point or more for at least 3 months (or 0.5 point between EDSS 6 and 7).
Comi *et al* [73]	clinically definite MS; [327] RR course; a diagnosis of MS for at least 1 year; aged 18- 50 years inclusive; EDSS score 0-5; at least one documented relapse in the preceding 2 years; at least one enhancing lesion on their screening brain MRI; clinically relapse-free and without steroid treatment in the 30 days before their pre-entry MRI.	previous use of GA or oral myelin; prior lymphoid irradiation; use of immunosuppressant or cytotoxic agents in the past 2 years, or the use of azathioprine, cyclosporine, interferons, deoxyspergualine, or chronic corticosteroids during the previous 6 months; concomitant therapy with an experimental drug for MS or for another disease were ineligible; serious intercurrent systemic or psychiatric illnesses; pregnant or unwilling to practice reliable methods of contraception during the course of the study; known hypersensitivity to gadolinium-DTPA (Gd); unable to undergo repeated MRI studies	the appearance of one or more new neurological symptoms, or the reappearance of one or more previously experienced ones…lasting at least 48 hours preceded by a relatively stable or improving neurological state in the prior 30 days…corresponding to an increase of at least 0.5 points on the EDSS, or one grade in the score of two or more Functional Systems (FS), or two grades in one FS. Deterioration associated with fever or infection that can cause transient, secondary impairment of neurological function in MS patients were not considered relapses. Nor was a change in bowel, bladder, or cognitive function alone accepted as a relapse	*NR*

Table A8.2 Inclusion/Exclusion Criteria and Relapse/Progression Definitions of Included Studies

Study Name	Inclusion Criteria	Exclusion Criteria	Relapse definition	Progression Definition
Durelli *et al* (INCOMIN) [309]	aged 18 - 50 years; Clinically definite relapsing-remitting MS; [327] a baseline EDSS score between 1 and 3·5' two clinically documented relapses during the preceding 2 years; no relapse (and no corticosteroid treatment) for at least 30 days before study entry.	any previous systemic treatment with beta interferon or treatment with other immunosuppressive or immunomodulatory drugs (except corticosteroids); pregnancy, lactation, or an unwillingness to practise acceptable birth control; major depression or suicidal attempt in medical history; and clinically significant heart, liver, renal, or bone marrow disease	the occurrence of a new neurological symptom or worsening of an old one, with an objective change of at least one point in Kurtzke's functional system scale score, lasting at least 24 h, without fever, and which followed a period of clinical stability or of improvement of at least 30 days.	an increase in EDSS of at least one point sustained for at least 6 months and confirmed at the end of follow-up
Panitch *et al* (EVIDENCE) [308]	definite RRMS [327] and EDSS scores of 0 - 5.5; at least two exacerbations of MS in the prior 2 years.	previous use of IFN, cladribine, or total lymphoid irradiation; use of glatiramer acetate or cytokine therapy in the prior 3 months; use of IV immunoglobulin in the prior 6 months; and use of other immunomodulatory agents in the prior 12 months.	the appearance of a new symptom or worsening of an old symptom, accompanied by an appropriate objective finding on neurologic examination by the blinded evaluator, lasting at least 24 hours in the absence of fever and preceded by at least 30 days of clinical stability or improvement	progression by one point on the EDSS scale confirmed at a visit 3 or 6 months later without an intervening EDSS value that would not meet the criteria for progression.
Polman *et al* (AFFIRM) [83]	aged 8-50 years; a diagnosis of RRMS; [328] a score of 0 to 5.0 on the EDSS; undergone magnetic resonance imaging (MRI) showing lesions consistent with multiple sclerosis; had at least one medically documented relapse within the 12 months before the study began.	primary progressive, secondary progressive, or progressive relapsing; a relapse within 50 days before the administration of the first dose of the study drug; treatment with cyclophosphamide or mitoxantrone within the previous year, or treatment with interferon beta, glatiramer acetate, cyclosporine, azathioprine, methotrexate, or intravenous immune globulin within the previous 6 months; treatment with interferon beta, glatiramer acetate, or both for more than six months	new or recurrent neurologic symptoms not associated with fever or infection that lasted for at least 24 hours and were accompanied by new neurologic signs found by the examining neurologist.	an increase of 1.0 or more on the EDSS from a baseline score of ≥1.0 or an increase of ≥1.5 from a baseline score of 0 that was sustained for 12 weeks (progression could not be confirmed during a relapse).

Table A8.2 Inclusion/Exclusion Criteria and Relapse/Progression Definitions of Included Studies

Study Name	Inclusion Criteria	Exclusion Criteria	Relapse definition	Progression Definition
Mikol *et al* (REGARD) [310]	aged 18 - 60 years; interferon beta and glatiramer acetate naïve; RRMS diagnosed with the McDonald criteria; [328] EDSS score of 0–5.5; at least one attack in the preceding 12 months; clinically stable or neurologically improving during the 4 weeks before randomisation	pregnancy or breastfeeding; progressive MS; treatment with steroids (oral or systemic) or adrenocorticotrophic hormone within the previous 4 weeks; previous treatment with interferon beta, glatiramer acetate, or cladribine; total lymphoid irradiation; plasma exchange within the previous 3 months; intravenous gamma globulin use within the previous 6 months; cytokine or anticytokine therapy within the previous 3 months; immunosuppressant use within the past 12 months	new or worsening neurological symptoms, without fever, that lasted for 48 h or more and was accompanied by a change in Kurtzke's functional system score	confirmed at the 6-month follow-up visit ...if EDSS score at baseline was 0, a change of ≥1.5 points was required; if EDSS was 0.5–4.5 at baseline, a change of ≥1.0 point was required; if EDSS at baseline was ≥5 a change of 0.5 points was required
International Campath-1H in Multiple Sclerosis trial Investigators (CAMMS223) [93]	diagnosis of RRMS; [328] onset of symptoms no more than 36 months before the time of screening; at least two clinical episodes during the previous 2 years; a score of 3 or less on the EDSS; one or more enhancing lesions, as seen on at least one of up to four monthly cranial magnetic resonance imaging (MRI) scans.	previous disease modifying treatments, a history of clinically significant autoimmunity, the presence of serum antithyrotropin-receptor antibodies.	new or worsening symptoms with an objective change in neurologic examination attributable to MS that lasted for at least 48 hours, that were present at normal body temperature, and that were preceded by at least 30 days of clinical stability.	an increase of at least 1.5 points for patients with a baseline score of 0 and of at least 1.0 point for patients with a baseline score of 1.0 or more; confirmed twice during a 6-month period.

Table A8.2 Inclusion/Exclusion Criteria and Relapse/Progression Definitions of Included Studies

Study Name	Inclusion Criteria	Exclusion Criteria	Relapse definition	Progression Definition
O'Connor *et al* (BEYOND) [307]	treatment-naive patients with RRMS; [328] aged 18–55 years; at least one relapse in the year before entry into the study; baseline EDSS score of 0–5.	signs or symptoms that were better explained by a disease other than MS; progressive forms of MS or heart disease; treatment-experienced or had participated in previous trials of drugs for multiple sclerosis; history of severe depression, alcohol or drug misuse, or had made suicide attempts or had current suicidal ideations; serious or acute liver, renal, or bone marrow dysfunction, monoclonal gammaglobinopathy, or uncontrolled epilepsy; had intolerance, contraindication, or allergy to any of the drugs used in the study; unable to have MRI or unable to administer the study drug or have it administered by a care giver.	new or recurrent neurological abnormalities that were separated by at least 30 days from the onset of the preceding event, lasting at least 24 h, and occurring without fever or infection...associated with an increase in EDSS or functional system scores—as determined by the masked, evaluating physician—that was appropriate to the reported symptoms	1-point change in the score that was sustained for 3 months
Kappos *et al* (FREEDOMS) [88]	aged 8-55 years; a diagnosis of multiple sclerosis, according to the revised McDonald criteria; [329]a relapsing–remitting course; [30] one or more documented relapses in the previous year or two or more in the previous 2 years; and a score of 0 to 5.5 on the EDSS	relapse or corticosteroid treatment within 30 days before randomization, active infection, macular edema, diabetes mellitus, immune suppression (drug- or disease-induced), or clinically significant systemic disease. Interferon-beta or glatiramer acetate therapy had to have been stopped 3 or more months before randomization	symptoms accompanied by an increase of at least half a point in the EDSS score, of one point in each of two EDSS functional system scores, or of two points in one EDSS functional-system score (excluding scores for the bowel–bladder or cerebral functional systems).	an increase of one point in the EDSS score (or half a point if the baseline EDSS score was equal to 5.5), confirmed after 3 months, with an absence of relapse at the time of assessment and with all EDSS scores measured during that time meeting the criteria for disability progression

Table A8.2 Inclusion/Exclusion Criteria and Relapse/Progression Definitions of Included Studies

Study Name	Inclusion Criteria	Exclusion Criteria	Relapse definition	Progression Definition
Cohen *et al* (TRANSFORMS) [87]	aged 8-55 years; a diagnosis of RRMS; [30 329] one or more documented relapses in the previous year or two or more in the previous 2 years; and a score of 0 to 5.5 on the EDSS	documented relapse or corticosteroid treatment within 30 days before randomization, active infection, macular edema, immunosuppression (either drug- or disease-induced), and clinically significant coexisting systemic disease.	new, worsening, or recurrent neurologic symptoms that occurred at least 30 days after the onset of a preceding relapse, that lasted at least 24 hours without fever or infection, and that were accompanied by an increase of at least half a point on the EDSS or an increase of at least one point in two functional-systems scores or of at least two points in one functional-system score (excluding changes in bowel or bladder function and cognition).	a one-point increase in the EDSS score (or a half-point increase for patients with a baseline score ≥5.5) that was confirmed 3 months later in the absence of relapse.
O'Connor *et al* (TEMSO) [97]	aged 18 -55 years of age; diagnosis of multiple sclerosis; [329] relapsing clinical course, with or without progression; score of 5.5 or lower on the EDSS; at least two clinical relapses in the previous 2 years or one relapse during the preceding year; no relapses in the 60 days before randomization.	other systemic diseases, pregnant, planned to conceive during the trial period	the appearance of a new clinical sign or symptom, or clinical worsening of a previous sign or symptom that had been stable for at least 30 days and that persisted for a minimum of 24 hours in the absence of fever... an increase of 1 point in each of two EDSS functional-system scores or of 2 points in one EDSS functional-system score (excluding bowel and bladder function and cerebral function) or an increase of 0.5 points in the EDSS score from the previous clinically stable assessment.	an increase from baseline of at least 1.0 point in the EDSS score (or at least 0.5 points for patients with a baseline EDSS score greater than 5.5) that persisted for at least 12 weeks

Table A8.2 Inclusion/Exclusion Criteria and Relapse/Progression Definitions of Included Studies

Study Name	Inclusion Criteria	Exclusion Criteria	Relapse definition	Progression Definition
Saida *et al*[311]	aged 18–60 years; diagnosis of MS according to the revised McDonald criteria; [329] a relapsing course of the disease (relapsing–remitting or secondary progressive); had one or more relapses in the previous year *or* two or more relapses in the previous two years, or at least one gadolinium (Gd)-enhanced T1-weighted brain lesion within the 30 days prior to study commencement; at least one T2-weighted brain lesion and a score of 0–6.0 on the EDSS	patients with NMO; primary progressive MS, relapse or corticos-teroid treatment within 30 days before randomization, malignancy, macular oedema, diabetes mellitus, active infection, immune suppression (drug or disease induced), clinically significant systemic disease, or pregnancy; cladribine, cyclophosphamide, mitoxantrone, or other immunosuppressive use or immunoglobulin medication in the six months prior to randomization; plasmapheresis immunoadsorption or interferon beta therapy in the three months prior to randomization	new, worsening, or recurrent neurological symptoms that occurred at least 30 days after the onset of a preceding relapse, lasted at least 24 hours without fever or infection and were accompanied by an increase of at least half a point on the EDSS or an increase of at least one point in two functional systems scores or of at least two points in one functional-system score (excluding changes in bowel or bladder function and cognition).	*NR*

Table A8.2 Inclusion/Exclusion Criteria and Relapse/Progression Definitions of Included Studies

Study Name	Inclusion Criteria	Exclusion Criteria	Relapse definition	Progression Definition
Comi *et al* (ALLEGRO) [53]	diagnosis of RRMS; [329] aged 18- 55 years; a score of no more than 5.5 on the EDSS; a disease duration of at least 6 months before screening; one or more documented relapses in the 12 months before screening, two or more documented relapses in the 24 months before screening, or one documented relapse between 12 and 24 months before screening with at least one gadolinium-enhancing lesion in the previous year.	progressive forms MS, an onset of relapse or receipt of any glucocorticoid treatment between screening and the baseline visit, or clinically significant or unstable medical or surgical conditions that would preclude safe and complete participation in the study; use of investigative drugs or immunosuppressive agents (including mitoxantrone) within 6 months before screening; use of glatiramer acetate, any interferon, or intravenous immune globulin within 2 months before screening; use of glucocorticoids for at least 30 days within 2 months before screening; any previous use of natalizumab, cladribine, or laquinimod; and use of inhibitors of CYP3A4 within 2 weeks before the baseline visit.	the appearance of one or more new neurologic abnormalities or the reappearance of one or more previously observed neurologic abnormalities lasting for at least 48 hours and occurring after an improved neurologic state for at least 30 days... accompanied by objective neurologic changes as indicated by at least one of the following: an increase of at least 0.5 points in the EDSS score, an increase of one grade in two or more of the seven functional systems that are graded in the EDSS (pyramidal, cerebellar, brain stem, sensory, bowel and bladder, visual, and cerebral), or an increase of two grades in one functional system	an increase in the EDSS score of at least 1.0 point from baseline if the baseline score was between 0 and 5.0 or an increase of at least 0.5 points if the baseline score was 5.5. To confirm disability progression, these increases had to be sustained for at least 3 months
Gold *et al* (DEFINE) [52]	aged 18 - 55 years, RRMS diagnosis; [30 329] a baseline score of 0 to 5.0 on the EDSS; at least one clinically documented relapse within 12 months before randomization or a brain magnetic resonance imaging (MRI) scan, obtained within 6 weeks before randomization, that showed at least one gadolinium-enhancing lesion	progressive forms of MS; another major disease that would preclude participation in a clinical trial, abnormal results on prespecified laboratory tests, or recent exposure to contraindicated medications	new or recurrent neurologic symptoms, not associated with fever or infection, that lasted for at least 24 hours and that were accompanied by new objective neurologic findings according to the examining neurologist's evaluation.	at least a 1.0-point increase on the EDSS in patients with a baseline score of 1.0 or higher or at least a 1.5-point increase in patients with a baseline score of 0, with the increased score sustained for at least 12 weeks

Table A8.2 Inclusion/Exclusion Criteria and Relapse/Progression Definitions of Included Studies

Study Name	Inclusion Criteria	Exclusion Criteria	Relapse definition	Progression Definition
Fox *et al* (CONFIRM) [102]	diagnosis of RRMS; [329] aged 18 - 55 years; a score of 0- 5 on the EDSS; at least one clinically documented relapse in the previous 12 months or at least one gadolinium-enhancing lesion 0 to 6 weeks before randomization	progressive forms of MS. Other clinically significant illness, prespecified laboratory abnormalities, and prior exposure to Glatiramer acetate or contraindicated medications	new or recurrent neurologic symptoms not associated with fever or infection, lasting at least 24 hours, accompanied by new objective neurologic findings, and separated from the onset of other confirmed relapses by at least 30 days	an increase in the EDSS score of at least 1.0 point in patients with a baseline score of 1.0 or more or an increase of at least 1.5 points in patients with a baseline score of 0, confirmed at least 12 weeks later
Cohen *et al* (CARE-MS1) [92]	aged 18–55 years; RRMS; [329] disease duration of up to 5 years, at least two relapses in the previous 2 years and at least one in the previous year, EDSS scores of 3.0 or lower, and cranial abnormalities on MRI attributable to MS	progressive disease course, previous MS disease therapy (apart from corticosteroids), previous immunosuppressive, investigational, or monoclonal antibody therapy, and clinically significant auto immunity other than MS.	new or worsening neurological symptoms attributable to MS, lasting at least 48 h, without pyrexia, after at least 30 days of clinical stability, with an objective change on neurological examination (one point on two functional system scales or two points on one functional system scale or increase in EDSS score).	as an increase from baseline of at least one EDSS point (or ≥1.5 points if baseline EDSS score was 0) confirmed over 6 months.
Coles *et al* (CARE-MS2) [91]	aged 18–55 years; RRMS; [329] disease duration of 10 years or less; at least two attacks in the previous 2 years with at least one in the previous year; at least one relapse while on interferon beta or glatiramer after at least 6 months of treatment; EDSS scores of 5.0 or less; cranial and spinal MRI lesions fulfilling protocol-defined criteria.	progressive forms of MS, previous cytotoxic drug use or investigational therapy, treatment within the previous 6 months with natalizumab, methotrexate, azathioprine or ciclosporin, a history of clinically significant autoimmunity other than MS.	new or worsening neurological symptoms attributable to MS, lasting at least 48 h, without pyrexia, after at least 30 days of clinical stability with an objective change on neurological examination (one point on two functional system scales or two points on one functional system scale or increase in EDSS score).	an increase from baseline of at least one EDSS point (or ≥1.5 points if the baseline EDSS score was 0) confirmed over 6 months.

Appendix 8d) –NMA Results: Sensitivity Analyses

SA 1 to 3 *(Disability Progression Outcome)*

Table A8.3a Sensitivity Analyses (SA) 1-3

Mean Hazard Ratio of disability progression	**Basecase**		**SA 1**		**SA 2**		**SA 3**	
Comparison	**Mean HR**	**95% CI**	**Mean HR**	**95% CI**	**Mean HR**	**95% CI**	**Mean HR**	**95% CI**
IFN β-1a IM 30mcg vs Placebo	0.85	(0.59-1.22)	0.70	(0.48-1.02)	-	-	0.85	(0.52-1.40)
GA vs Placebo	0.81	(0.64-1.04)	0.43*	(0.23-0.76)	0.81	(0.63-1.03)	0.84	(0.51-1.38)
IFN β-1a SC 22mcg vs Placebo	0.82	(0.58-1.16)	-	-	0.81	(0.56-1.16)	0.80	(0.55-1.14)
IFN β-1a SC 22mcg vs Placebo	0.73	(0.53-1.01)	0.61*	(0.42-0.88)	0.70	(0.48-1.04)	0.69	(0.47-1.00)
IFN β-1b IM 250mcg vs Placebo	0.83	(0.62-1.11)	0.30*	(0.14-0.66)	0.82	(0.62-1.11)	-	-
natalizumab vs Placebo	0.56*	(0.43-0.73)	0.44*	(0.33-0.62)	0.56*	(0.43-0.73)	0.55*	(0.42-0.73)
fingolimod 0.5mg vs Placebo	0.66*	(0.50-0.86)	0.62*	(0.44-0.88)	0.65*	(0.48-0.88)	0.68*	(0.51-0.91)
fingolimod 1.25mg vs Placebo	0.67*	(0.51-0.87)	0.57*	(0.40-0.80)	0.70*	(0.52-0.95)	0.67*	(0.50-0.89)
Teriflunomide 7mg vs Placebo	0.78	(0.58-1.04)	-	-	0.77	(0.58-1.03)	0.77	(0.57-1.03)
Teriflunomide 14mg vs Placebo	0.72*	(0.53-0.96)	-	-	0.71*	(0.53-0.96)	0.71*	(0.52-0.95)
laquinimod vs Placebo	0.65*	(0.47-0.90)	-	-	0.64*	(0.46-0.89)	0.65*	(0.46-0.90)
BG-12 bd vs Placebo	0.61*	(0.48-0.76)	-	-	0.61*	(0.48-0.77)	0.55*	(0.41-0.75)
BG-12 tds vs Placebo	0.66*	(0.52-0.82)	-	-	0.66*	(0.53-0.82)	0.63*	(0.47-0.84)
Alemtuzumab vs Placebo	0.27*	(0.15-0.48)	0.32*	(0.20-0.51)	0.26*	(0.14-0.49)	-	-
IFN β-1a IM 30mcg vs GA	1.05	(0.67-1.63)	1.65	(0.90-3.06)	-	-	1.01	(0.50-2.04)
IFN β-1a IM 30mcg vs IFN β-1a SC 22mcg	1.04	(0.67-1.62)	-	-	-	-	1.07	(0.59-2.00)
IFN β-1a IM 30mcg vs IFN β-1a SC 22mcg	1.16	(0.82-1.62)	1.15	(0.77-1.76)	-	-	1.23	(0.67-2.31)
IFN β-1a IM 30mcg vs IFN β-1b IM 250mcg	1.03	(0.65-1.64)	2.33*	(1.21-4.68)	-	-	-	-
IFN β-1a IM 30mcg vs natalizumab	1.53	(0.97-2.42)	1.58	(0.97-2.57)	-	-	1.55	(0.87-2.74)
IFN β-1a IM 30mcg vs fingolimod 0.5mg	1.29	(0.89-1.88)	1.13	(0.69-1.88)	-	-	1.25	(0.79-1.96)

Table A8.3a Sensitivity Analyses (SA) 1-3

Mean Hazard Ratio of disability progression	Basecase		SA 1		SA 2		SA 3	
Comparison	**Mean HR**	**95% CI**	**Mean HR**	**95% CI**	**Mean HR**	**95% CI**	**Mean HR**	**95% CI**
IFN β-1a IM 30mcg vs fingolimod 1.25mg	1.27	(0.89-1.84)	1.24	(0.74-2.07)	-	-	1.27	(0.81-2.01)
IFN β-1a IM 30mcg vs Teriflunomide 7mg	1.10	(0.68-1.75)	-	-	-	-	1.11	(0.62-1.98)
IFN β-1a IM 30mcg vs Teriflunomide 14mg	1.19	(0.75-1.87)	-	-	-	-	1.20	(0.68-2.14)
IFN β-1a IM 30mcg vs laquinimod	1.31	(0.80-2.12)	-	-	-	-	1.32	(0.73-2.38)
IFN β-1a IM 30mcg vs BG-12 bd	1.40	(0.90-2.17)	-	-	-	-	1.54	(0.86-2.75)
IFN β-1a IM 30mcg vs BG-12 tds	1.30	(0.85-1.99)	-	-	-	-	1.35	(0.76-2.41)
IFN β-1a IM 30mcg vs Alemtuzumab	3.10*	(1.74-5.63)	2.23*	(1.36-3.69)	-	-	-	-
GA vs IFN β-1a SC 22mcg	0.99	(0.65-1.52)	-	-	1.00	(0.65-1.56)	1.06	(0.58-1.96)
GA vs IFN β-1a SC 22mcg	1.10	(0.73-1.66)	0.70	(0.44-1.10)	1.15	(0.73-1.77)	1.22	(0.66-2.27)
GA vs IFN β-1b IM 250mcg	0.98	(0.77-1.23)	1.41	(0.56-3.52)	0.98	(0.78-1.23)	-	-
GA vs natalizumab	1.46*	(1.02-2.10)	0.96	(0.49-1.87)	1.45*	(1.01-2.09)	1.53	(0.87-2.70)
GA vs fingolimod 0.5mg	1.23	(0.86-1.77)	0.68	(0.35-1.34)	1.24	(0.84-1.82)	1.24	(0.70-2.18)
GA vs fingolimod 1.25mg	1.21	(0.85-1.74)	-	-	1.15	(0.79-1.67)	1.26	(0.71-2.22)
GA vs Teriflunomide 7mg	1.04	(0.71-1.52)	-	-	1.04	(0.71-1.53)	1.10	(0.62-1.94)
GA vs Teriflunomide 14mg	1.13	(0.77-1.66)	-	-	1.13	(0.77-1.66)	1.19	(0.67-2.12)
GA vs laquinimod	1.24	(0.83-1.85)	-	-	1.25	(0.85-1.89)	1.30	(0.72-2.36)
GA vs BG-12 bd	1.33	(0.99-1.80)	-	-	1.33	(0.98-1.79)	1.52	(0.85-2.72)
GA vs BG-12 tds	1.23	(0.92-1.66)	-	-	1.23	(0.91-1.64)	1.34	(0.75-2.37)
GA vs Alemtuzumab	2.95*	(1.60-5.50)	1.35	(0.79-2.30)	3.06*	(5.95-1.60)	-	-
IFN β-1a SC 22mcg vs IFN β-1a SC 22mcg	1.12	(0.77-1.61)	-	-	1.15	(0.79-1.71)	1.15	(0.78-1.70)
IFN β-1a SC 22mcg vs IFN β-1b IM 250mcg	0.99	(0.62-1.55)	-	-	0.98	(0.61-1.55)	-	-
IFN β-1a SC 22mcg vs natalizumab	1.47	(0.94-2.27)	-	-	1.46	(0.93-2.25)	1.44	(0.92-2.24)
IFN β-1a SC 22mcg vs fingolimod 0.5mg	1.24	(0.82-1.90)	-	-	1.24	(0.77-1.99)	1.17	(0.73-1.83)

Table A8.3a Sensitivity Analyses (SA) 1-3

Mean Hazard Ratio of disability progression	Basecase		SA 1		SA 2		SA 3	
Comparison	**Mean HR**	**95% CI**	**Mean HR**	**95% CI**	**Mean HR**	**95% CI**	**Mean HR**	**95% CI**
IFN β-1a SC 22mcg vs fingolimod 1.25mg	1.23	(0.80-1.85)	-	-	1.15	(0.70-1.82)	1.19	(0.75-1.88)
IFN β-1a SC 22mcg vs Teriflunomide 7mg	1.05	(0.66-1.64)	-	-	1.04	(0.64-1.65)	1.03	(0.65-1.63)
IFN β-1a SC 22mcg vs Teriflunomide 14mg	1.14	(0.72-1.81)	-	-	1.13	(0.70-1.81)	1.12	(0.70-1.79)
IFN β-1a SC 22mcg vs laquinimod	1.26	(0.77-2.02)	-	-	1.25	(0.77-2.07)	1.23	(0.74-2.03)
IFN β-1a SC 22mcg vs BG-12 bd	1.35	(0.88-2.02)	-	-	1.33	(0.86-2.06)	1.44	(0.90-2.28)
IFN β-1a SC 22mcg vs BG-12 tds	1.25	(0.82-1.87)	-	-	1.23	(0.80-1.87)	1.26	(0.80-1.99)
IFN β-1a SC 22mcg vs Alemtuzumab	2.99*	(1.64-5.62)	-	-	3.07*	(5.78-1.62)	-	-
IFN β-1a SC 22mcg vs IFN β-1b IM 250mcg	0.89	(0.57-1.35)	2.02	(0.91-4.55)	0.86	(0.54-1.38)	-	-
IFN β-1a SC 22mcg vs natalizumab	1.32	(0.88-1.99)	1.37	(0.83-2.24)	1.27	(0.80-1.99)	1.25	(0.79-1.98)
IFN β-1a SC 22mcg vs fingolimod 0.5mg	1.11	(0.76-1.63)	0.98	(1.64-0.60)	1.08	(0.67-1.74)	1.01	(0.63-1.61)
IFN β-1a SC 22mcg vs fingolimod 1.25mg	1.10	(0.76-1.59)	1.07	(0.64-1.80)	1.00	(0.61-1.61)	1.03	(0.64-1.65)
IFN β-1a SC 22mcg vs Teriflunomide 7mg	0.94	(0.61-1.44)	-	-	0.91	(0.57-1.45)	0.90	(0.55-1.44)
IFN β-1a SC 22mcg vs Teriflunomide 14mg	1.02	(0.65-1.58)	-	-	0.99	(0.61-1.60)	0.97	(0.60-1.56)
IFN β-1a SC 22mcg vs laquinimod	1.13	(0.70-1.80)	-	-	1.09	(0.67-1.82)	1.07	(0.64-1.78)
IFN β-1a SC 22mcg vs BG-12 bd	1.21	(0.81-1.78)	-	-	1.16	(0.74-1.80)	1.25	(0.77-1.99)
IFN β-1a SC 22mcg vs BG-12 tds	1.12	(0.76-1.66)	-	-	1.07	(0.70-1.67)	1.09	(0.68-1.74)
IFN β-1a SC 22mcg vs Alemtuzumab	2.67*	(1.66-4.36)	1.93*	(1.48-2.56)	2.67*	(4.41-1.61)	-	-
IFN β-1b IM 250mcg vs natalizumab	1.49	(0.99-2.20)	0.68	(0.28-1.54)	1.48*	(1.00-2.22)	-	-
IFN β-1b IM 250mcg vs fingolimod 0.5mg	1.25	(0.84-1.86)	0.48	(1.15-0.21)	1.27	(0.83-1.90)	-	-
IFN β-1b IM 250mcg vs fingolimod 1.25mg	1.24	(0.84-1.81)	0.53	(0.22-1.26)	1.17	(0.77-1.77)	-	-
IFN β-1b IM 250mcg vs Teriflunomide 7mg	1.06	(0.70-1.60)	-	-	1.06	(0.70-1.59)	-	-
IFN β-1b IM 250mcg vs Teriflunomide 14mg	1.15	(0.78-1.73)	-	-	1.15	(0.76-1.76)	-	-
IFN β-1b IM 250mcg vs laquinimod	1.27	(0.82-1.95)	-	-	1.28	(0.83-1.98)	-	-

Table A8.3a Sensitivity Analyses (SA) 1-3

Mean Hazard Ratio of disability progression	**Basecase**		**SA 1**		**SA 2**		**SA 3**	
Comparison	**Mean HR**	**95% CI**	**Mean HR**	**95% CI**	**Mean HR**	**95% CI**	**Mean HR**	**95% CI**
IFN β-1b IM 250mcg vs BG-12 bd	1.36	(0.95-1.95)	-	-	1.35	(0.95-1.94)	-	-
IFN β-1b IM 250mcg vs BG-12 tds	1.26	(0.89-1.77)	-	-	1.25	(0.89-1.77)	-	-
IFN β-1b IM 250mcg vs Alemtuzumab	3.01*	(1.61-5.73)	0.96	(0.40-2.27)	3.12*	(6.31-1.55)	-	-
natalizumab vs fingolimod 0.5mg	0.84	(0.58-1.23)	0.71	(1.15-0.44)	0.85	(0.58-1.28)	0.81	(0.54-1.20)
natalizumab vs fingolimod 1.25mg	0.83	(0.57-1.21)	0.78	(0.49-1.25)	0.79	(0.53-1.16)	0.82	(0.55-1.22)
natalizumab vs Teriflunomide 7mg	0.71	(0.48-1.08)	-	-	0.72	(0.49-1.07)	0.72	(0.48-1.07)
natalizumab vs Teriflunomide 14mg	0.78	(0.51-1.17)	-	-	0.78	(0.52-1.17)	0.78	(0.52-1.16)
natalizumab vs laquinimod	0.85	(0.55-1.30)	-	-	0.86	(0.57-1.30)	0.85	(0.55-1.31)
natalizumab vs BG-12 bd	0.91	(0.64-1.32)	-	-	0.91	(0.64-1.30)	0.99	(0.66-1.50)
natalizumab vs BG-12 tds	0.85	(0.59-1.20)	-	-	0.84	(0.60-1.20)	0.87	(0.58-1.31)
natalizumab vs Alemtuzumab	2.03*	(1.09-3.88)	1.41	(0.79-2.49)	2.11*	(4.27-1.10)	-	-
fingolimod 0.5mg vs fingolimod 1.25mg	0.99	(0.75-1.30)	0.91	(1.34-0.62)	0.92	(0.67-1.27)	1.02	(0.77-1.34)
fingolimod 0.5mg vs Teriflunomide 7mg	0.85	(0.57-1.25)	-	-	0.84	(0.55-1.29)	0.89	(0.59-1.33)
fingolimod 0.5mg vs Teriflunomide 14mg	0.92	(0.61-1.38)	-	-	0.91	(0.60-1.40)	0.96	(0.64-1.45)
fingolimod 0.5mg vs laquinimod	1.01	(0.65-1.55)	-	-	1.01	(0.65-1.59)	1.05	(0.69-1.62)
fingolimod 0.5mg vs BG-12 bd	1.09	(0.76-1.54)	-	-	1.07	(0.73-1.56)	1.23	(0.81-1.87)
fingolimod 0.5mg vs BG-12 tds	1.00	(0.70-1.43)	-	-	0.99	(0.68-1.43)	1.08	(0.72-1.62)
fingolimod 0.5mg vs Alemtuzumab	2.40*	(1.32-4.53)	1.98*	(1.09-3.51)	2.47*	(4.95-1.24)	-	-
fingolimod 1.25mg vs Teriflunomide 7mg	0.86	(0.58-1.26)	-	-	0.91	(0.61-1.38)	0.87	(0.58-1.30)
fingolimod 1.25mg vs Teriflunomide 14mg	0.93	(0.62-1.37)	-	-	0.99	(0.66-1.51)	0.94	(0.63-1.42)
fingolimod 1.25mg vs laquinimod	1.03	(0.67-1.54)	-	-	1.09	(0.71-1.72)	1.03	(0.67-1.59)
fingolimod 1.25mg vs BG-12 bd	1.10	(0.77-1.57)	-	-	1.16	(0.79-1.68)	1.21	(0.80-1.84)
fingolimod 1.25mg vs BG-12 tds	1.02	(0.71-1.42)	-	-	1.07	(0.73-1.56)	1.06	(0.71-1.59)

Table A8.3a Sensitivity Analyses (SA) 1-3

Mean Hazard Ratio of disability progression	**Basecase**		**SA 1**		**SA 2**		**SA 3**	
Comparison	**Mean HR**	**95% CI**	**Mean HR**	**95% CI**	**Mean HR**	**95% CI**	**Mean HR**	**95% CI**
fingolimod 1.25mg vs Alemtuzumab	2.44*	(1.33-4.50)	1.80*	(1.00-3.22)	2.67*	(5.35-1.35)	-	-
Teriflunomide 7mg vs Teriflunomide 14mg	1.09	(0.77-1.51)	-	-	1.09	(0.78-1.50)	1.09	(0.79-1.50)
Teriflunomide 7mg vs laquinimod	1.19	(0.77-1.82)	-	-	1.20	(0.78-1.89)	1.19	(0.77-1.86)
Teriflunomide 7mg vs BG-12 bd	1.28	(0.88-1.88)	-	-	1.27	(0.88-1.84)	1.39	(0.91-2.14)
Teriflunomide 7mg vs BG-12 tds	1.18	(0.81-1.70)	-	-	1.18	(0.82-1.69)	1.22	(0.81-1.85)
Teriflunomide 7mg vs Alemtuzumab	2.83*	(1.50-5.51)	-	-	2.94*	(5.88-1.49)	-	-
Teriflunomide 14mg vs laquinimod	1.10	(0.70-1.70)	-	-	1.11	(0.71-1.72)	1.09	(0.70-1.70)
Teriflunomide 14mg vs BG-12 bd	1.18	(0.82-1.73)	-	-	1.17	(0.80-1.71)	1.28	(0.84-1.97)
Teriflunomide 14mg vs BG-12 tds	1.09	(0.76-1.56)	-	-	1.08	(0.74-1.55)	1.12	(0.74-1.70)
Teriflunomide 14mg vs Alemtuzumab	2.61*	(1.36-5.09)	-	-	2.70*	(5.48-1.37)	-	-
laquinimod vs BG-12 bd	1.07	(0.73-1.58)	-	-	1.06	(0.71-1.58)	1.17	(0.75-1.84)
laquinimod vs BG-12 tds	0.99	(0.67-1.47)	-	-	0.98	(0.66-1.46)	1.02	(0.66-1.59)
laquinimod vs Alemtuzumab	2.38*	(1.24-4.60)	-	-	2.44*	(4.96-1.20)	-	-
BG-12 bd vs BG-12 tds	0.92	(0.71-1.18)	-	-	0.92	(0.72-1.20)	0.88	(0.62-1.22)
BG-12 bd vs Alemtuzumab	2.21*	(1.21-4.19)	-	-	2.31*	(4.59-1.20)	1.45	(1.19-2.25)
BG-12 tds vs Alemtuzumab	2.40*	(1.29-4.50)	-	-	2.50*	(4.93-1.31)	-	-

SA 3-4 *(ARR Outcome)*

Table A8.3b Sensitivity Analyses (SA) 3-4

Mean Relative Annualised Relapse Rate	**Basecase**		**SA 3**		**SA 4**	
Comparison	**Mean Relative ARR**	**95% CI**	**Mean Relative ARR**	**95% CI**	**Mean Relative ARR**	**95% CI**
IFN β-1a IM 30mcg vs Placebo	0.83*	(0.74-0.94)	0.79	(0.60-1.03)	0.83*	(0.74-0.94)
GA vs Placebo	0.67*	(0.61-0.74)	0.70*	(0.59-0.83)	0.67*	(0.61-0.74)
IFN β-1a SC 22mcg vs Placebo	0.73*	(0.64-0.83)	0.72*	(0.62-0.82)	0.73*	(0.64-0.83)
IFN β-1a SC 44mcg vs Placebo	0.68*	(0.62-0.76)	0.67*	(0.58-0.77)	0.68*	(0.62-0.76)
IFN β-1b IM 250mcg vs Placebo	0.69*	(0.61-0.77)	-	-	0.69*	(0.61-0.77)
natalizumab vs Placebo	0.31*	(0.27-0.36)	0.31*	(0.27-0.36)	0.31*	(0.27-0.36)
fingolimod 0.5mg vs Placebo	0.44*	(0.37-0.53)	0.42*	(0.34-0.52)	0.44*	(0.37-0.53)
fingolimod 1.25mg vs Placebo	0.43*	(0.36-0.51)	0.44*	(0.35-0.54)	0.43*	(0.36-0.51)
Teriflunomide 7mg vs Placebo	0.68*	(0.58-0.80)	0.68*	(0.58-0.80)	0.68*	(0.58-0.80)
Teriflunomide 14mg vs Placebo	0.68*	(0.58-0.80)	0.68*	(0.58-0.80)	0.68*	(0.58-0.80)
laquinimod vs Placebo	0.76*	(0.65-0.89)	0.77*	(0.66-0.89)	0.76*	(0.65-0.89)
BG-12 bd vs Placebo	0.50*	(0.43-0.58)	0.47*	(0.37-0.58)	0.50*	(0.43-0.58)
BG-12 tds vs Placebo	0.50*	(0.43-0.58)	0.52*	(0.41-0.63)	0.50*	(0.43-0.58)
Alemtuzumab vs Placebo	0.31*	(0.26-0.36)	-	-	0.31*	(0.26-0.36)
IFN β-1a IM 30mcg vs GA	1.24*	(1.08-1.43)	1.13	(0.81-1.55)	1.24*	(1.08-1.43)
IFN β-1a IM 30mcg vs IFN β-1a SC 22mcg	1.15	(0.97-1.36)	1.09	(0.80-1.49)	1.15	(0.97-1.36)
IFN β-1a IM 30mcg vs IFN β-1a SC 44mcg	1.22*	(1.07-1.39)	1.18	(0.86-1.60)	1.22*	(1.07-1.39)
IFN β-1a IM 30mcg vs IFN β-1b IM 250mcg	1.22*	(1.05-1.41)	-	-	1.22*	(1.05-1.41)
IFN β-1a IM 30mcg vs natalizumab	2.65*	(2.20-3.19)	2.50*	(1.84-3.40)	2.65*	(2.20-3.19)
IFN β-1a IM 30mcg vs fingolimod 0.5mg	1.87*	(1.56-2.26)	1.87*	(1.50-2.35)	1.87*	(1.56-2.26)
IFN β-1a IM 30mcg vs fingolimod 1.25mg	1.95*	(1.63-2.33)	1.80*	(1.44-2.26)	1.95*	(1.63-2.33)

Table A8.3b Sensitivity Analyses (SA) 3-4

Mean Relative Annualised Relapse Rate	**Basecase**		**SA 3**		**SA 4**	
Comparison	**Mean Relative ARR**	**95% CI**	**Mean Relative ARR**	**95% CI**	**Mean Relative ARR**	**95% CI**
IFN β-1a IM 30mcg vs Teriflunomide 7mg	1.22*	(1.01-1.49)	1.15	(0.83-1.58)	1.22*	(1.01-1.49)
IFN β-1a IM 30mcg vs Teriflunomide 14mg	1.22*	(1.01-1.49)	1.15	(0.84-1.59)	1.22*	(1.01-1.49)
IFN β-1a IM 30mcg vs laquinimod	1.09	(0.90-1.33)	1.03	(0.75-1.41)	1.09	(0.90-1.33)
IFN β-1a IM 30mcg vs BG-12 bd	1.68*	(1.39-2.03)	1.68*	(1.18-2.40)	1.68*	(1.39-2.03)
IFN β-1a IM 30mcg vs BG-12 tds	1.67*	(1.39-2.03)	1.53*	(1.08-2.17)	1.67*	(1.39-2.03)
IFN β-1a IM 30mcg vs Alemtuzumab	2.73*	(2.26-3.30)	-	-	2.73*	(2.26-3.30)
GA vs IFN β-1a SC 22mcg	0.92	(0.79-1.08)	0.97	(0.78-1.21)	0.92	(0.79-1.08)
GA vs IFN β-1a SC 44mcg	0.98	(0.86-1.11)	1.04	(0.83-1.30)	0.98	(0.86-1.11)
GA vs IFN β-1b IM 250mcg	0.98	(0.88-1.08)	-	-	0.98	(0.88-1.08)
GA vs natalizumab	2.13*	(1.79-2.53)	2.21*	(1.77-2.77)	2.13*	(1.79-2.53)
GA vs fingolimod 0.5mg	1.51*	(1.24-1.84)	1.66*	(1.27-2.19)	1.51*	(1.24-1.84)
GA vs fingolimod 1.25mg	1.57*	(1.29-1.91)	1.60*	(1.22-2.10)	1.57*	(1.29-1.91)
GA vs Teriflunomide 7mg	0.98	(0.81-1.19)	1.02	(0.81-1.29)	0.98	(0.81-1.19)
GA vs Teriflunomide 14mg	0.98	(0.82-1.19)	1.02	(0.81-1.29)	0.98	(0.82-1.19)
GA vs laquinimod	0.88	(0.73-1.05)	0.91	(0.72-1.14)	0.88	(0.73-1.05)
GA vs BG-12 bd	1.35*	(1.14-1.60)	1.49*	(1.13-1.98)	1.35*	(1.14-1.60)
GA vs BG-12 tds	1.35*	(1.14-1.59)	1.35*	(1.03-1.78)	1.35*	(1.14-1.59)
GA vs Alemtuzumab	2.19*	(1.82-2.64)	-	-	2.19*	(1.82-2.64)
IFN β-1a SC 22mcg vs IFN β-1a SC 44mcg	1.06	(0.92-1.22)	1.07	(0.93-1.25)	1.06	(0.92-1.22)
IFN β-1a SC 22mcg vs IFN β-1b IM 250mcg	1.06	(0.89-1.25)	-	-	1.06	(0.89-1.25)
IFN β-1a SC 22mcg vs natalizumab	2.31*	(1.90-2.81)	2.28*	(1.86-2.79)	2.31*	(1.90-2.81)
IFN β-1a SC 22mcg vs fingolimod 0.5mg	1.63*	(1.31-2.04)	1.71*	(1.33-2.20)	1.63*	(1.31-2.04)

Table A8.3b Sensitivity Analyses (SA) 3-4

Mean Relative Annualised Relapse Rate	Basecase		SA 3		SA 4	
Comparison	**Mean Relative ARR**	**95% CI**	**Mean Relative ARR**	**95% CI**	**Mean Relative ARR**	**95% CI**
IFN β-1a SC 22mcg vs fingolimod 1.25mg	1.70*	(1.36-2.11)	1.65*	(1.28-2.15)	1.70*	(1.36-2.11)
IFN β-1a SC 22mcg vs Teriflunomide 7mg	1.07	(0.87-1.31)	1.05	(0.85-1.30)	1.07	(0.87-1.31)
IFN β-1a SC 22mcg vs Teriflunomide 14mg	1.07	(0.87-1.31)	1.05	(0.85-1.30)	1.07	(0.87-1.31)
IFN β-1a SC 22mcg vs laquinimod	0.95	(0.77-1.17)	0.94	(0.76-1.15)	0.95	(0.77-1.17)
IFN β-1a SC 22mcg vs BG-12 bd	1.46*	(1.19-1.78)	1.54*	(1.18-2.01)	1.46*	(1.19-1.78)
IFN β-1a SC 22mcg vs BG-12 tds	1.46*	(1.19-1.78)	1.39*	(1.09-1.80)	1.46*	(1.19-1.78)
IFN β-1a SC 22mcg vs Alemtuzumab	2.38*	(1.95-2.88)	-	-	2.38*	(1.95-2.88)
IFN β-1a SC 44mcg vs IFN β-1b IM 250mcg	1.00	(0.87-1.15)	-	-	1.00	(0.87-1.15)
IFN β-1a SC 44mcg vs natalizumab	2.18*	(1.83-2.60)	2.13*	(1.72-2.61)	2.18*	(1.83-2.60)
IFN β-1a SC 44mcg vs fingolimod 0.5mg	1.54*	(1.26-1.88)	1.59*	(1.24-2.06)	1.54*	(1.26-1.88)
IFN β-1a SC 44mcg vs fingolimod 1.25mg	1.60*	(1.31-1.96)	1.53*	(1.18-2.00)	1.60*	(1.31-1.96)
IFN β-1a SC 44mcg vs Teriflunomide 7mg	1.00	(0.83-1.22)	0.98	(0.79-1.22)	1.00	(0.83-1.22)
IFN β-1a SC 44mcg vs Teriflunomide 14mg	1.01	(0.83-1.22)	0.98	(0.79-1.22)	1.01	(0.83-1.22)
IFN β-1a SC 44mcg vs laquinimod	0.90	(0.75-1.09)	0.87	(0.71-1.08)	0.90	(0.75-1.09)
IFN β-1a SC 44mcg vs BG-12 bd	1.38*	(1.15-1.65)	1.43*	(1.10-1.86)	1.38*	(1.15-1.65)
IFN β-1a SC 44mcg vs BG-12 tds	1.38*	(1.15-1.65)	1.30*	(1.01-1.68)	1.38*	(1.15-1.65)
IFN β-1a SC 44mcg vs Alemtuzumab	2.24*	(1.95-2.57)	-	-	2.24*	(1.95-2.57)
IFN β-1b IM 250mcg vs natalizumab	2.18*	(1.82-2.62)	-	-	2.18*	(1.82-2.62)
IFN β-1b IM 250mcg vs fingolimod 0.5mg	1.54*	(1.26-1.89)	-	-	1.54*	(1.26-1.89)
IFN β-1b IM 250mcg vs fingolimod 1.25mg	1.60*	(1.31-1.96)	-	-	1.60*	(1.31-1.96)
IFN β-1b IM 250mcg vs Teriflunomide 7mg	1.01	(0.83-1.22)	-	-	1.01	(0.83-1.22)
IFN β-1b IM 250mcg vs Teriflunomide 14mg	1.01	(0.83-1.22)	-	-	1.01	(0.83-1.22)

Table A8.3b Sensitivity Analyses (SA) 3-4

Mean Relative Annualised Relapse Rate	**Basecase**		**SA 3**		**SA 4**	
Comparison	**Mean Relative ARR**	**95% CI**	**Mean Relative ARR**	**95% CI**	**Mean Relative ARR**	**95% CI**
IFN β-1b IM 250mcg vs laquinimod	0.90	(0.74-1.09)	-	-	0.90	(0.74-1.09)
IFN β-1b IM 250mcg vs BG-12 bd	1.38*	(1.15-1.65)	-	-	1.38*	(1.15-1.65)
IFN β-1b IM 250mcg vs BG-12 tds	1.38*	(1.15-1.65)	-	-	1.38*	(1.15-1.65)
IFN β-1b IM 250mcg vs Alemtuzumab	2.24*	(1.84-2.73)	-	-	2.24*	(1.84-2.73)
natalizumab vs fingolimod 0.5mg	0.71*	(0.57-0.89)	0.75*	(0.58-0.96)	0.71*	(0.57-0.89)
natalizumab vs fingolimod 1.25mg	0.74*	(0.59-0.92)	0.72*	(0.56-0.93)	0.74*	(0.59-0.92)
natalizumab vs Teriflunomide 7mg	0.46*	(0.37-0.57)	0.46*	(0.37-0.57)	0.46*	(0.37-0.57)
natalizumab vs Teriflunomide 14mg	0.46*	(0.37-0.57)	0.46*	(0.37-0.57)	0.46*	(0.37-0.57)
natalizumab vs laquinimod	0.41*	(0.33-0.51)	0.41*	(0.33-0.51)	0.41*	(0.33-0.51)
natalizumab vs BG-12 bd	0.63*	(0.51-0.78)	0.67*	(0.52-0.88)	0.63*	(0.51-0.78)
natalizumab vs BG-12 tds	0.63*	(0.51-0.77)	0.61*	(0.79-0.47)	0.63*	(0.51-0.77)
natalizumab vs Alemtuzumab	1.03	(0.82-1.28)	-	-	1.03	(0.82-1.28)
fingolimod 0.5mg vs fingolimod 1.25mg	1.04	(0.85-1.27)	0.96	(1.17-0.79)	1.04	(0.85-1.27)
fingolimod 0.5mg vs Teriflunomide 7mg	0.65*	(0.51-0.83)	0.61*	(0.47-0.80)	0.65*	(0.51-0.83)
fingolimod 0.5mg vs Teriflunomide 14mg	0.65*	(0.51-0.83)	0.61*	(0.47-0.80)	0.65*	(0.51-0.83)
fingolimod 0.5mg vs laquinimod	0.58*	(0.46-0.74)	0.55*	(0.42-0.71)	0.58*	(0.46-0.74)
fingolimod 0.5mg vs BG-12 bd	0.89	(0.71-1.13)	0.90	(0.66-1.21)	0.89	(0.71-1.13)
fingolimod 0.5mg vs BG-12 tds	0.89	(0.71-1.13)	0.81	(1.09-0.61)	0.89	(0.71-1.13)
fingolimod 0.5mg vs Alemtuzumab	1.45*	(1.14-1.85)	-	-	1.45*	(1.14-1.85)
fingolimod 1.25mg vs Teriflunomide 7mg	0.63*	(0.49-0.79)	0.64*	(0.49-0.84)	0.63*	(0.49-0.79)
fingolimod 1.25mg vs Teriflunomide 14mg	0.63*	(0.50-0.80)	0.64*	(0.49-0.84)	0.63*	(0.50-0.80)
fingolimod 1.25mg vs laquinimod	0.56*	(0.44-0.71)	0.57*	(0.44-0.74)	0.56*	(0.44-0.71)

Table A8.3b Sensitivity Analyses (SA) 3-4

Mean Relative Annualised Relapse Rate	**Basecase**		**SA 3**		**SA 4**	
Comparison	**Mean Relative ARR**	**95% CI**	**Mean Relative ARR**	**95% CI**	**Mean Relative ARR**	**95% CI**
fingolimod 1.25mg vs BG-12 bd	0.86	(0.68-1.08)	0.93	(0.69-1.27)	0.86	(0.68-1.08)
fingolimod 1.25mg vs BG-12 tds	0.86	(0.68-1.08)	0.85	(1.14-0.63)	0.86	(0.68-1.08)
fingolimod 1.25mg vs Alemtuzumab	1.40*	(1.10-1.78)	-	-	1.40*	(1.10-1.78)
Teriflunomide 7mg vs Teriflunomide 14mg	1.00	(0.83-1.19)	1.00	(0.84-1.20)	1.00	(0.83-1.19)
Teriflunomide 7mg vs laquinimod	0.89	(0.72-1.12)	0.89	(0.72-1.11)	0.89	(0.72-1.12)
Teriflunomide 7mg vs BG-12 bd	1.37*	(1.10-1.70)	1.46*	(1.11-1.92)	1.37*	(1.10-1.70)
Teriflunomide 7mg vs BG-12 tds	1.37*	(1.10-1.70)	1.32*	(1.74-1.01)	1.37*	(1.10-1.70)
Teriflunomide 7mg vs Alemtuzumab	2.23*	(1.76-2.82)	-	-	2.23*	(1.76-2.82)
Teriflunomide 14mg vs laquinimod	0.89	(0.72-1.12)	0.89	(0.71-1.11)	0.89	(0.72-1.12)
Teriflunomide 14mg vs BG-12 bd	1.37*	(1.10-1.71)	1.46*	(1.12-1.93)	1.37*	(1.10-1.71)
Teriflunomide 14mg vs BG-12 tds	1.37*	(1.10-1.71)	1.32*	(1.71-1.02)	1.37*	(1.10-1.71)
Teriflunomide 14mg vs Alemtuzumab	2.23*	(1.76-2.82)	-	-	2.23*	(1.76-2.82)
laquinimod vs BG-12 bd	1.53*	(1.24-1.91)	1.64*	(1.25-2.15)	1.53*	(1.24-1.91)
laquinimod vs BG-12 tds	1.53*	(1.23-1.90)	1.49*	(1.94-1.14)	1.53*	(1.23-1.90)
laquinimod vs Alemtuzumab	2.50*	(1.98-3.16)	-	-	2.50*	(1.98-3.16)
BG-12 bd vs BG-12 tds	1.00	(0.83-1.19)	0.91	(1.16-0.70)	1.00	(0.83-1.19)
BG-12 bd vs Alemtuzumab	1.63*	(1.29-2.05)	1.81	(1.41-2.97)	1.63*	(1.29-2.05)
BG-12 tds vs Alemtuzumab	1.63*	(1.29-2.05)	-	-	1.63*	(1.29-2.05)

Appendix 8e) – WinBUGs Code and Data

WinBUGs Code

i) ARR Model

```
model{
for (i in 1:ns){
        delta[i,bi[i]] <- 0
        mu[i] ~ dnorm(m[bi[i]],tau)
        for (k in 1:na[i]){
                y[i,k] ~ dpois(lambda[i,k])
                lambda[i,k] <- pt[i,k]*p[i,k]
                log(p[i,k]) <- mu[i] + delta[i,t[i,k]]
                }
        for (k in 2:noT[i]){
                delta[i,si[i,k]] <- d[si[i,k]] - d[bi[i]]
                }
        }
d[1]<-0
tau<-1/var
var<-pow(sd,2)
sd ~ dunif(0,7)
for (k in 1:nb){m[ub[k]]~dnorm(0,0.0001)}
for (k in 2:nt){ d[k] ~dnorm(0,0.0001)}
for (c in 1:(nt-1)) {
        for (k in (c+1):nt){
                IC[c,k] <- d[c] - d[k]
                }}
}
```

ii) Disability Progression Model

```
model{
for (i in 1:ns){
        delta[i,bi[i]] <- 0
        mu[i] ~ dnorm(m[bi[i]],tau)
        for (k in 1:na[i]){
                r[i,k] ~ dbin(p[i,k],n[i,k])
                p[i,k] <- 1- exp(-w[i]*exp(loga[i,k]))
                loga[i,k] <- mu[i] + delta[i,t[i,k]]
                rhat[i,k] <- p[i,k]*n[i,k]
                }
        for (k in 2:noT[i]) {
                delta[i,si[i,k]] <- d[si[i,k]] - d[bi[i]]
                }
        }
        for (k in 2:nt) {av[k] <- d[k] + m[1]}
        d[1] <- 0
```

```
        tau<-1/var
        var<-pow(sd,2)
        sd ~ dunif(0,2)
        for(i in 1: nb){m[ub[i]] ~ dnorm(0,.0001)}
        for (k in 2:nt){d[k] ~ dnorm(0,0.0001) }
        for (c in 1:(nt-1)) {
                for (k in (c+1):nt) {
                        lHRR[c,k] <- d[c]-d[k]}}
}
```

Input Data

i) ARR Model

list(y= structure(.Data= c(2.66000E+02, 1.73000E+02, NA, NA, 2.10000E+02, 1.61000E+02, NA, NA, 2.49650E+02, 2.19340E+02, NA, NA, 4.77410E+02, 3.43040E+02, 3.17450E+02, NA, 9.12000E+01, 6.06900E+01, NA, NA, 5.38740E+02, 3.07740E+02, NA, NA, 2.06000E+02, 8.60000E+01, 1.01000E+02, NA, 1.79000E+02, 1.05000E+02, 8.90000E+01, NA, 3.65180E+02, 2.53280E+02, 2.45620E+02, NA, 2.67500E+01, 1.04600E+01, 1.31300E+01, NA, 3.74210E+02, 2.92330E+02, NA, NA, 2.38960E+02, 1.13470E+02, 1.26510E+02, NA), .Dim=c(12, 4)), pt= structure(.Data= c(2.09450E+02, 2.05950E+02, NA, NA, 2.50000E+02, 2.72880E+02, NA, NA, 3.04450E+02, 3.27380E+02, NA, NA, 3.63000E+02, 3.65000E+02, 3.62010E+02, NA, 7.53700E+01, 7.49300E+01, NA, NA, 7.38000E+02, 1.33800E+03, NA, NA, 5.15000E+02, 5.37500E+02, 5.61110E+02, NA, 5.42420E+02, 5.25000E+02, 5.56250E+02, NA, 6.76260E+02, 6.84540E+02, 6.63830E+02, NA, 2.70200E+01, 2.55200E+01, 2.62700E+01, NA, 9.59510E+02, 9.74450E+02, NA, NA, 6.56490E+02, 6.59710E+02, 6.69360E+02, NA), .Dim=c(12, 4)), nt=1.40000E+01, ns=1.20000E+01, na=c(2, 2, 2, 3, 2, 2, 3, 3, 3, 3, 2, 3), bi=c(1, 1, 1, 1, 1, 1, 1, 2, 1, 1, 1, 1), si= structure(.Data= c(NA, 6, NA, NA, 3, NA, NA, 2, NA, NA, 4, 5, NA, 3, NA, NA, 7, NA, NA, 8, 9, NA, 8, 9, NA, 1.00000E+01, 1.10000E+01, NA, 8, 9, NA, 1.20000E+01, NA, NA, 1.30000E+01, 1.40000E+01), .Dim=c(12, 3)), t= structure(.Data= c(1, 6, NA, NA, 1, 3, NA, NA, 1, 2, NA, NA, 1, 4, 5, NA, 1, 3, NA, NA, 1, 7, NA, NA, 1, 8, 9, NA, 2, 8, 9, NA, 1, 1.00000E+01, 1.10000E+01, NA, 1, 8, 9, NA, 1, 1.20000E+01, NA, NA, 1, 1.30000E+01, 1.40000E+01, NA), .Dim=c(12, 4)), noT=c(2, 2, 2, 3, 2, 2, 3, 3, 3, 3, 2, 3), ub=c(1, 2), nb=2)

ii) Disability Progression Model

list(r= structure(.Data= c(3.37300E+01, 2.50000E+01, NA, NA, 3.10000E+01, 2.70000E+01, NA, NA, 6.98900E+01, 5.60800E+01, 4.84900E+01, NA, 4.90000E+01, 4.30000E+01, NA, NA, 9.13500E+01, 1.06590E+02, NA, NA, 3.63000E+01, 3.06400E+01, NA, NA, 8.96000E+01, 1.88370E+02, NA, NA, 1.00740E+02, 7.12100E+01, 7.52300E+01, NA, 3.40500E+01, 2.85400E+01, 2.53100E+01, NA, 9.91000E+01, 7.92100E+01, 7.23200E+01, NA, 8.72900E+01, 6.10500E+01, NA, NA, 1.10160E+02, 6.56000E+01, 7.48800E+01, NA, 6.17100E+01, 5.60000E+01, 4.66700E+01, 4.48500E+01), .Dim=c(13, 4)), n= structure(.Data= c(1.23000E+02, 1.24000E+02, NA, NA, 1.26000E+02,

1.25000E+02, NA, NA, 1.87000E+02, 1.89000E+02, 1.84000E+02, NA, 3.38000E+02, 3.39000E+02, NA, NA, 3.15000E+02, 6.27000E+02, NA, NA, 1.11000E+02, 2.22000E+02, NA, NA, 4.48000E+02, 8.97000E+02, NA, NA, 4.18000E+02, 4.29000E+02, 4.25000E+02, NA, 4.31000E+02, 4.26000E+02, 4.29000E+02, NA, 3.63000E+02, 3.65000E+02, 3.58000E+02, NA, 5.56000E+02, 5.50000E+02, NA, NA, 4.08000E+02, 4.10000E+02, 4.16000E+02, NA, 3.63000E+02, 3.50000E+02, 3.59000E+02, 3.45000E+02), .Dim=c(13, 4)), t= structure(.Data= c(1, 6, NA, NA, 1, 3, NA, NA, 1, 4, 5, NA, 2, 5, NA, NA, 1, 7, NA, NA, 5, 1.50000E+01, NA, NA, 3, 6, NA, NA, 1, 8, 9, NA, 2, 8, 9, NA, 1, 1.00000E+01, 1.10000E+01, NA, 1, 1.20000E+01, NA, NA, 1, 1.30000E+01, 1.40000E+01, NA, 1, 3, 1.30000E+01, 1.40000E+01), .Dim=c(13, 4)), na=c(2, 2, 3, 2, 2, 2, 2, 3, 3, 3, 2, 3, 4), nt=1.50000E+01, ns=1.30000E+01, bi=c(1, 1, 1, 2, 1, 5, 3, 1, 2, 1, 1, 1, 1), si= structure(.Data= c(NA, 6, NA, NA, NA, 3, NA, NA, NA, 4, 5, NA, NA, 5, NA, NA, NA, 7, NA, NA, NA, 1.50000E+01, NA, NA, NA, 6, NA, NA, NA, 8, 9, NA, NA, 8, 9, NA, NA, 1.00000E+01, 1.10000E+01, NA, NA, 1.20000E+01, NA, NA, NA, 1.30000E+01, 1.40000E+01, NA, NA, 3, 1.30000E+01, 1.40000E+01), .Dim=c(13, 4)), w=c(2, 2, 2, 1, 2, 2, 2, 2, 1, 2, 2, 2, 2), nb=4, ub=c(1, 2, 5, 3), noT=c(2, 2, 3, 2, 2, 2, 2, 3, 3, 3, 2, 3, 4))

Appendix 9 – Analysis of natural history of MS relapses data

R Syntax for estimation of relapse rate for each EDSS state

```
tm<-z[1:10,2:11]
names(tm)<-1:10

NumYrs=50
SizeOfSim=10000
MxSimVals=matrix(rep(NA,NumYrs*SizeOfSim),
     ncol=SizeOfSim)

MxSimVals[1,]=as.numeric(rMultinom(tm,SizeOfSim)[1,]) #tm=EDSS state transition
matrix#
for(idx in 2:NumYrs){
 tmx<-as.numeric(rMultinom(tm,SizeOfSim))
 MxSimVals[idx,]=tmx[((1:SizeOfSim)-1)*10+MxSimVals[idx-1,]]
}

MxLambda=matrix(rep(x$ARR,SizeOfSim),ncol=SizeOfSim)
MxRelapses=matrix(rpois(NumYrs*SizeOfSim,lambda=MxLambda),ncol=SizeOfSim)

AvgRRbyState<-rep(NA,10)

for(idxS in 1:10){
StateV=idxS
myT=table(MxRelapses[which(MxSimVals==StateV)])
AvgRRbyState[idxS]=sum(myT[1:length(myT)]*as.integer(names(myT)))/sum(myT)
}
AvgRRbyState
```

Appendix 10 – Additional CEA Results from Chapter 8

Additional scatterplot and CEACs from the societal perspective

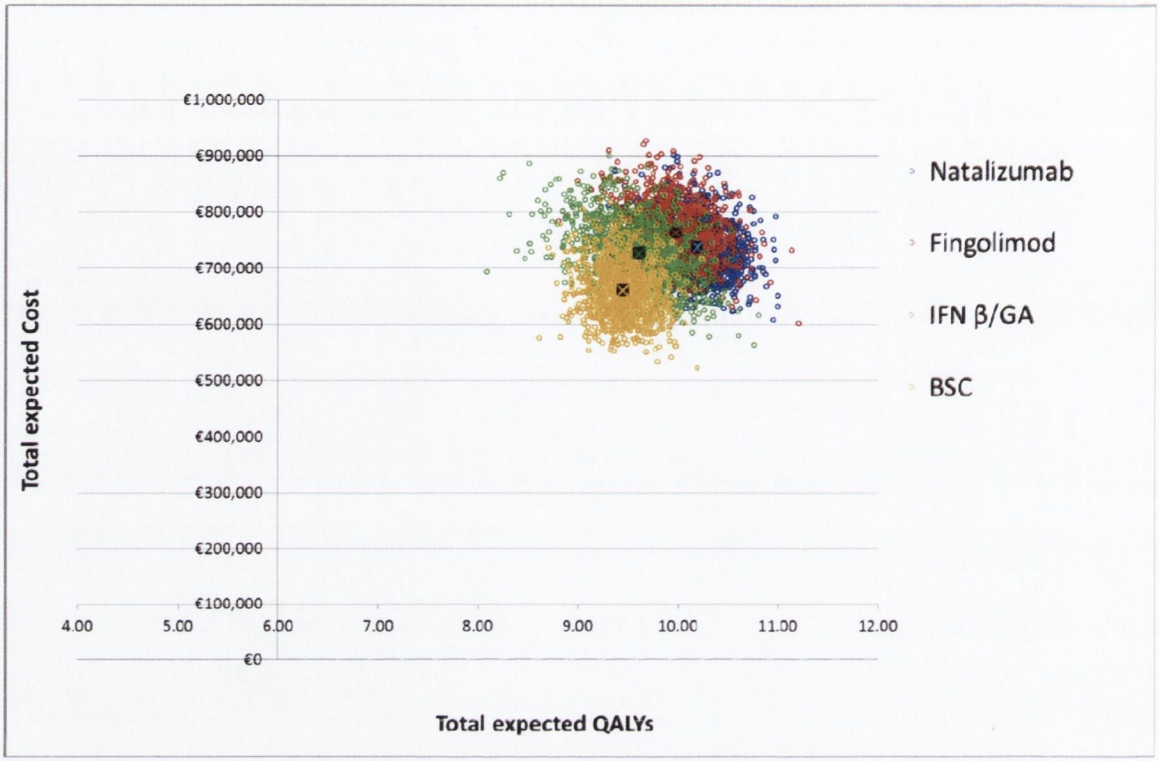


Figure A10.1 Scatterplot of Total Expected Costs and QALYs

Costs are in €2012. Each dot represents the costs and QALs estimated by each of 1000 iterations of the analysis. The black markers on the scatters indicate the mean cost per QALY.
Abbreviations: BSC=best supportive care. QALY=quality adjusted life year.

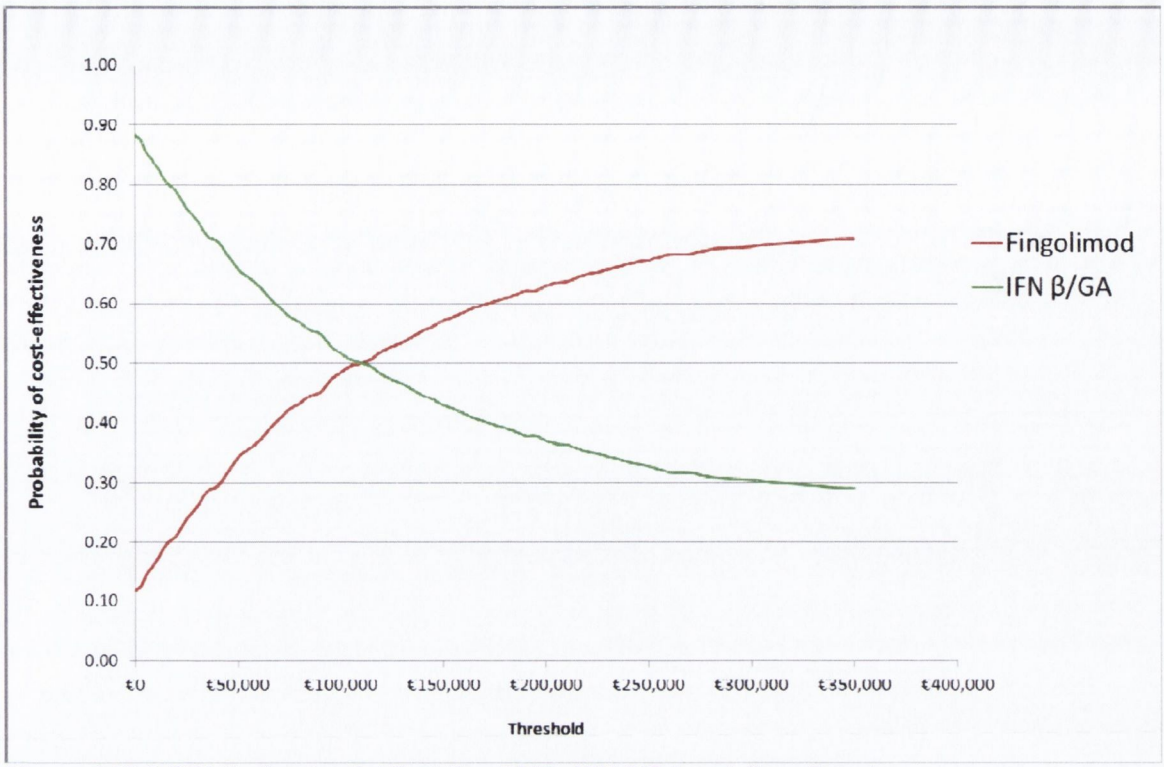


Figure A10.2 CEAC of potential first-line DMTs IFN β/GA and fingolimod

Costs are in €2012.IFN ß/GA=weighted average of interferon beta and glatiramer acetate products.

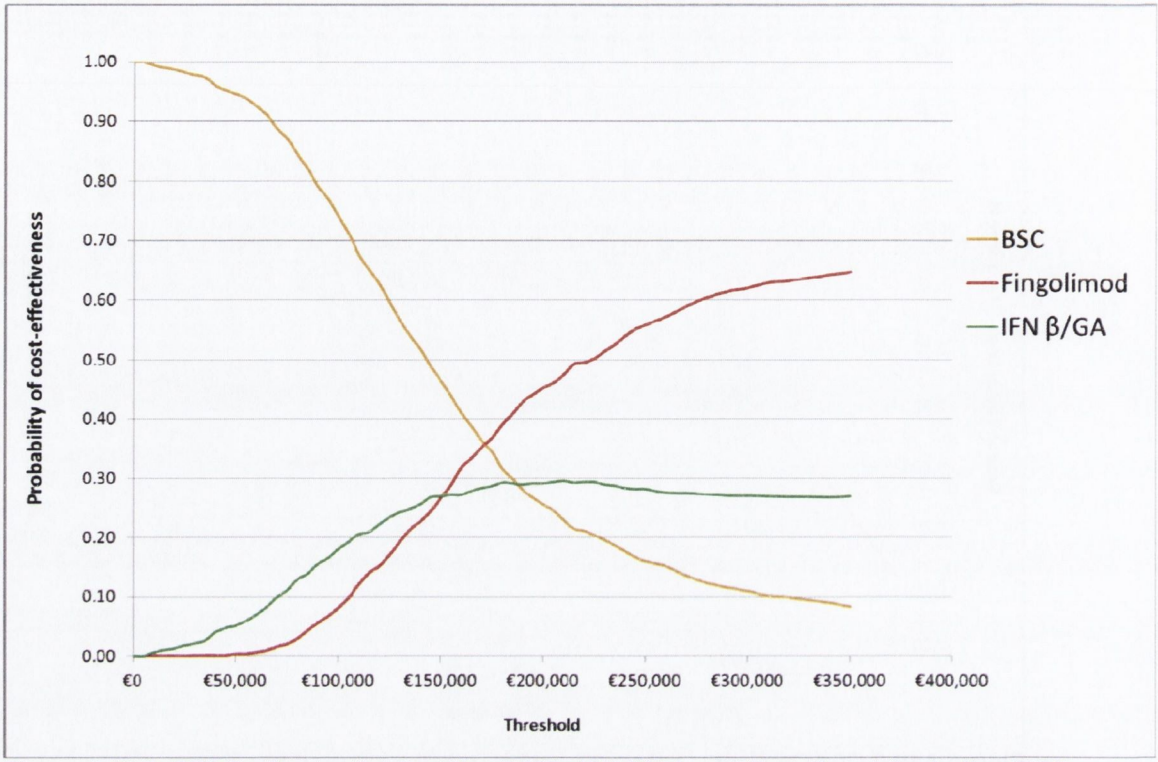


Figure A10.3 CEAC of potential first-line DMTs IFN β/GA and fingolimod (including BSC alone)

Costs are in €2012. IFN ß/GA=weighted average of interferon beta and glatiramer acetate products. BSC=best supportive care.

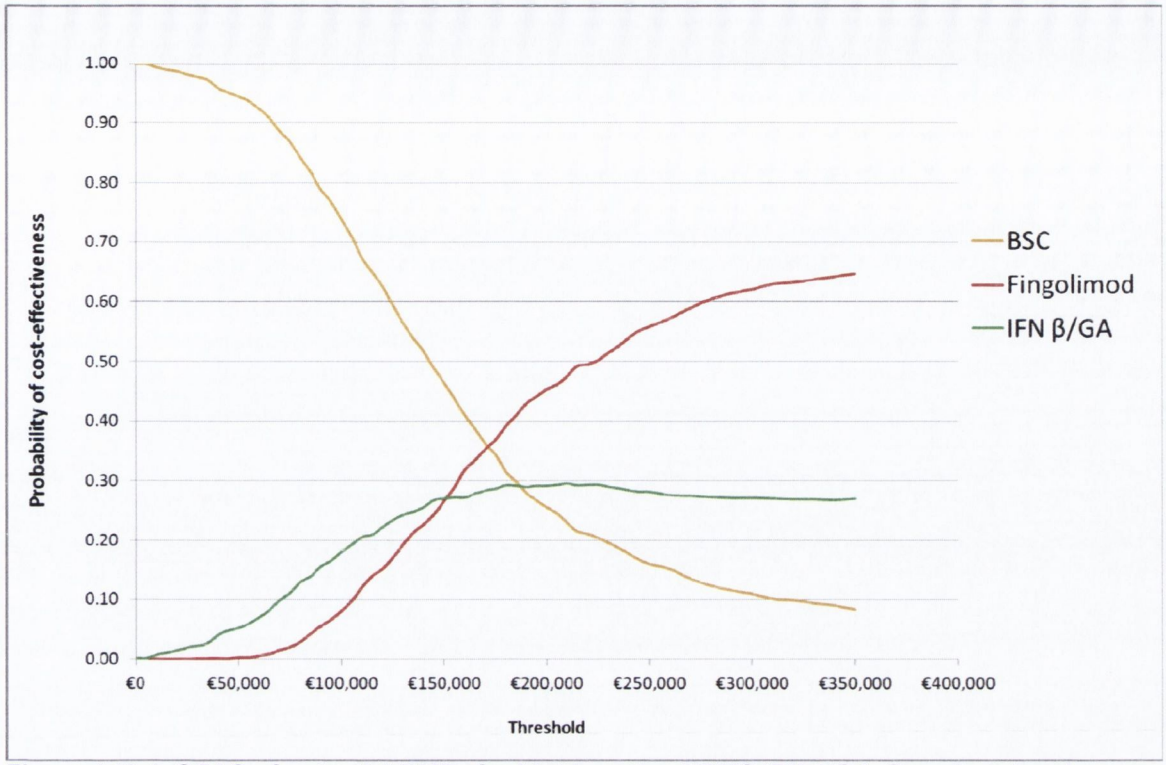


Figure A10.4 CEAC of potential DMTs for highly-active RRMS IFN β/GA, fingolimod and natalizumab.

Costs are in €2012. IFN ß/GA=weighted average of interferon beta and glatiramer acetate products.

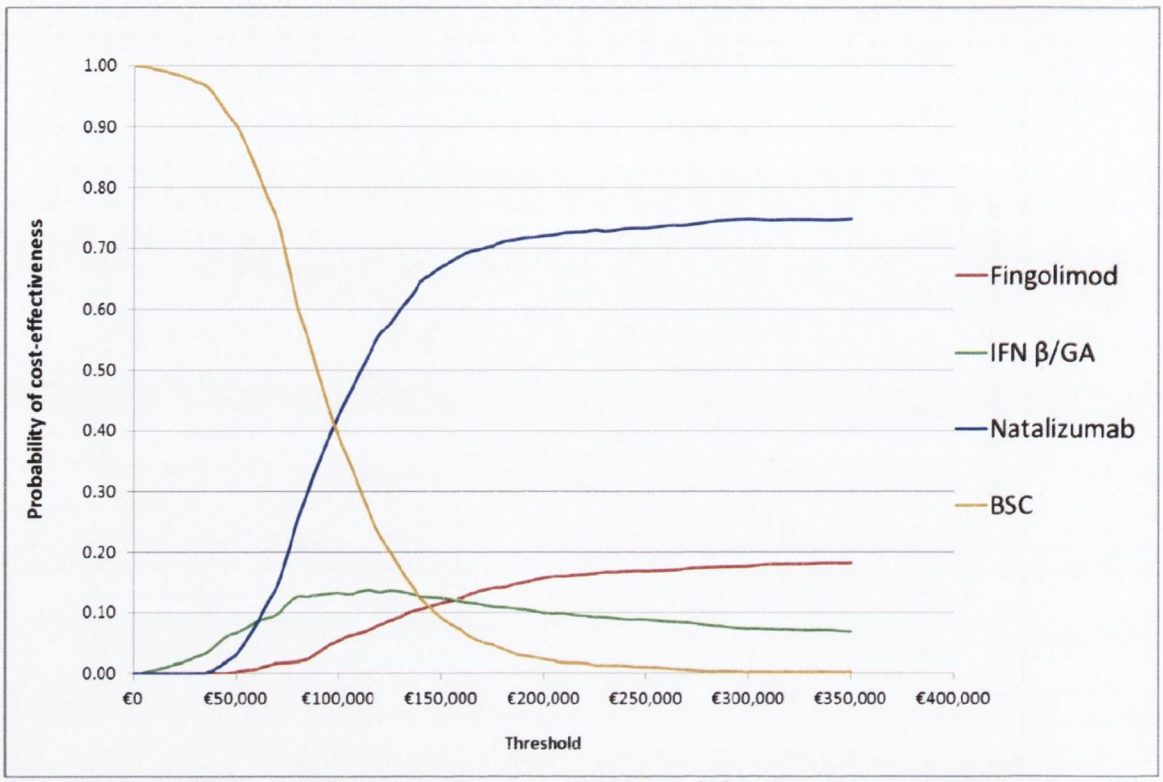


Figure A10.5 CEAC of DMTs for highly-active RRMS IFN β/GA, fingolimod, natalizumab (including BSC alone).

Costs are in €2012. IFN ß/GA=weighted average of interferon beta and glatiramer acetate products. BSC=best supportive care.

Additional results of deterministic sensitivity analysis for comparisons of natalizumab and fingolimod versus IFN β/GA , from the societal perspective, and versus BSC from healthcare payer and societal perspectives

Table A10.1 Deterministic Sensitivity Analysis Results (treatments versus BSC from the healthcare payer perspective)

	Natalizumab Mean ICER **Fingolimod Mean ICER**	**€148,713** **€231,797**	**Natalizumab**		**Fingolimod**	
	Parameter	**Mean/Basecase assumption (range/alternative assumption)**	**Low**	**High**	**Low**	**High**
Hazard Ratio of disability progression	Natalizumab	0.55 (0.42 - 0.73)	€100,400	€346,544	NA	NA
	Fingolimod	0.66 (0.50 - 0.86)	NA	NA	€129,095	€1,525,251
	IFN B/GA	0.81 (0.59 - 1.10)	NA	NA	NA	NA
Relative Risk of Relapse	Natalizumab	0.31 (0.27 - 0.36)	€148,230	€149,269	NA	NA
	Fingolimod	0.44 (0.37 - 0.53)			€230,197	€233,725
	IFN B/GA	0.72 (0.64 - 0.85)	NA	NA	NA	NA
Risk of Discontinuation Year 0/1	Natalizumab	0.116 (0.110 - 0.122)	€147,824	€149,639	NA	NA
	Fingolimod	0.098 (0.093 - 0.103)	NA	NA	€229,949	€233,720
	IFN B/GA	0.1 (0.095 - 0.105)	NA	NA	NA	NA
Risk of Discontinuation Year ≥2	Natalizumab	0.058 (0.055 - 0.060)	€148,017	€149,439	NA	NA
	Fingolimod	0.058 (0.055 - 0.060)	NA	NA	€229,543	€234,096
	IFN B/GA	0.058 (0.055 - 0.060)	NA	NA	NA	NA
Other Parameters	Health State Costs	10 parameters changed (see Table 8.2)	€165,656	€126,836	€249,135	€209,416
	Health State Utilities	10 parameters changed (see Table 8.2)	€141,951	€155,339	€221,139	€242,054
	Baseline risk of relapse	10 parameters changed (see Table 8.2)	€148,958	€148,469	€232,183	€231,412
	Baseline rate of disability progression	4 parameters changed (see Table 8.2)	€169,569	€131,239	€259,980	€208,410
	Relapse Cost	€2535(€865 - €4204)	€150,272	€147,154	€233,621	€229,974
	Relapse Disutility	0.22 (0.198-0.242)	€149,099	€148,329	€232,501	€231,098
	Risk of Conversion	0.045 (0.041 - 0.049)	€150,955	€146,958	€238,193	€226,719

Table A10.1 Deterministic Sensitivity Analysis Results (treatments versus BSC from the healthcare payer perspective)

	Natalizumab Mean ICER	**€148,713**	**Natalizumab**		**Fingolimod**	
	Fingolimod Mean ICER	**€231,797**				
	Parameter	**Mean/Basecase assumption (range/alternative assumption)**	**Low**	**High**	**Low**	**High**
Drug Cost	Natalizumab	+/- 20%	€109,981	€187,446	NA	NA
	Fingolimod	+/- 20%	NA	NA	€176,154	€287,441
	IFN B/GA	+/- 20%	NA	NA	NA	NA
Other Parameters	Age	42 years (37-47 years)	€132,284	€169,618	€210,610	€259,223
	Discount Rate	4% (0%-6%)	€70,364	€196,065	€121,064	€298,285
			Alt.1	**Alt.2**	**Alt.1**	**Alt.2**
	Time horizon*	50 years (10 years - 20 years)	€556,957	€246,261	€800,494	€365,207
	Standardised mortality ratio*	Disabilty related, 1.60-4.44 (non-disability related, 2.89)	€151,181	-	€239,408	-
	IFN B/GA Disutility*	none (0.05 for first 6 months)	NA	-	NA	-
	Duration of treatment efficacy*	indefinite (50% reduction after 5 years)	€228,610	-	€364,880	-
	Source of baseline relapse data*	Tremlett et al (Patzold *et al* - Confavreux *et al*)	€133,622	€137,997	€208,657	€215,521

*Parameters denoted with an asterisk (*) are changed to reflect alternative scenarios/assumptions and are not necessarily representative of "low" or "high" alternatives.

Dominated=more costly and less effective. Dominant=less costly and more effective.

Abbreviations: Alt=alternative; IFN ß/GA=weighted average of interferon beta and glatiramer acetate products; ICER=incremental cost-effectiveness ratio (euros per QALY)

Table A10.2 Deterministic Sensitivity Analysis Results (treatments versus IFN β/GA from the societal perspective)

	Natalizumab Mean ICER	**€22,949**	**Natalizumab**		**Fingolimod**	
	Fingolimod Mean ICER	**€107,785**				
	Parameter	**Mean/Basecase assumption (range/alternative assumption)**	**Low**	**High**	**Low**	**High**
Hazard Ratio of disability progression	Natalizumab	0.55 (0.42 - 0.73)	Dominant	€272,812	NA	NA
	Fingolimod	0.66 (0.50 - 0.86)	NA	NA	€12,150	Dominated
	IFN B/GA	0.81 (0.59 - 1.10)	€704,364	Dominant	Dominated	Dominant
Relative Risk of Relapse	Natalizumab	0.31 (0.27 - 0.36)	€22,640	€23,305	NA	NA
	Fingolimod	0.44 (0.37 - 0.53)	NA	NA	€106,267	€109,626
	IFN B/GA	0.72 (0.64 - 0.85)	€23,515	€22,326	€109,348	€106,076
Risk of Discontinuation Year 0/1	Natalizumab	0.116 (0.110 - 0.122)	€24,420	€21,391	NA	NA
	Fingolimod	0.098 (0.093 - 0.103)	NA	NA	€107,787	€107,784
	IFN B/GA	0.1 (0.095 - 0.105)	€22,064	€23,798	€108,465	€107,143
Risk of Discontinuation Year ≥2	Natalizumab	0.058 (0.055 - 0.060)	€25,515	€20,403	NA	NA
	Fingolimod	0.058 (0.055 - 0.060)	NA	NA	€108,838	€106,770
	IFN B/GA	0.058 (0.055 - 0.060)	€21,462	€24,267	€108,380	€107,234
Other Parameters	Health State Costs	10 parameters changed (see Table 8.2)	€44,747	-€3,109	€128,863	€82,518
	Health State Utilities	10 parameters changed (see Table 8.2)	€21,914	€23,978	€102,864	€112,588
	Baseline risk of relapse	10 parameters changed (see Table 8.2)	€23,037	€22,861	€107,962	€107,608
	Baseline rate of disability progression	4 parameters changed (see Table 8.2)	€33,731	€13,827	€126,361	€92,317
	Relapse Cost	€2535(€865 - €4204)	€24,125	€21,774	€109,146	€106,425
	Relapse Disutility	0.22 (0.198-0.242)	€22,994	€22,904	€108,029	€107,542
	Risk of Conversion	0.045 (0.041 - 0.049)	€20,566	€25,146	€104,385	€110,882
Drug Cost	Natalizumab	+/- 20%	-€29,096	€74,994	NA	NA
	Fingolimod	+/- 20%	NA	NA	€21,892	€193,678

Table A10.2 Deterministic Sensitivity Analysis Results (treatments versus IFN β/GA from the societal perspective)

	Natalizumab Mean ICER	**€22,949**	**Natalizumab**		**Fingolimod**	
	Fingolimod Mean ICER	**€107,785**				
	Parameter	**Mean/Basecase assumption (range/alternative assumption)**	**Low**	**High**	**Low**	**High**
	IFN B/GA	+/- 20%	€51,354	-€6,991	€152,714	€60,428
Other Parameters	Age	42 years (37-47 years)	€11,433	€36,863	€91,158	€128,683
	Discount Rate	4% (0%-6%)	-€9,297	€45,449	€42,363	€150,043
			Alt.1	**Alt.2**	**Alt.1**	**Alt.2**
	Time horizon*	50 years (10 years - 20 years)	€233,796	€60,812	€487,594	€184,958
	Standardised mortality ratio*	Disabilty related, 1.60-4.44 (non-disability related, 2.89)	€7,630	-	€98,187	-
	IFN B/GA Disutility*	none (0.05 for first 6 months)	€21,959	-	€100,613	-
	Duration of treatment efficacy*	indefinite (50% reduction after 5 years)	€55,008	-	€168,036	-
	Source of baseline relapse data*	Tremlett et al (Patzold *et al* - Confavreux *et al*)	€17,218	€18,780	€96,520	€99,680

*Parameters denoted with an asterisk (*) are changed to reflect alternative scenarios/assumptions and are not necessarily representative of "low" or "high" alternatives.

Dominated=more costly and less effective. Dominant=less costly and more effective.

Abbreviations: Alt=alternative; IFN ß/GA=weighted average of interferon beta and glatiramer acetate products; ICER=incremental cost-effectiveness ratio (euros per QALY)

Table A10.3 Deterministic Sensitivity Analysis Results (treatments versus BSC from the societal perspective)

	Natalizumab Mean ICER **Fingolimod Mean ICER**	**€101,537** **€186,111**	**Natalizumab**		**Fingolimod**	
	Parameter	**Mean/Basecase assumption (range/alternative assumption)**	**Low**	**High**	**Low**	**High**
Hazard Ratio of disability progression	Natalizumab	0.55 (0.42 - 0.73)	€51,082	€303,338	NA	NA
	Fingolimod	0.66 (0.50 - 0.86)	NA	NA	€80,734	€1,490,733
	IFN B/GA	0.81 (0.59 - 1.10)	NA	NA	NA	NA
Relative Risk of Relapse	Natalizumab	0.31 (0.27 - 0.36)	€101,149	€101,983	NA	NA
	Fingolimod	0.44 (0.37 - 0.53)	NA	NA	€184,737	€187,767
	IFN B/GA	0.72 (0.64 - 0.85)	NA	NA	NA	NA
Risk of Discontinuation Year 0/1	Natalizumab	0.116 (0.110 - 0.122)	€100,617	€102,495	NA	NA
	Fingolimod	0.098 (0.093 - 0.103)	NA	NA	€184,207	€188,092
	IFN B/GA	0.1 (0.095 - 0.105)	NA	NA	NA	NA
Risk of Discontinuation Year ≥2	Natalizumab	0.058 (0.055 - 0.060)	€101,043	€102,073	NA	NA
	Fingolimod	0.058 (0.055 - 0.060)	NA	NA	€184,087	€188,194
	IFN B/GA	0.058 (0.055 - 0.060)	NA	NA	NA	NA
Other Parameters	Health State Costs	10 parameters changed (see Table 8.2)	€122,509	€76,492	€206,306	€161,961
	Health State Utilities	10 parameters changed (see Table 8.2)	€96,920	€106,061	€177,554	€194,347
	Baseline risk of relapse	10 parameters changed (see Table 8.2)	€101,734	€101,340	€186,442	€185,781
	Baseline rate of disability progression	4 parameters changed (see Table 8.2)	€119,728	€86,378	€211,663	€165,000
	Relapse Cost	€2535(€865 - €4204)	€103,096	€99,978	€187,935	€184,288
	Relapse Disutility	0.22 (0.198-0.242)	€101,800	€101,275	€186,676	€185,550
	Risk of Conversion	0.045 (0.041 - 0.049)	€103,476	€100,069	€192,176	€181,351
Drug Cost	Natalizumab	+/- 20%	€62,804	€140,269	NA	NA
	Fingolimod	+/- 20%	NA	NA	€130,468	€241,755

Table A10.3 Deterministic Sensitivity Analysis Results (treatments versus BSC from the societal perspective)

	Natalizumab Mean ICER **Fingolimod Mean ICER**	**€101,537** **€186,111**	**Natalizumab**		**Fingolimod**	
	Parameter	**Mean/Basecase assumption (range/alternative assumption)**	**Low**	**High**	**Low**	**High**
	IFN B/GA	+/- 20%	NA	NA	NA	NA
Other Parameters	Age	42 years (37-47 years)	€85,279	€121,961	€164,999	€213,176
	Discount Rate	4% (0%-6%)	€37,811	€142,877	€89,864	€246,651
			Alt.1	**Alt.2**	**Alt.1**	**Alt.2**
	Time horizon*	50 years (10 years - 20 years)	€471,848	€176,077	€716,915	€297,001
	Standardised mortality ratio*	Disabilty related, 1.60-4.44 (non-disability related, 2.89)	€91,809	-	€181,635	-
	IFN B/GA Disutility*	none (0.05 for first 6 months)	NA	-	NA	-
	Duration of treatment efficacy*	indefinite (50% reduction after 5 years)	€180,532	-	€317,437	-
	Source of baseline relapse data*	Tremlett et al (Patzold *et al* - Confavreux *et al*)	€89,410	€92,926	€166,241	€172,135

*Parameters denoted with an asterisk (*) are changed to reflect alternative scenarios/assumptions and are not necessarily representative of "low" or "high" alternatives.

Dominated=more costly and less effective. Dominant=less costly and more effective.

Abbreviations: Alt=alternative; IFN ß/GA=weighted average of interferon beta and glatiramer acetate products; ICER=incremental cost-effectiveness ratio (euros per QALY)

SUMMARY

This study aimed to evaluate the economic and health-related quality of life (HRQoL) burden of multiple sclerosis (MS) in Ireland, and to develop a framework for assessing the cost effectiveness of disease-modifying therapies (DMT). In achieving these aims, a cost-of-illness (CoI) study estimated the direct and indirect costs of MS from the Irish healthcare payer and societal perspectives; the relationship between MS disability and HRQoL was explored; and the relative efficacy of DMT was assessed by network meta-analysis (NMA). Each of these elements was integrated into a decision-analytic model which was developed to estimate the cost effectiveness of DMT in Ireland.

The CoI study established MS as a high cost therapeutic area with significant economic implications for the Irish healthcare system, individual patients and society as a whole. The mean annual direct (indirect) costs per person were approximately €10,000 (€9,500), €13,000 (€32,000) and €56,500 (€39,500) in mild, moderate and severe MS respectively. Progression from mild or moderate to severe disease was associated with the greatest economic consequences for the healthcare payer.

In its first reported use in an MS population, the five-level Euroqol-5D (EQ-5D-5L) displayed an inverse relationship with MS disability (measured on the EDSS scale). A linear decline in utility was observed as EDSS progresses from 0 to 6, followed by sharp declines in utility, falling below 0 at EDSS 8 and 9.

A systematic review identified twenty randomised, placebo-controlled and direct comparative trials of DMTs in relapsing-remitting MS, including interferon-beta, glatiramer-acetate, natalizumab, alemtuzumab, fingolimod, teriflunomide, laquinimod, and BG-12. An NMA was conducted to determine the relative efficacy of DMTs in reducing relapses and slowing short-term progression of disability. All DMTs were significantly superior to placebo in reducing relapse rates with many newer agents demonstrating significant improvements in efficacy compared with older DMTs. Significant benefits in reducing short-term disability progression compared with no treatment were limited to the newer DMTs. The analysis found little to distinguish the effects of different DMTs on short-term disability progression, with the exception of alemtuzumab which was superior to other comparators.

Health state costs and utility values estimated from the CoI and HRQoL studies, and treatment efficacy estimates from the NMA informed a decision-model of DMT for RRMS in Ireland. Analysis revealed that from the healthcare payer perspective, the

probability that fingolimod or natalizumab is cost-effective compared with current standard-of-care at a threshold of €45,000 per QALY is very low (10% and 27%, respectively). DMTs accounted for a substantial proportion of lifetime healthcare costs, while yielding less than one additional QALY. The primary economic benefit of DMT arose from delaying disability progression. A fully incremental analysis revealed best-supportive care (no treatment) as the appropriate comparator for new DMTs, as the existing standard-of-care (represented by a weighted average of interferon β and glatiramer acetate) is extendedly dominated. The price at which existing and new DMTs entering the market would be considered cost-effective compared with current standard-of-care, based on current evidence and model assumptions, was estimated. Price reductions of 12% and 27% were estimated for natalizumab and fingolimod respectively.

Limitations of the CoI and HRQoL study include the recruitment of patients from one specialist MS outpatient clinic. Extension of these studies to a wider population of patients with MS in Ireland would further enhance the reliability of the findings. The definition of disability progression was identified as a key determinant of relative efficacy in the NMA. The inclusion of trials which defined disability progression on the basis of a 6-month confirmation interval (as opposed to a 3-month interval used in the base case) had a substantial favourable impact on the efficacy versus placebo of the older agents and a slight negative impact on alemtuzumab. Key areas of uncertainty in the decision-model included lack of evidence on the long-term efficacy of various DMTs.. The decision-model does not account for sequential use of DMTs which would more accurately reflect current practice and which necessitates evidence on the efficacy of second-line therapy following failure on first-line agents. Aggregated data on the natural history of MS was used in the model whereas patient-level data would have enhanced the reliability of individual estimates and allowed analysis in subgroups of interest.

The findings of this study present numerous issues for consideration by decision-makers. Based on the inputs and assumptions applied in the decision model, the prices at which DMTs are currently reimbursed are not cost-effective. It is essential that future therapies, which may not offer incremental benefits in terms of efficacy or other measure of innovation, are reimbursed at a price which represents value for money, at least over current "standard-of-care".