COST-UTILITY ANALYSIS OF INTERFERON β-1B IN THE TREATMENT OF DIFFERENT TYPES OF MULTIPLE SCLEROSIS

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SSE/EFI Working Paper Series in Economics and Finance No. 459

ABSTRACT

Background

Economic evaluation of treatments in multiple sclerosis (MS) presents a challenge. The disease affects a number of different body functions and leads to severe disability over time, without however a strong effect on mortality. At onset, the majority of patients will have relapsing-remitting disease (RRMS) and will then convert to secondary-progressive disease (SPMS) overtime. However, the course of the disease is unpredictable, and the conversion to SPMS can take place at different times since onset and at different levels of disability for different patients. Relapses appear to occur with the same frequency at all levels of disability, but will diminish over time. The effectiveness of treatments can be measured in different ways such as disease activity, the number and the severity of relapses or the progression of functional disability, regardless of the type of MS.

However, improvements in outcome achieved over a short term may have an effect on the disease in the longer term, and effectiveness data from clinical trials must therefore be extrapolated to the longer term, using modelling techniques. This requires good epidemiological data on the natural course of the disease, where disease progression is expressed with the same measures as in the clinical trials. Also to perform economic evaluations, a global outcome measure is required to capture the impact of treatments on the disease and the most frequently used such measure is quality-adjusted life years (QALYs). However, for QALYs to be used in cost-effectiveness analysis of MS, they must be related to a measure of the disease and disease progression. The Expanded Disability Status Scale (EDSS) provides a good measure of the disease and has been widely used in epidemiological studies and clinical trials, in all types of MS. Lastly, detailed economic data that can be related to the different levels of disability (EDSS) are required.

Objective

We have earlier proposed a basic framework for cost-effectiveness modelling in MS, and the original model has been updated, as new data have become available. The current study proposes a further development of the modelling technique and estimates the cost-effectiveness of treatment with interferon β-1b (IFNB-1b) in a defined patient population with active disease, both RRMS and SPMS, from a societal perspective in Sweden.

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Methods

The framework of the earlier Markov model is used, where states are defined according to EDSS. Transition probabilities for the first years in the model are calculated from clinical trial data, and for the extrapolation from a large epidemiological database on the natural history of MS. In view of the fact that the number of relapses at given levels of disability did not differ between patients with RRMS or SPMS in any of the three datasets used in this analysis, and that conversion from RRMS to SPMS did not occur at well defined levels of disability, we combined data from two large clinical trials in RRMS and SPMS. Patients were selected on whether or not they had active disease at enrolment, defined as an increase in the EDSS by at least 1 point (0.5 points for scores between EDSS 6 and 7) or at least 2 relapses in the preceding 2 years. This allows simulating treatment start at any stage and for any type of the disease and estimating long-term consequences within the same model. The combination of the two types of MS is further supported by the fact that it has been shown in 3 observational studies that costs and quality of life at given EDSS levels are not different for patients with different types of the disease.

Transition probabilities between the Markov states are estimated for both the clinical trial and the natural history cohorts using an ordered probit model. Transitions thus depend on several factors, including what state a patient is in, whether or not she/he has a relapse, age, age at onset of the disease, time since onset of the disease, age at treatment start.

The base case simulations use mean costs and mean utilities in each state from a large observational study in Sweden. However, the model allows calculating acceptability curves, i.e. the probability with which the cost effectiveness ratio of a treatment scenario is below given levels of willingness-to-pay for a QALY, using the entire distribution of costs and utilities at each EDSS level. Costs and benefits are discounted with 3%.

Results

The base case assumes treatment with IFNB-1b during 36 months, with no further effect when treatment is stopped, and includes both patients with active RRMS and SPMS. Sensitivity analysis is presented for treatment during 54 months. The annual cost of IFNB-1b treatment was 102 587 SEK plus 1600 SEK for special monitoring, and was adjusted for compliance in the clinical trial. In the base-case treatment adds 13 000 to costs over 10 years, and the cost per QALY gained is 71 400 SEK. When the time horizon is increased to 15-25 years, treatment dominates no treatment (higher utility and lower cost). With treatment during 54 months, the cost per QALY is 353 800 SEK, all costs included. When treatment is started early, the cost-effectiveness ratio is higher, e.g. 643 100 SEK in state 2, as patients in these states progress only very slowly.

In the net benefit approach, there is a 80% probability that the treatment initiated in states 3 or 4 (EDSS 4.0-5.5) is cost-effective, if the willingness to pay for a QALY is 400 000 to 600 000 SEK. At that level of willingness to pay, the probability in state 2 is 45%.

Conclusions

With this new model, which combines active RRMS and SPMS, the effect of early treatment on the long-term outcome can be estimated for the first time using patient-level clinical data for RRMS and SPMS, as well as natural history data. The combination of the two types of MS into one model is supported by the finding that, at given levels of EDSS, there was no difference in the number of annual relapses in the three clinical datasets used, nor in the mean cost and mean utilities in the observational study. The model is more flexible than previous models, as it includes individual patient demographics and the entire distribution of costs and utilities in the different states. It thus represents a valuable tool to estimate the cost-effectiveness of treating different patient groups with IFNB-1b.

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1 Introduction

1.1 Background

It is estimated that multiple sclerosis (MS) affects over 1 million people worldwide [1]. In industrialized countries, prevalence rates vary between 15 and 145 per 100'000 [2]. Disease onset is typically between 20 and 40 years of age, with a higher incidence in females, and MS is the most common cause of disability in young adults [3].

The course of the disease is unpredictable, although a high frequency of severe exacerbations in the first two years has been related to a poor prognosis [4]. A majority of patients (~80%) will have relapsing-remitting disease (RRMS) at onset, and a high proportion of these patients will convert to secondary progressive disease (SPMS), with a gradual progression of functional impairment with or without superimposed exacerbations (recurrent relapses). A small proportion of patients (15-20%) will have progressive disease at onset (PPMS).

1.1.1 The challenge to measure effectiveness

At present, the aetiology of the disease is poorly understood and no cure exists. Current treatments focus on reducing and managing exacerbations, and research has focused on treatments that can affect the progression of the disease. Several new treatments have been introduced that have shown an effect on the frequency and severity of exacerbations in RRMS [5-8]. Of the three trials with interferons in progression in SPMS, one has shown a significant effect on disease progression [9], and all three have shown a significant effect on relapses. The effectiveness of these treatments has been measured using several measures of disease activity (relapses, MRI lesions) and progression measured with the Expanded Disability Status Scale (EDSS) [10]. The relationship between relapses during the course of the disease and disease progression is not clear. Similarly, a relationship between disease activity

shown with MRI and disease progression has not yet been established. Exacerbations appear to occur with the same frequency at all levels of disease (i.e. at all EDSS levels). However, they are more frequent in the first years after onset of the disease and then diminish over time, i.e. the number of relapses is influenced by the disease duration rather than by the level of disability, and patients who have had the disease for a longer time appear to have fewer relapses, regardless of the EDSS level. At the same time, relapses can be more frequent in some patients over certain time periods [11 12].

The conversion from RRMS to SPMS is difficult to define with precision, as the transition is gradual and occurs at different levels of disability (EDSS) for different patients. Generally, conversion is considered to take place around EDSS 3.0-4.0, but can be at lower or higher levels as well. In one epidemiological study [13], conversion has been defined as a progression of at least one EDSS point, outside a relapse, confirmed at follow-up with one-year interval. In this database, patients converted to SPMS between EDSS 1.0 and 6.5 (mean 3.0, SD 1.0), 1 to 36 years after onset of the disease (mean 10.7, SD 7.4), between the age of 18 and 86 years (mean 40 years) [14].

1.1.2 Challenges for economic evaluation in MS

The new treatments are more expensive than previously used agents and there has been a concern about rising costs [15]. This raises a number of clinical, ethical and economic questions. Which patients will benefit most from the treatments and which patients should receive the treatment? How can the costs and the benefits of the treatments be balanced? What resources should be allocated to these treatments, considering other uses? These choices are difficult but cannot be avoided. Economic evaluations (cost-effectiveness analyses) attempt to estimate the trade-offs involved and provide information that can support such decisions. They can also inform the public debate about priorities in health care. This is well illustrated in

the current debate in the United Kingdom around the decisions to be made by the National Institute of Clinical Excellence (NICE) [16]. A number of economic evaluations, using different methodological approaches and data, have been performed [17-22] One of the problems is that different studies have come to different conclusions, illustrating the difficulty of cost-effectiveness analysis in MS:

- Which clinical trial data should be used as a basis for assessment of effectiveness? Results may vary between products and trials.
- The progressive and chronic nature of MS, and its unpredictable course, requires modelling to extrapolate from clinical trials to the longer term. This in turn requires good epidemiological data that are not readily available.
- The number of different body functions affected and multitude of symptoms of MS requires a comprehensive outcome measure that incorporates both the disease progression and patients' quality of life over time. Although different clinical outcome measures can be used to illustrate the effect of treatments, the only measure that incorporates all aspects and can therefore be used in economic evaluation is the quality-adjusted life-year (QALY). QALYs incorporate quantity of life (life-years) and adjust these by the quality of life (utility).
- For QALYs to be used in cost-effectiveness analysis of MS, it is however necessary that utilities can be related to a measure of the disease and hence disease progression. The EDSS provides a good measure of the disease, and although it has been argued that the scale focuses too much on ambulation, it has the advantage of being very widely used, both in epidemiological studies and clinical trials. In addition, it is used in all types of MS, providing a common measure for both RRMS and SPMS.
- Lastly, economic evaluations require good economic data that can be related to the different levels of EDSS. A large number of studies of the cost of MS have been published, and many of them have shown that costs are

substantially higher in advanced disease, while QoL is decreased[23-33]. However, only three of these studies have related costs and utilities to EDSS scores rather than to mild, moderate and severe patient groups, and have collected all costs caused by MS rather than only health care costs [31-33].

1.1.3 Development of new models

We have earlier proposed a basic framework for cost-effectiveness modelling in MS [20], using a 3-year clinical trial in SPMS [9]. The basic model has been further developed as new data became available and new knowledge and methods develop. A second version incorporated detailed observational data on costs and utilities by EDSS levels [21], and a third version combined clinical trial and natural history data for the extrapolation beyond the trial [14].

This study proposes a further development of the modelling technique and estimates the cost-effectiveness in a defined patient population with active disease.

1.2 Study Objective

The objective of this study is to estimate the cost per QALY of interferon β-1b (IFNB-1b) in the treatment of RRMS and SPMS, compared to no prophylactic treatment, from a societal perspective in Sweden.

The cost-utility of IFNB-1b may depend on a number of factors that have not previously been included in the models:

- patient characteristics such as gender, age at onset of MS, time since disease onset, disease type, level of disability, age at treatment start, etc
- indication and duration of treatment, i.e. EDSS levels at treatment start, duration of treatment, etc.
- effects/assumptions about the course of events after treatment discontinuation.

Results may further depend on how much costs and utilities vary among patients at the same level of EDSS. Previous versions of the model used mean values for costs and utilities for each Markov state, giving no information on the distribution of the estimates.

The model proposed in this study allows taking all of the different patient variables into account and to use the entire distribution of costs and utilities.

Most importantly, all previous models have been constructed to evaluate treatment of either RRMS or SPMS. In view of the fact that

- the number of relapses does not appear to vary between different EDSS levels or types of MS, but rather depends on the time since onset of disease
- no difference in the number of relapses was found in the three clinical datasets used in this model
- the conversion from RRMS to SPMS is not very well defined and can take place at different levels of EDSS
- the observational studies in Sweden, the UK and Germany have shown that costs and utilities at given EDSS levels are not different between patients with RRMS or SPMS
- there is a continuum between RRMS and SPMS in that SPMS is the long-term outcome of RRMS [34]

we combined data for both types of disease in the model. This allows simulating treatment start at any stage of the disease and following long-term consequences within the same model.

2 Materials and methods

2.1 The model

A Markov simulation model is used to combine the clinical, epidemiological and observational data, and to extrapolate in time beyond the clinical trials. Markov states are defined according to functional disability measured by EDSS. The grouping of EDSS scores into states is done in such a way that it also fits with the DSS (the earlier of the EDSS), as the epidemiological data set used the DSS. This is a change from the previous model in SPMS [14 20 21], where states were defined according to the inclusion criteria in the clinical trials with IFNB-1b, EDSS above 3.0, leading to e.g. state 1 including patients below or at 3.0, state 2 patients at 3.5-4.0, etc.

In this model, patients are divided into the seven disease states according to their EDSS or DSS score, as shown below.

Table 2.1 The Markov states according to EDSS/DSS.

EDSS score	State in model
EDSS 1.0-2.5	state 1
EDSS 3.0-3.5	state 2
EDSS 4.0-4.5	state 3
EDSS 5.0-5.5	state 4
EDSS 6.0-6.5	state 5
EDSS 7.0-7.5	state 6
EDSS 8.0-9.5	state 7

There is also a state for patients who die during the time of the simulation. The effect of MS on mortality is considered small, and currently no epidemiological or clinical data with INFB-1b are available that would allow calculating transition probabilities for an MS-specific increased mortality risk. However, registry data e.g.

in Denmark [35] have recently indicated a substantially higher mortality for MS patients (RR ~3), and if these data become accessible in more detail, it is possible to integrate them into the model. The current model only includes normal mortality. However, sensitivity analysis using a relative risk of 2 and 3, is shown as a sensitivity analysis.

All transitions are allowed, except that patients cannot leave the state "dead".

Transition probabilities are estimated using an ordered probit model, and depend on several factors, including whether or not the patient has a relapse during the current time period, age, age at onset of MS and time since onset of MS. Gender had no influence and was excluded.

The probability of a relapse during the period is estimated by a logistic regression model. Both transition probabilities and probabilities of a relapse are different for untreated and treated patients.

2.2 Patient data

Two double blind clinical trials were used to estimate the transition probabilities for treated and untreated patients for the first years in the model: one trial in RRMS [5] and one trial in SPMS [9]. For both of these trials, open extension studies beyond the double-blind period to 54 months were available. For the extrapolation beyond the trial period, data from an epidemiological study of the natural history of the disease [13] was used. These studies are described below.

2.2.1 Clinical trial in RRMS

The trial included patients with relapsing disease between EDSS 0 and 5.5 who had had 2 or more exacerbations in the two years preceding enrolment. 372 patients were randomised to three treatment groups: placebo (123 patients), IFNB-1b 1.6 MIU/kg (125 patients) and IFNB-1b 8 MIU/kg (124 patients). The approved standard dose of IFNB-1b is 8 MIU, and hence only the placebo group and the higher dose treatment group were used for this analysis (247 patients).

EDSS assessments were done during an outpatient visit at approximately 3-month intervals for up to 5 years. The average follow-up time was 172 weeks (range 0 to 264 weeks).

As the model runs in 3-month cycles, but visits did not take place exactly at 3 months (but plus minus 4-5 weeks), EDSS scores for 3-month intervals had to be estimated. Each visit was numbered with the week since study start that it took place and a full panel data set was generated with all 247 subjects and 265 time periods (week 0-264), in total 65455 observations. For observations (weeks) where no visit took place, the EDSS score at this week was estimated by linear interpolation between the two visits closest in time. All observations except for those at weeks 0, 12, 24, 36…264 were then excluded. No extrapolation was made outside the data material.

Since linear interpolation was used to estimate EDSS scores, these could be any decimal number (not only 2, 2.5, 3.5 etc.). In order to group patients into the Markov states at each 3-month interval, we classified patients with an estimated EDSS score of less than 2.75 into state 1, patients with a score at or above 2.75 and below 3.75 into state 2, etc.

2.2.2 Clinical trial in SPMS

This study included patients with secondary progressive disease between EDSS scores 3.5 and 6.5. 718 patients were randomised to placebo (358 patients) or active treatment with interferon beta (360 patients) and treated for 36 months. After this double blind period, all patients were given the possibility to receive IFNB-1b treatment in an open label extension for up to 18 months. Thus, patients in the treatment group received treatment for up to 54 months. In the model, only patients who received treatment in the double blind phase were used for the extension period, while patients who had switched from the placebo group after 3 years were excluded. In addition, patients who had not received treatment for more than 90 days (one cycle) between the double blind and the extension study were excluded from the extension period.

Patients were followed in 3-month intervals, and EDSS scores were available for all patients at 3 months (+/- 1 week). Thus, no interpolation was required and patients were directly grouped into the Markov states.

2.2.3 Combined RRMS-SPMS dataset

The main cost-effectiveness analysis is performed for patients with both RRMS and SPMS. In order to combine the two types of the disease, a subset of patients in the SPMS trial, with similar disease activity as those enrolled in the RRMS trial, were identified. Patients were defined as having "active disease", i.e.

- patients with RRMS who had two or more relapses in the past two years, i.e. all 372 patients enrolled in the RRMS trial
- patients with SPMS who had two or more relapses or at least one point progression on EDSS (½ point in the range between 6 and 7) in the two years preceding the clinical trial, i.e. 527 of the 718 patients, 254 in the treatment group and 273 in the placebo group. Of the 254 patients in the treatment group, 181 patients entered the open label extension.

Details of the cohort used in the model are in the table below.

Table 2.2 RRMS: Baseline characteristics (N=372)

	Placebo	INFB-1b	
Baseline variables (Mean, SE)	(n=123)	(n=249)	p-value*
Age (yr)	36.0	35.3	0.3793
Disease duration (yr)	7.7	8.2	0.4096
Age at onset of MS (yr)	28.3	27. 1	0.1018
Time since diagnosis of RRMS (yr)	3.9	4.7	0.0670

*two-sided t-test

Table 2.3 SPMS: Baseline characteristics, active patients, double blind phase (N=527)

	Placebo	IFNB-1b	
Baseline variables (mean, SE)	(n=273)	(n=254)	p-value
Age (yr)	41.7 (0.5)	41.1 (0.5)	0.3960
Disease duration (yr)	13.90 (0.46)	12.89 (0.40)	0.3780
Age at onset of MS (yr)	27.80 (0.50)	28.30 (0.50)	0.5797
Time since diagnosis of RRMS (yr)	8.59 (0.39)	8.15 (0.34)	0.8754
Time since diagnosis of SPMS (yr)	2.13 (0.14)	2.19 (0.15)	0.5392
Change of EDSS score in 2 years preceding the DB trial	1.51 (0.05)	1.54 (0.06)	0.6363

Table 2.4 SPMS: Baseline characteristics, active patients, extension phase (N=383)

	Assigned to placebo in DB	Assigned to IFNB-1b in DB	
Baseline variables (mean, SE)	(n=202)	(n=181)	p-value*
Age (yr)	40.6 (0.6)	40.5 (0.6)	0.9520
Disease duration (yr)	12.9 (0.52)	12.7 (0.46)	0.7319
Age at onset of MS (yr)	27.8 (0.5)	27.9 (0.6)	0.9694
Time since diagnosis of RRMS (yr)	8.03 (0.4)	7.68 (0.4)	0.6073
Time since diagnosis of SPMS (yr)	1.96 (0.16)	1.94 (0.15)	0.4668
Change of EDSS score in 2 years preceding the DB trial	1.73 (0.07)	1.78 (0.07)	0.5172

2.2.4 Natural history data

The natural history of MS has been described based on a geographically based study in Canada [13]. In this study, 1099 patients were followed from onset of MS at the MS Clinic in London, Ontario, Canada. Annual data on disability are available in the form of DSS scores [36] for all patients. For the modelling process, a special data set with demographic and disease data for patients with relapsing-remitting disease (RRMS) at onset was extracted from the database. The file contained information on age, gender, mortality (MS specific or not), age at onset of MS, current type of MS, time from onset to conversion to SPMS, disability at conversion to SPMS and annual disability scores. The dataset included 824 patients with a mean follow-up time of 24.4 years (SD 10.2). Details on this dataset are below.

Table 2.5 Description of the natural history data set

	No Patients	% or Mean (SD)
Entire Dataset	824	
Females	566	68.7%
Age at onset of MS	819	28.6 (9.0)
Dead at last follow-up	216	26.1%
RRMS t last follow-up	256	31.1%
SPMS at last follow-up	568	68.9%

Table 2.6 Description of the natural history dataset by type of disease

	No Patients	Mean (SD)
RRMS (n = 256)		
- age at onset	256	26.6 (8.22)
- mean follow-up time	243	20.2 (8.9)
SPMS (n = 568)		
- age at onset	563	29.5 (9.2)
- mean follow-up time	562	26.1 (10.2)
- age at conversion from RRMS	521	40.3 (10.3)
- time to conversion to SPMS	521	10.7 (7.4)
- EDSS at conversion to SPMS	492	3.0 (1.0)

The annual follow-up data were expanded to quarterly observations, to match the cycle length in the model, using linear interpolation. Thus, an EDSS score for each patient at every 3-month interval was estimated. Patients were then divided into states using the usual cut-off points.

2.3 Transition probabilities

In earlier models, transition probabilities were calculated without reference to patient characteristics. However, it can be argued that transition probabilities may be dependent on factors such as sex, age, age at disease onset, time since disease onset, age and level of disability at treatment start. In this model, all of these factors (except sex which was not significant) are used as independent variables when calculating transition probabilities.

2.3.1 Merged clinical trials

Patients from the RRMS and SPMS trials were merged into one database and transition probabilities calculated using the probit model, where

- "S2 to S7" are dummies for states 2-7 (reference state 1)
- "age" is the age at start of treatment
- "ageatons" is the age at onset of MS
- "time" is the number of 3-month periods since the start of treatment
- "int 1" is an interaction term between treatment and a dummy for being in state 3 through 7; as there was no significant effect of the treatment on transition probabilities in states 1 and 2 in the clinical dataset, the calculation assumes that treatment affects transition probabilities only when a patient is in states 3 to 7 (EDSS 4-9.5)
- "relapse" is a dummy for relapse (reference no relapse) during the current period

All the coefficients have the expected signs and are significant ($p < 0.001$). Being in a more severe state increases the probability to go to the next higher state in the next cycle, compared to being in state 1. Age is positive, i.e. the probability of being in a more severe state in the next period increases slightly when treatment is started at a higher age (0.008 for each year). Age at onset is negative, i.e. the younger a patient at disease onset, the higher the probability to be in a more severe state (-0.005 for each year). Time is positive, i.e. the probability to be in a higher state in the next cycle increases by 0.007 for each additional 3-month period that has elapsed since baseline. Having a relapse increases the probability to be in a higher state in the next cycle by 0.22.

The interaction between treatment and states 3 to 7 was introduced to account for the fact that in the early stages of MS, where the vast majority of patients has RRMS, treatment reduces the number of relapses, but has no effect on progression, as patients recover after a relapse. Progression is affected once a patient converts to SPMS, generally around EDSS 3.0 or 3.5. This is clearly seen in the merged clinical dataset, where patients in the RRMS trial were clustered in states 1 and 2, with limited progression. A total of 35% of the dataset were in states 1 and 2 (EDSS <3.5) at baseline.

Table 2.7 Probit model, transition probabilities in the clinical trials

```
Iteration 0:   log likelihood =  -17535.09
Iteration 1:   log likelihood = -9606.0457
Iteration 2:   log likelihood = -8149.0398
Iteration 3:   log likelihood = -7909.5119
Iteration 4:   log likelihood = -7900.8964
Iteration 5:   log likelihood = -7900.8812

Ordered probit estimates                          Number of obs   =      10069
                                                  Wald chi2(11)   =    2562.37
                                                  Prob > chi2     =     0.0000
Log likelihood = -7900.8812                       Pseudo R2       =     0.5494

                              (standard errors adjusted for clustering on id)
------------------------------------------------------------------------------
             |               Robust
       state |      Coef.   Std. Err.       z     P>|z|       (95% Conf. Interval)
-------------+----------------------------------------------------------------
          s2 |   1.960251   .0809251     24.223   0.000       1.801641    2.118861
          s3 |   3.476992   .1129868     30.773   0.000       3.255542    3.698442
          s4 |   4.742726   .1378524     34.404   0.000        4.47254    5.012912
          s5 |   6.733288   .1564043     43.051   0.000       6.426742    7.039835
          s6 |   8.776759   .1819334     48.242   0.000       8.420176    9.133341
          s7 |   10.38026   .3004678     34.547   0.000       9.791356    10.96917
         age |   .0081904   .0019119      4.284   0.000       .0044431    .0119377
    ageatons |  -.0054619   .0018886     -2.892   0.004      -.0091634   -.0017604
        time |   .0075081   .0020557      3.652   0.000       .0034791    .0115371
        int1 |  -.0803573   .0309238     -2.599   0.009      -.1409667   -.0197478
     relapse |   .2265549   .0407262      5.563   0.000       .1467331    .3063768
-------------+----------------------------------------------------------------
       _cut1 |   1.326034    .079766            (Ancillary parameters)
       _cut2 |   2.871344   .1091634
       _cut3 |   4.289891   .1382199
       _cut4 |   5.544517   .1565744
       _cut5 |   8.383985   .1778311
       _cut6 |    9.91157   .2174867
```

2.3.2 Natural history cohort

The calculation of transition probabilities in the epidemiological dataset is shown below.

The results are similar to the clinical dataset, and being in a more severe state increases the probability to go to the next higher state in the next cycle, compared to being in state 1. However, in this dataset, gender was significant as well, and males had a higher probability to go to a more severe state in the next period ($p<0.01$). Age at inclusion into the study was negative, i.e. patients that were younger at the start of follow-up had a higher probability to go to the next higher state in the next cycle. Time since inclusion was not significant and therefore excluded.

Table 2.8 Probit model, transition probabilities in the natural history dataset

```
Ordered probit estimates                          Number of obs   =      72176
                                                  Wald chi2(9)    =    4077.01
                                                  Prob > chi2     =     0.0000
Log likelihood =   -11881.9                       Pseudo R2       =     0.9015

                              (standard errors adjusted for clustering on id)
------------------------------------------------------------------------------
             |               Robust
       state |      Coef.   Std. Err.       z     P>|z|       [95% Conf. Interval]
-------------+----------------------------------------------------------------
          s2 |   5.369649   .2095633     25.623   0.000       4.958912    5.780385
          s3 |   9.370129   .2388048     39.238   0.000       8.902081    9.838178
          s4 |   13.01429   .2815082     46.231   0.000       12.46255    13.56604
          s5 |   17.04609   .3859744     44.164   0.000       16.28959    17.80258
          s6 |   21.25233   .4259271     49.897   0.000       20.41753    22.08713
          s7 |   26.36626   .4562622     57.788   0.000         25.472    27.26051
         age |   -.005872   .0017244     -3.405   0.001      -.0092516   -.0024923
        male |   .0616268   .0218665      2.818   0.005       .0187691    .1044844
    ageonset |   .0083327   .0018869      4.416   0.000       .0046344    .0120309
-------------+----------------------------------------------------------------
       _cut1 |   2.098103   .0419231            (Ancillary parameters)
       _cut2 |   6.789731   .2205148
       _cut3 |   10.39137   .2507423
       _cut4 |   14.13039   .2945314
       _cut5 |   18.48295   .3966199
       _cut6 |   22.70499   .4275972
------------------------------------------------------------------------------
```

- "S2 to S7" are dummies for states 2-7 (reference state 1)
- "age" is the age at start of the follow-up
- "male" is the gender (reference female)
- "ageatons" is the age at onset of MS

2.4 Relapse rates

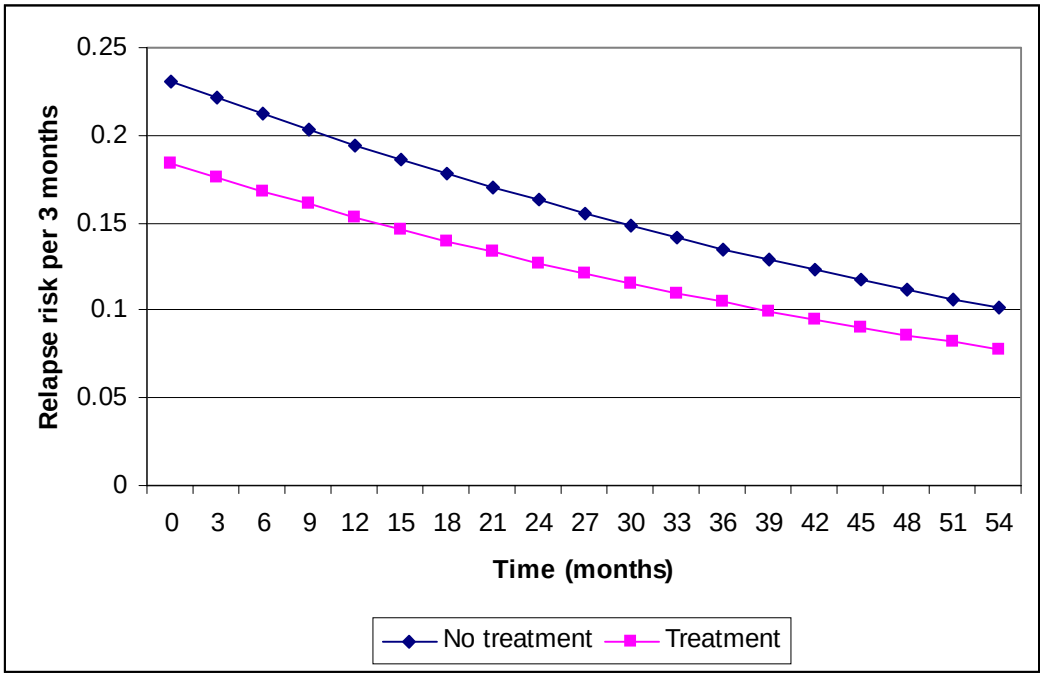
The risk of having a relapse in each 3-month period is estimated by a logistic regression model, controlling for gender, age at onset of disease, age at start of treatment, time since start of treatment and a dummy for active treatment. The odds ratio for relapses with treatment is 0.75.

Table 2.9 Regression model, relapse rates in the clinical trial cohort

```
Logit estimates                                   Number of obs   =      10260
                                                  Wald chi2(5)    =     109.91
                                                  Prob > chi2     =     0.0000
Log likelihood = -4245.4684                       Pseudo R2       =     0.0223

                              (standard errors adjusted for clustering on id)
------------------------------------------------------------------------------
             |               Robust
     relapse | Odds Ratio   Std. Err.       z     P>|z|       (95% Conf. Interval)
-------------+----------------------------------------------------------------
         age |   .9656662   .0068715     -4.910   0.000       .9522918    .9792284
    ageatons |   1.022928   .0080145      2.893   0.004       1.007339    1.038757
        male |   .8262499   .0747127     -2.111   0.035       .6920581    .9864618
        time |   .9470245   .0067515     -7.635   0.000       .9338839    .9603501
       treat |   .7491483   .0639578     -3.383   0.001       .6337198    .8856015
------------------------------------------------------------------------------
```

Figure 2.1 The risk of relapse with or without treatment



2.5 Compliance

The model uses intention to treat (ITT) data from the clinical trials, i.e. data from all patients included in the clinical trials are used, irrespective of whether patients withdrew from treatment or not. EDSS scores thus include non-compliance to the treatment, and the cost of treatment needs therefore to be adjusted by the actual compliance rate. The fraction of patients who are compliant at each point in time is estimated by the Kaplan-Meier method (see below).

The compliance after 36 months in the combined clinical cohort is 93%.

Table 2.10 Compliance in the merged clinical dataset

Time	Beg. Total	Fail	Net Lost	Survivor Function	Std. Error	(95% Conf.	Int.)
3	716	0	8	1.0000	.	.	.
6	708	0	2	1.0000	.	.	.
9	706	3	5	0.9958	0.0024	0.9869	0.9986
12	698	2	2	0.9929	0.0032	0.9830	0.9970
15	694	6	8	0.9843	0.0047	0.9719	0.9913
18	680	6	7	0.9756	0.0058	0.9611	0.9848
21	667	5	4	0.9683	0.0066	0.9523	0.9790
24	658	2	15	0.9654	0.0069	0.9488	0.9767
27	641	6	8	0.9563	0.0078	0.9381	0.9693
30	627	5	11	0.9487	0.0085	0.9293	0.9629
33	611	6	12	0.9394	0.0092	0.9186	0.9550
36	593	9	419	0.9251	0.0102	0.9024	0.9428
39	165	1	1	0.9195	0.0116	0.8935	0.9394
42	163	2	4	0.9082	0.0139	0.8768	0.9320
45	157	6	1	0.8735	0.0193	0.8301	0.9065
48	150	3	3	0.8561	0.0214	0.8082	0.8928
51	144	6	0	0.8204	0.0250	0.7652	0.8637
54	138	5	133	0.7907	0.0274	0.7309	0.8387

2.6 Costs and utilities by state and during a relapse

Costs and utilities in different states, as well as the extra costs and utility loss due to a relapse are estimated from an observational study in Sweden [31]. This cross-sectional bottom-up study included 413 patients and collected all costs, as well as utilities and EDSS scores. The mean age of patients was 49 years and 71% were female. Age at onset of the disease was 32 years, and 34% of patients had benign disease or relapsing-remitting disease, 37% had secondary progressive and 26% primary progressive disease. 9.4% of patients had suffered from a relapse in the month preceding data collection.

The total cost was on average 363 480 SEK per year, 58% being direct medical costs, 37% indirect costs and 5% costs of informal care. The average utility in the Swedish observational study was 0.424, or 0.462 when negative utilities were set to zero.

A linear regression model was used to estimate the cost in different EDSS states as well as the extra cost due to a relapse. Age, gender or age at onset of disease did not have any significant effect on costs, so these variables were excluded from the regression equation. The EDSS states were included as dummy variables, together with a dummy variable for whether the patient has had a relapse during the last month.
Table 2.11 shows the costs by state.

The utility in different states and the utility loss from a relapse were estimated in a similar way by linear regression. Age was found to have a significant independent effect on utility, older patients having lower utility than younger, as expected.
Table 2.11 show the utilities by state.

Table 2.11 **Costs and utilities in the different Markov States**

State	EDSS	Costs per 3 months (SEK, 1999)				Utility
		Direct	Indirect	Informal	Total	EQ-5D*
1	0-2.5	2277	17608	0**	19885	0.6923
2	3.0-3.5	16283	26290	2937	45510	0.5959
3	4.0-4.5	18519	26562	2099	47180	0.5565
4	5.0-5.5	33535	30591	1155	65281	0.5186
5	6.0-6.5	49438	41039	5237	95713	0.4443
6	7.0-7.5	107978	39611	11525	159114	0.2842
7	8.0-9.5	167160	67526	13498	248185	0.0357

* individual negative utilities were set to zero prior to the calculations

** The cost of informal care in state 1 was predicted to –40 SEK by the regression model. Since a negative costs make little sense in this context, the cost is set to zero.

Assuming that a relapse lasts for one month, the utility loss is 0.0104 QALYs (equal to 3.8 quality-adjusted days). For a relapse lasting 3 months, the QALY loss would be 0.0312, or 11.4 quality-adjusted days.

The extra cost due to a relapse lasting 1 month was estimated to 14668 SEK, direct costs constituting 70%, indirect costs 27% and informal care 3% of the total cost of relapse.

Table 2.12 Cost and utility loss due to relapse

Duration	Costs (SEK, 1999)				Utility loss
	Direct	Indirect	Informal	Total	EQ-5D*
1 month	10286	3969	413	14668	0.0104
3 months	30858	11908	1238	44004	0.0312

2.7 Intervention

Treatment with IFNB-1b for the first 3 years is compared to placebo, based on the clinical trials and after 12 cycles, transitions from the natural history data are used for both groups. When treatment is stopped, no further treatment effect is assumed. When treatment is extended to 18 cycles, transitions are compared to the natural history cohort, as no placebo group was available for this time period.

The recommended dosage is 8 million units by subcutaneous injection every second day. The price for 15 vials is 8426 SEK, which brings the annual drug cost to 102587 SEK. 1600 SEK per year is added for treatment administration and monitoring. In the model, the annual cost of IFNB-1b is adjusted for compliance.

3 Results

3.1 Base case

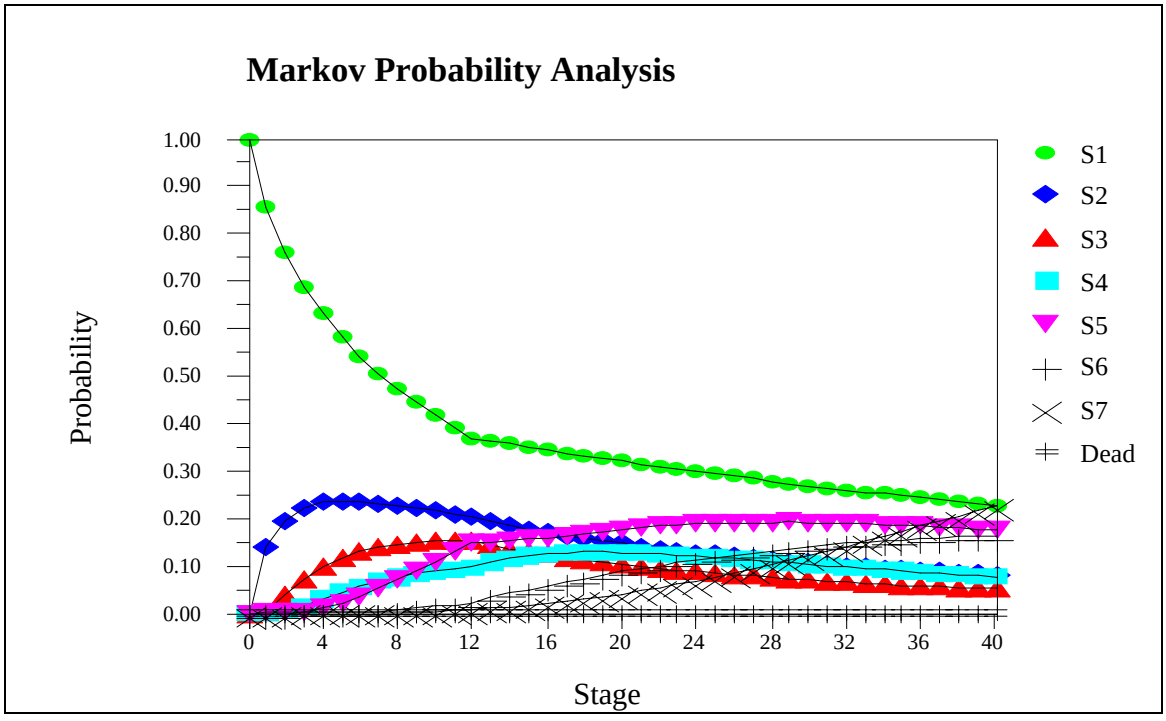
The base case presents a cohort with the same baseline characteristics as the merged clinical trial cohort (mean age 39 years, age at disease onset 28 years, 73.5% females). The simulation runs for 40 cycles (10 years) and the duration of the intervention in the base case is 12 cycles (3 years).

Table 3.1 – Distribution of the clinical cohort (merged trials) into states at baseline

State	Initial distribution (%)
1	0.154
2	0.191
3	0.192
4	0.172
5	0.292
6	0
7	0

Figure 3.1. below shows how the cohort distribution develops over time in the model, for a cohort where all patients are in state 1 at the start of the simulation.

Figure 3.1 Cohort distribution over 10 years for patients starting in state 1



The cost per QALY for the clinical cohort, and for patients starting treatment at different levels of disability (states) is shown below, excluding or including normal mortality. These calculations use the mean values for costs and utilities in each state.

Table 3.2 Cost utility, cohort as in clinical trial. No mortality.

Strategy	Cost	Incr. cost	Utility	Incr utility	Incr cost-utility
No treatment	3 743 408		3.610		
Treatment	3 751 763	8 355	3.807	0.197	42 500

Table 3.3 Cost utility for treatment start in different states (levels of disability)

Starting state	**SEK/QALY**
Merged clinical cohort	42 500
1	2 277 966
2	600 552
3	Cost-saving
4	Cost-saving
5	Cost-saving

Treatment only adds a small cost, 8355 SEK, as illustrated in the base case for the clinical cohort (table 3.2.). However, there is a utility gain, 0.197 QALYs, which is equal to 72 days with perfect health. This gain must be considered in relation to the total utility over 10 years (3.6 QALYs discounted) and represents therefore a substantial gain.

As expected, in a 10-year horizon, treatment is more cost-effective in patients who progress, as both the progression and the relapse rate are affected. In the very early stages, the effect of treatment is on the relapse rate only, and the cost per QALY is therefore higher.

When normal mortality is included in the model, the utility gain decreases and the cost effectiveness ratios are higher.

Table 3.4 Cost utility, cohort as in clinical trial. Normal mortality.

Strategy	Cost	Incr. cost	Utility	Incr utility	Incr cost-utility
No treatment	3 652 941		3.548		
Treatment	3 666 660	13 719	3.740	0.192	71 428

Table 3.5 Cost utility for treatment start in different states; normal mortality included

Starting state	**SEK/QALY**
Merged clinical cohort	71 428
1	2 357 538
2	643 136
3	Cost-saving
4	Cost-saving
5	Cost-saving

Including a relative mortality risk of 2, the cost per QALY is 100 663 SEK. With a mortality risk of 3, it the cost per QALY is 130 201 SEK.

3.2 Sensitivity analyses

Sensitivity analyses are presented for

- different definitions of costs (indirect and/or informal care costs excluded)
- different durations of treatment (54 months)
- different time horizons (10-25 years)
- different assumptions regarding
    - duration of a relapse (1-3 months)
    - compliance rates (10-30% withdrawals)

All of these analyses include normal mortality.

Table 3.6 Cost-utility for treatment start in different states; direct costs.

Starting state	SEK/QALY
Merged clinical cohort	454 651
1	2 743 329
2	1 028 396
3	225 354
4	99 070
5	191 677

Table 3.7 Cost-utility for treatment start in different states; direct and informal care costs.

Starting state	SEK/QALY
Merged clinical cohort	363 527
1	2 655 317
2	938 911
3	135 404
4	7 126
5	99 068

Table 3.8 Cost-utility for treatment start in different states and 54-month intervention

Starting state	SEK/QALY
Merged clinical cohort	353 811
1	2 124 125
2	901 545
3	166 096
4	7 294
5	49 133

Table 3.9 Sensitivity analysis for different costs of a relapse (base case, clinical cohort)

Relapse cost	SEK/QALY
-100%	105 931
-50%	88 679
±0%	71 428
+50%	54 177
+100%	36 925

Table 3.10 Sensitivity analysis for the duration of a relapse (base case, clinical cohort)

Duration of relapse	SEK/QALY
1 month (base case)	71 428
2 months	69 723
3 months	68 098

When the timeframe of the analysis is increased to 15-20 years, the the treatment becomes cost-saving since additional long-term effects of treatment are included in the analysis.

Table 3.11 Sensitivity analysis for time horizon of the simulation (base case, clinical cohort).

Simulation duration	SEK/QALY
10 years (base case)	71 428
15 years	Cost-saving
20 years	Cost-saving
25 years	Cost-saving

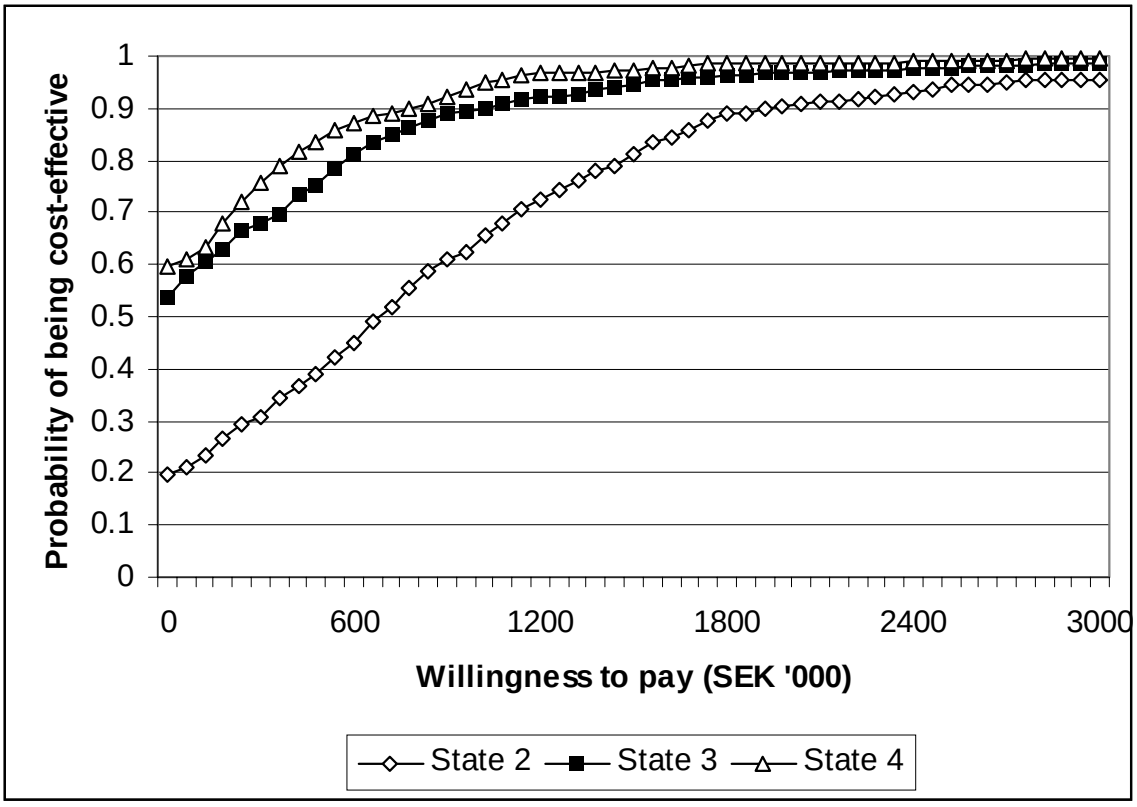
3.3 Net Benefit

The base case uses mean costs and utilities for the Markov states, ignoring the variability and distribution. In view of the large number of observations in the observational study, it is possible to estimate the stability of the estimates, by using the net benefit approach and acceptability curves for a certain willingness to pay for a QALY.

The acceptability curves are generated by Monte Carlo simulation, using 500 individual draws from the distributions of costs and utilities in different states. In this calculation, a willingness to pay for a QALY is defined and the probability estimated, with which the cost/QALY with the treatment will be below this amount when the entire distribution of costs and utilities is used in the calculation.

For example, for patients starting in states 3 or 4, the probability that the treatment is acceptable is roughly 80% if the willingness to pay for a QALY is between 4-500 000 SEK, or a 90% probability if the willingness to pay is 900 000 SEK. At that same willingness to pay, there is a 60% probability that the treatment is acceptable in state 2. The chance of the treatment being cost-saving is about 60% in states 3-4 and 20% in state 2.

Figure 3.2 Acceptability curves for patients starting in different states



4 Discussion

The objective of treatment in MS is to avoid temporary disability by reducing the number and the intensity of relapses, and more importantly, to delay progression to permanent severe disability. There is currently a debate whether the new treatments represent an efficient use of resources, as all clinical trials have shown a significant effect on relapses, but only one trial has demonstrated a significant effect on progression. Also, the treatments are expensive, and economic evaluations have estimated high cost-effectiveness ratios, particularly for treating relapsing-remitting disease.

There are several challenges when performing economic evaluation in MS, and the economic model presented in this report attempts to address a number of these issues:

- The course of the disease is unpredictable and limited data on progression, particularly on risk factors that would affect progression, are available. Data on the effect of the disease on mortality are scarce. This makes estimates of the effect of a treatment on long-term outcome difficult.
- All of the new treatments are approved for use in RRMS, and clinical data are mostly available for short-term effects on relapses. Only one of the treatments has been approved for use in SPMS on the basis of one trial and limited data are thus available to estimate the effect of treatment on progression. However, it is the delay of progression to severe disability and its consequences on costs and quality of life that would justify investment in a costly treatment, as has been shown in several published economic models.
- The disease mechanisms underlying RRMS and SPMS appear to be similar, and the conversion from relapsing to progressive disease has not been clearly defined. Patients convert at different levels of disability (EDSS) and at different times after disease onset. This increases the difficulty to estimate

the effect of early treatment, of patients with RRMS, on disease progression and long-term outcome.

- No conclusions appear to have been reached regarding the reasons why one trial with IFNB-1b (in Europe) showed a significant effect on progression, while the second trial (in the USA) did not reach significance. One explanation that has been offered is that the US trial had enrolled patients with less active disease, but no assessment of the cost-effectiveness of treating patients with active disease has been done so far.
- The disease affects a number of physical functions, and none of the frequently used clinical outcome measures expresses the overall effect of the disease or a treatment, as required for economic evaluation. However, it has been shown in several studies that physical disability measured with the EDSS correlates well with a general measure of quality of life (utility), and the QALY has become the most frequently used effectiveness measure in economic evaluations.
- Detailed data on resource utilisation for patients at all levels of disability are required in order to estimate the savings associated with a delay in disease progression. Clinical trials will not provide sufficient data, as only defined patient groups, either in the early or the middle ranges of the EDSS, are included. The number of patients progressing to severe disability during the trial is therefore too small to estimate resource utilisation.
- The variability of the disease itself, but particularly of the costs and QoL effects associated with it requires large datasets to ensure that the full spectrum is taken into account.

The model presented here attempts to address a number of these issues by combining RRMS and SPMS into one model and incorporating the natural history of the disease as well as detailed data on costs and QoL at all levels of disability. This allows simulating treatment for patients with different types of the disease, at

different levels of EDSS and estimate confidence intervals for the cost-effectiveness calculations.

The first 3-5 years in the model are based on a defined subgroup of patients from two large clinical trials in RRMS and SPMS. To be included in the dataset, patients had to have active disease, defined as at least 2 relapses or 1 EDSS point progression in the two years preceding the trial. All patients in the RRMS trial were included, as the number of relapses was part of the inclusion criteria, while only a subgroup of patients (527 of 718) in the SPMS trial were selected. It could be argued that the two groups were not fully comparable, as a number of patients with SPMS were selected based only on progression rather than on relapse rates. However, 56% of the patients fulfilled both criteria, while 72% had one or more relapses, and the definition was therefore accepted.

A further argument against combining the two types of MS could be that the course of the disease is different for RRMS and SPMS. There are however several reasons that speak for merging the data. First, conversion from RRMS and SPMS can take place at a range of EDSS levels, and hence there will always be patients with both types of the disease at many EDSS levels. This is illustrated by the 568 patients in the natural history database who had converted from RRMS to SPMS. The mean and median EDSS scores at conversion were 3.0, but the range covered EDSS 1.0 to 6.5. Second, the observational studies in the UK, Sweden and Germany have all shown that costs and quality of life are dependent on EDSS levels but not on the type of the disease. Third, the difference in time to given levels of disability for patients with RRMS or SPMS is fully taken into account in the transition probabilities, as all patients are used for these calculations. This is illustrated by the fact that progression is very slow in the early EDSS levels with predominantly RRMS patients (states 1 and 2, EDSS 1.0-3.5). Also, there was no significant effect of treatment on progression at these levels in the clinical data, and within a 10-year timeframe, the effect of early treatment on the long-term course is therefore limited. This is

illustrated by the higher cost per QALY when treatment is started in states 1 and 2, compared to a treatment start in states 3 and 4. The treatment becomes cost-saving when the time horizon is increased to 15-25 years.

The extrapolation beyond the clinical trials, from 3-5 to 10, and up to 25 years is based on epidemiological data. Incorporation of the natural history data represent another difficulty, as the 824 patients with RRMS at onset represent all patients, rather than patients with active disease. Reliable data on relapse rates were only available for certain points in time (at disease onset and at conversion to SPMS), and it was therefore not possible to extract a large enough sub-sample of patients with active disease. Therefore the entire dataset was used, which may represent an underestimate for this group of patients and hence a potential underestimate of the long-term effect of treatment. A previous model [14] had however shown that progression of patients with SPMS in the natural history dataset was faster than what was estimated by extrapolating the average progression in the untreated clinical trial cohort. This was interpreted to be due to a trial effect (placebo effect), as well as to fact that very few patients above EDSS 6.0 were enrolled into the trial and therefore very limited data on progression beyond this level are available. Therefore, it was decided that the estimates in this model would be more accurate if the full natural history dataset was used for the extrapolation, despite the limitations.

An unexpected finding in the data was that relapse rates were not significantly different at different EDSS levels. This is contrary to general clinical opinion that relapse rates decrease as the disease progresses. However, there was no significant difference between relapse rates in the different states in either of the three datasets used, the two clinical trials and the natural history database at the time points that were available. There are several possible explanations for this. It is possible that there is a confusion between relapses at given levels of disability and time since onset of disease. In both clinical trials, the number of relapses decreased

the longer patients had had the disease, but with the variable course of the disease, this did not translate into a reduction of relapses at higher levels of EDSS. Another possibility is that there could be underreporting of relapses at the higher levels of EDSS in clinical practice, as the difference in disability during or between a relapse is rather small, while the effect of an exacerbation in early stages is far more visible. In clinical trials or cohort studies, this reporting artefact will be eliminated and all relapses, however limited, will be reported. Lastly, there was a difference in resource consumptions in the observational study between patients who had had a relapse in the past 3 months and those who didn't at the lower EDSS levels, while there was no difference at medium and higher levels. This could be interpreted as a more limited impact of a relapse at high EDSS levels and would support the explanation of underreporting in clinical practice.

The incremental cost per QALY with IFNB-1b for the merged clinical cohort is lower than previously estimated, supporting the hypothesis that patients with more active disease might experience a larger treatment effect. Also, estimates are more reliable, as the model controls for differences in patient demographics such as age, time since disease onset, age at treatment start for both the treatment time and the extrapolation. Most importantly however, the model presents measures of the precision of the estimates in the form of acceptability curves for the cost-effectiveness ratios, using the entire distribution of costs and utilities in the data sets.

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6 Appendix

6.1 Cohort distributions, merged clinical dataset

Table 6.1 Cohort distribution clinical dataset, no treatment

Time	State 1		State 2		State 3		State 4		State 5		State 6		State 7	
Relapse	*No*	*Yes*	*No*	*Yes*	*No*	*Yes*	*No*	*Yes*	*No*	*Yes*	*No*	*Yes*	*No*	*Yes*
0	45	14	61	7	52	19	49	21	82	36				
1	54	18	49	16	41	17	51	11	92	27	5	5	1	
2	54	19	47	14	49	11	39	13	99	23	6		4	
3	58	11	49	10	42	15	40	13	106	21	8	1	3	1
4	58	15	33	15	44	8	42	10	106	16	13	3	7	
5	53	15	43	12	34	7	40	6	112	13	18	4	6	
6	54	8	35	14	41	11	33	12	112	11	19	3	6	
7	50	18	28	5	39	10	34	9	106	21	28		7	
8	53	11	31	8	39	7	39	7	105	16	22	6	11	
9	51	8	35	4	36	5	39	6	104	11	27	8	10	1
10	53	9	33	5	31	4	40	4	103	8	32	3	12	2
11	44	9	29	8	35	4	30	3	96	3	36	1	12	1
12	40	9	27	7	29	3	27	1	86	5	26		20	1
13	32	10	17	2	5	2	5	1	8	3	3		1	
14	35	7	11	2	9	1		2	8	1	4			
15	38	3	12	3	4	2	5		5	3	4		1	
16	33	4	8	4	5	4	2	3	7	1	5		1	
17	28	1	4	1	7	4	2		8	1	1		1	
18	22	3	5		4	1	2		5	1	2		1	
19	12	2	4		1		1		4		1		2	
20	5		3						1					
21	1								1					

Table 6.2 Cohort distribution clinical dataset, treatment

Time	State 1		State 2		State 3		State 4		State 5		State 6		State 7	
Relapse	*No*	*Yes*	*No*	*Yes*	*No*	*Yes*	*No*	*Yes*	*No*	*Yes*	*No*	*Yes*	*No*	*Yes*
0	46	12	59	18	66	9	51	10	91	13				
1	55	11	57	17	54	9	51	10	85	22	5	1		
2	48	8	71	13	58	9	40	9	83	16	6	1	2	
3	52	8	55	13	60	12	35	8	96	13	8		2	
4	62	8	48	5	54	10	43	3	95	17	6		4	
5	62	9	43	10	52	5	41	7	99	10	9	2	2	
6	54	10	54	6	50	5	43	3	88	16	15	3	1	
7	49	11	47	9	55	5	40	1	92	11	15	2	5	
8	52	15	42	8	40	7	41	4	96	13	15	1	6	
9	60	6	39	7	47	1	36	3	99	10	17	1	7	1
10	55	7	45	4	38	6	37	3	98	9	12	1	5	3
11	57	7	33	6	31	6	36	4	79	9	21	1	7	1
12	55	4	38	4	40	4	32	5	97	2	24	1	7	
13	44	7	20	4	29	6	18	4	61	4	10	1	5	
14	44	10	21	5	40	3	28	4	72	5	18	6	5	1
15	44	3	26	1	28	8	31	7	67	11	16	1	9	
16	42	5	19	3	35	6	25	5	72	11	19	1	8	
17	30	3	23	1	30	6	25	1	68	10	20	4	7	
18	22	1	22	2	30	2	23	2	74	8	18		8	2
19	14		3		1		5		4	1				
20	8		3			1	2		2					
21	2				1				1					
22	1													

6.2 Cohort distributions, natural history dataset

Table 6.3 Cohort distribution, epidemiological cohort

Year	State 1	State 2	State 3	State 4	State 5	State 6	State 7
0	723	48	5	5	9	1	2
1	650	73	18	11	17	10	3
2	598	81	26	23	27	14	9
3	547	95	36	27	31	22	16
4	511	94	33	39	43	24	23
5	467	92	48	41	58	28	29
6	433	98	43	49	60	40	36
7	414	91	46	46	73	40	50
8	385	91	42	54	77	43	65
9	356	88	41	59	87	47	75
10	327	93	39	56	87	55	91
11	294	95	44	54	85	66	103
12	270	93	48	58	81	75	113
13	249	89	43	54	92	79	127
14	225	71	50	46	92	86	143
15	197	75	46	41	92	89	160
16	180	66	34	46	91	85	172
17	158	60	32	40	90	81	189
18	134	61	30	39	85	80	195
19	119	51	32	32	79	78	203
20	97	52	21	38	68	75	214
21	82	46	19	28	60	79	215
22	64	46	24	20	52	74	215
23	54	37	18	20	44	71	225
24	38	34	20	21	38	61	221
25	31	31	19	17	29	61	219
26	25	26	16	13	26	51	221
27	20	22	13	12	24	35	230
28	17	16	11	11	24	27	216
29	15	15	9	9	21	26	209

6.3 Model illustration

Figure 6.1 The Markov model