Natalizumab (Tysabri®) for the Treatment of Adults with Highly Active Relapsing Remitting Multiple Sclerosis

Biogen Idec Single Technology Appraisal (STA) Submission to The National Institute for Health and Clinical Excellence

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Confidential Information:	Note that all confidential information within the submission has been removed

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Glossary

Term	Definition
9HPT	9 Hole Peg Test

Term	Definition
ABN	Association of British Neurologists
AE	Adverse Event
AI	Alpha interferon
ALT/SGPT	Alanine transaminase/serum glutamate-pyruvate transaminase
AML	Acute Myeloid Leukaemia
ANCOVA	Analysis of Covariance
ANOVA	Analysis of Variance
AST/SGOT	Aspartate transaminase/serum glutamic-oxaloacetic transaminase
CEAC	Cost-effectiveness Acceptability Curves
CENTRAL	Cochrane Central Register of Controlled trials
CHMP	Committee for Medicinal Products for Human Use
CI	Confidence interval
CNS	Central Nervous System
CSF	Cerebrospinal Fluid
DMT	Disease-modifying Treatments
DNA	Deoxyribonucleic acid
DSS	Disability Status Scale
EDSS	Expanded Disability Status Scale
EMEA	European Medicines Evaluation Agency
EPAR	European Public Assessment Report
FS	Functional Systems
GA	Glatiramer acetate
FYE	Full-year equivalent
HARRMS	Highly Active RRMS
ICER	Incremental Cost Effectiveness Ratio
IFN-beta	Interferon beta
ISPOR	International Society of Pharmacoeconomics and Outcomes Research
ITP	Idiopathic Thrombocytopenic Purpura
ITT	Intention to Treat
IV	Intravenous
IVIg	Intravenous immunoglobulin
LCL	Lower Confidence Limit
LP	Lumbar Puncture
MAUS	Multi-attribute Utility Scale
MRI	Magnetic Resonance Image
MS	Multiple Sclerosis
MSFC	Multiple Sclerosis Functional Composite Scale
MSM	Multi State Model (method by which transition probabilities derived from RCT)
MSQLI	Multiple Sclerosis Quality of Life Inventory
MSS	Multiple Sclerosis Society
MTA	Multiple technology assessment
MTX	Mitoxantrone
NAB	Neutralising antibody
NAT	Natalizumab
NCC-CC	National Collaborating Centre for Chronic Conditions
NHS EED	NHS Economic Evaluations Database
NICE	National Institute for Health and Clinical Excellence
PASAT 3	Paced Auditory Serial Addition Test 3
PBO	Placebo
PML	Progressive Multifocal Leukoencephalopathy
PPMS	Progressive Primary Multiple Sclerosis
PSA	Probabilistic Sensitivity Analysis
PT	Prothrombin time
QALY	Quality Adjusted Life Year
RCT	Randomised Controlled trial
RES	Rapidly Evolving Severe
RMS	Root mean squared
RR	Relative Risk
RRMS	Relapsing Remitting Multiple Sclerosis
SAE	Serious Adverse Events
ScHARR	School of Health and Related Research, University of Sheffield
SE	Standard Error
SMC	Scottish Medicines Consortium
SMR	Standardised Mortality Rate
SOT	Sub Optimal Therapy
SPC	Summary of Product Characteristics
SPMS	Secondary Progressive Multiple Sclerosis
SUR	Seemingly Unrelated Regression
UCL	Upper Confidence Limit
VAS	Visual Analogue Scale

Term	Definition
VFT	Visual Function Test
WBC	White Blood Cell

1 Executive summary

A new Markov model, based on the previous School of Health and Related Research (ScHARR) model commissioned by the National Institute for Health and Clinical Excellence (NICE), reviewed by recognised experts in the field of health economics in multiple sclerosis, and validated against the previous model, demonstrated that **the incremental cost-effectiveness ratio (ICER) of natalizumab compared with any comparator in the rapidly evolving severe subgroup is below the acceptable published threshold of £36 000 in all decision problems, and approximately £27 000 per quality adjusted life year (QALY) gained compared with active comparators (see section 6).**

Natalizumab uptake at forecast levels represents a modest budget impact in England and Wales (maximum forecast total incremental discounted cost in year 5 of £15.5 million).

Multiple sclerosis is a devastating disease that creates a burden on the health care system in the UK (see section 4)

In the large majority of patients multiple sclerosis is a relentlessly progressive chronic disease. Multiple sclerosis is the most common disabling neurological condition affecting young adults. Multiple sclerosis adversely impacts the lives of patients, caregivers and other stakeholders in many ways:

- multiple sclerosis can devastate the quality of life of the individual with the disease, and may lead to a state worse than death in late stages of the disease
- multiple sclerosis necessitates the support of friends and family
- multiple sclerosis impairs the quality of life of caregivers
- multiple sclerosis leads to an increased burden on caregivers
- multiple sclerosis leads to high unemployment
- multiple sclerosis patients require increased nursing care and home help
- multiple sclerosis has a high personal financial cost to sufferers and carers

Highly active relapsing remitting multiple sclerosis patients relapse more frequently and progress more rapidly to severe disability than a relapsing remitting multiple sclerosis population and therefore one would expect the above consequences to have even greater impact for this group of patients.

There are currently no other treatments that are licensed specifically for patients with highly active relapsing remitting multiple sclerosis and no clear guidelines on initiation of therapy in this patient group, or guidance on what to do in the event of a sub optimal response to current therapy.

It is notable that there are no specific guidelines for patients with highly active relapsing remitting multiple sclerosis. This provides a unique opportunity for NICE to be the first authoritative body to provide much-needed clarity by recognising natalizumab as the most appropriate

treatment for highly active relapsing remitting multiple sclerosis patients.

Natalizumab is a significant clinical advance in the treatment of highly active relapsing remitting multiple sclerosis (see sections 2 and 5)

There are currently no other therapies licensed specifically for people with highly active relapsing remitting multiple sclerosis. Highly active relapsing remitting multiple sclerosis patients have more frequent relapses and progress more rapidly to severe disability than the relapsing remitting multiple sclerosis population. The active comparators within this submission are interferon beta and glatiramer acetate. Best supportive care is also considered as a comparator.

Natalizumab is the first in a new class of drug for the treatment of highly active relapsing remitting multiple sclerosis. It is a selective adhesion-molecule inhibitor. Natalizumab has a unique and specific mechanism of action, which prevents white blood cells, the mediators of inflammation in multiple sclerosis, from entering the brain.

Natalizumab is licensed for the treatment of highly active relapsing remitting multiple sclerosis. These patients fall into two subgroups:

Rapidly evolving severe subgroup defined by 2 or more disabling relapses in one year, and with 1 or more Gadolinium-enhancing lesions on brain Magnetic Resonance Image (MRI) or a significant increase in T2 lesion load as compared to a previous MRI.

Sub optimally treated subgroup defined as patients who have had at least 1 relapse in the previous year while on therapy, and have at least 9 T2-hyperintense lesions in brain MRI or at least 1 Gadolinium-enhancing lesion.

Methodology

The AFFIRM and SENTINEL pivotal studies, upon which the licensed indications of natalizumab are based, are the largest prospective, interventional studies to be conducted in relapsing remitting multiple sclerosis to date.

Critical appraisal based upon the key components of the CONSORT statement indicates that the natalizumab pivotal studies were generally better conducted and better reported than equivalent studies of comparator treatments.

Efficacy results of natalizumab pivotal studies:

All clinical and surrogate primary and secondary endpoints, for both AFFIRM and SENTINEL, showed a clinical and statistically significant benefit in favour of natalizumab treated patients.

These benefits were seen early, were sustained throughout the duration of treatment and were typically superior to those observed in clinical studies of other disease modifying therapies in the treatment of relapsing remitting multiple sclerosis. At 2 years within AFFIRM, compared to placebo natalizumab treated patients experienced a:

- 68% reduction in annualised relapse rate ($p < 0.001$)
- 54% reduction in the hazard ratio for disability progression ($p < 0.001$)
- 81% reduction in annualised relapse rate in the rapidly evolving severe subgroup ($p < 0.001$)
- 64% reduction in the hazard ratio for disability progression in the rapidly evolving severe subgroup ($p = 0.008$)

A large effect on lesions identified by magnetic resonance imaging (MRI) was observed:

- 92% reduction in the mean number of Gd+ lesions ($p < 0.001$)
- 83% reduction in the mean number of new or enlarging T2 hyperintense lesions ($p < 0.001$)
- 76% reduction in the mean number T1 hypointense lesions ($p < 0.001$)

Nearly a third of patients treated with natalizumab remained disease free at 2 years:

- 28% of people were free of all measures of disease activity (disability progression, relapses, Gd+ lesions, new or enlarging T2 lesions or new T1 lesions)

In a 1-year open label extension study, the three-year annualised relapse rate for patients was 0.23. This was consistent with the 0.23 annualised relapse rate seen in the natalizumab arm of the two-year AFFIRM study.

Safety results of natalizumab pivotal studies

All common adverse events, except for fatigue and allergic reaction, were not significantly different from placebo.

The rates of serious adverse events were equivalent to placebo.

A risk of Progressive Multifocal Leukoencephalopathy associated with natalizumab monotherapy cannot be excluded. Progressive Multifocal Leukoencephalopathy has not been reported in patients with multiple sclerosis receiving natalizumab monotherapy.

Indirect comparison:

No head to head trials of natalizumab and the active comparators have been conducted. An indirect comparison of efficacy and safety outcomes from available clinical trials of disease modifying therapies, using placebo as the common comparator, demonstrated a consistent beneficial effect of natalizumab compared with both interferon beta and glatiramer acetate for disability progression and relapse frequency.

A superior adverse event profile compared to interferon beta and an equivalent profile to glatiramer acetate (except for patterned reaction, which has not been reported in natalizumab treated patients but has a relative risk of 3.29 in patients treated with glatiramer acetate compared with placebo).

Evidence from non-randomised controlled trials shows that:

Highly active relapsing remitting multiple sclerosis patients experience more rapid disability progression and higher relapse frequency than a relapsing remitting multiple sclerosis population, as evidenced by published natural history studies and a new multi state model constructed for this submission. The multi state model estimates that disability progresses approximately twice as fast in an untreated rapidly evolving severe subgroup compared with a relapsing remitting multiple sclerosis population (mean change in Expanded Disability Status Scale (EDSS) of 0.46 and 0.27 respectively over two years).

The standardised mortality rate for people with multiple sclerosis is worse than the general population and increases with disability. Given that disability progresses faster in patients with highly active relapsing remitting multiple sclerosis, it is probable that the standardised mortality rate in highly active relapsing remitting multiple sclerosis patients is higher than the broad population of relapsing remitting multiple sclerosis patients.

In 2005, evidence from the largest population based survey of multiple sclerosis patients conducted in the UK provided information on the effect of multiple sclerosis on:

- Direct and indirect resource consumption (resource consumption was directly associated with level of disability).
- Utility was inversely associated with disability until a state worse than death was reached in the most severe disability states.

Caregiver disutility is believed to be correlated with disease severity. We estimate that the disutility of being a caregiver reaches a maximum of 0.14 at an EDSS score of 9.

It is probable that compliance with natalizumab will be better than the current disease modifying therapies because natalizumab is dosed less frequently than the current drugs and is delivered in an outpatient setting rather than at home.

Natalizumab in highly active relapsing remitting multiple sclerosis is an acceptable use of NHS resources (see section 6)

Unlike any other medical technology in England and Wales, an acceptable cost-effectiveness threshold has been established for disease modifying treatments for multiple sclerosis of £36 000 per QALY gained.

The ICER for natalizumab compared with any comparator in the rapidly evolving severe subgroup is below this acceptable threshold for all evaluated decision problems. For natalizumab compared with interferon beta the ICER is £27 000 per QALY gained. Compared with glatiramer acetate and best supportive care the ICER is £27 400 and £34 900 respectively, in the same subgroup.

By comparison, using conservative values for key uncertain parameters, when natalizumab is compared with interferon beta in the sub optimally treated subgroup the ICER is £44 100 per QALY gained. When natalizumab is compared with glatiramer acetate and best supportive care in the sub optimally treated subgroup, the ICER is £45 000 and £57 000 respectively.

Given the threshold of £36 000 per QALY gained, the probabilistic sensitivity analysis resulted in a 70% probability of natalizumab being cost-effective in people with rapidly evolving severe

multiple sclerosis compared with interferon beta. The result for the comparison with glatiramer acetate in the same subgroup was found to be 65%. If an alternative (societal) perspective is chosen, these values increase to 84% and 86% respectively.

The key parameters that affect the ICER the most are patient baseline characteristics, natural history, efficacy, cost, perspective chosen and time horizon. Safety and tolerability, discount rate and utility parameters have a marginal effect on the ICER. There is a higher degree of certainty in the rapidly evolving severe subgroup economic evaluation than in the evaluation of the sub optimally treated subgroup.

Despite every effort to source appropriate data for all components of the model, sufficient uncertainty exists in some of the input data for the sub optimally treated subgroup evaluation that the cost-effectiveness could be considered artificially pessimistic.

The absence of natural history data in the sub optimally treated subgroup and the decision to use data from the intention-to-treat placebo arm of the phase III natalizumab registration study (AFFIRM) (rather than data from the rapidly evolving severe subgroup) could be considered overly conservative.

The absence of specific efficacy data in the sub optimally treated subgroup and the assumption used to apply a relative risk of disability progression and relapse frequency from a broad relapsing remitting multiple sclerosis population from the intention-to-treat analysis in AFFIRM (rather than data from the rapidly evolving severe subgroup) could also be considered overly conservative.

Using the less conservative, but arguably more realistic assumption that the sub optimally treated subgroup is equivalent to the rapidly evolving severe subgroup in all aspects except for a previous decision to treat with a comparator disease modifying treatment, then the cost-effectiveness of natalizumab in the sub optimally treated subgroup would become very similar to that of the rapidly evolving severe subgroup (at £27.0K, £27.4K and £34.9K per QALY compared with interferon beta and glatiramer acetate and best supportive care respectively).

A new Markov model (based on the ScHARR model previously commissioned by NICE) was developed for the submission since there are no relevant published, economic evaluations in the literature.

This highly active relapsing remitting multiple sclerosis specific model adopted the reference case approach specified by NICE.

Natural history data was sourced from the well-recognised London Ontario dataset, combined with a new multi state model based on the placebo arm of the AFFIRM study.

Clinical effects were based on meta-analyses of relevant available data for both natalizumab and the comparators.

The utility of treatment was taken from the largest survey of utility and resources ever conducted in multiple sclerosis in the UK (UK multiple sclerosis Survey 2005), supplemented by analyses of data from AFFIRM and previously published sources.

The UK multiple sclerosis Survey 2005 provided resource consumption data and unit costs were sourced from recognised

UK sources

All of the nine published flaws identified by Claxton of previous models submitted to NICE have been addressed within this model

Recognised experts in the economics of multiple sclerosis have critically appraised the methods and assumptions used in the model and confirmed that: it has high external validity compared with the previous model commissioned by NICE. In addition, the Scottish Medicines Consortium critical appraisal of the model concluded that, 'good internal and external validation information was provided'

Model validation showed that the model was able to reproduce very similar ICERs to the previous NICE model for interferon beta and glatiramer acetate compared with best supportive care. The ICERs we generate for interferon beta and glatiramer acetate respectively of £57.4k and £107.2k per QALY compare well with the reported ICERS of £42-72k and £98k per QALY respectively.

Natalizumab is a new class of drug for the treatment of highly active relapsing remitting multiple sclerosis (see sections 2 and 4)

The UK approved name for natalizumab is Tysabri®. Natalizumab received marketing authorisation on 27 June 2006.

Natalizumab is a selective adhesion-molecule inhibitor and binds to the α4 subunit of human integrins, which is highly expressed on the surface of all leukocytes, with the exception of neutrophils. Specifically, natalizumab binds to the α4β1 integrin, blocking the interaction with its cognate receptor, vascular cell adhesion molecule 1, and ligands osteopontin, and an alternatively spliced domain of fibronectin, connecting segment 1. Natalizumab blocks the interaction of α4β7 integrin with the mucosal addressing cell adhesion molecule 1. Disruption of these molecular interactions prevents transmigration of mononuclear leukocytes across the endothelium into inflamed parenchymal tissue. A further mechanism of action of natalizumab may be to suppress ongoing inflammatory reactions in diseased tissues by inhibiting the interaction of α4 expressing leukocytes with their ligands in the extracellular matrix and on parenchymal cells. As such, natalizumab may act to suppress inflammatory activity present at the disease site, and inhibit further recruitment of immune cells into inflamed tissues.

Natalizumab is available in single vials of 300 mg concentrate for solution for infusion. Each vial is for single use only. Natalizumab is administered once every 4 weeks. The price per vial is £1130.

Natalizumab uptake at forecast levels represents a modest budget impact in England and Wales (see section 7)

The maximum forecast total incremental discounted cost of natalizumab in year 5 is £15.5 million.

Rapidly evolving severe:

The budget impact in the rapidly evolving severe subgroup is forecast to be £0.8 million in year 1, rising to £4.4 million in year 5.

Sub optimally treated:

The budget impact in the sub optimally treated subgroup is forecast to be £0.3 million in year 1, rising to £11.1 million in year 5.

Large cost offsets of approximately half the acquisition cost of natalizumab may be realised due to a reduction in use in interferon beta and glatiramer acetate.

The budget impact model does not include costs associated with disability progression and is likely overestimate the incremental cost of natalizumab introduction.

The forecast is based on Biogen Idec estimates of market penetration.

2 Description of technology under assessment

There are currently no other therapies licensed specifically for people with highly active relapsing remitting multiple sclerosis. Highly active relapsing remitting multiple sclerosis patients have more frequent relapses and progress more rapidly to severe states of disability and impairment than the broader relapsing remitting multiple sclerosis population. The active comparators within this submission are interferon beta and glatiramer acetate. Best supportive care is also considered as a comparator.

Natalizumab is the first in a new class of drug for the treatment of highly active relapsing remitting multiple sclerosis. It is a selective adhesion-molecule inhibitor. Natalizumab has a unique and specific mechanism of action, which prevents white blood cells, the mediators of inflammation in multiple sclerosis, from entering the brain.

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Rapidly evolving severe subgroup defined by 2 or more disabling relapses in one year, and with 1 or more Gadolinium-enhancing lesions on brain Magnetic Resonance Image (MRI) or a significant increase in T2 lesion load as compared to a previous MRI. See section 2.3.1

Sub optimally treated subgroup defined as patients who have had at least 1 relapse in the previous year while on therapy, and have at least 9 T2-hyperintense lesions in brain MRI or at least 1 Gadolinium-enhancing lesion. See section 2.3.2.

2.1 Give the brand name, approved name and, where appropriate, therapeutic class.

Brand name:	Tysabri®
Approved name:	Natalizumab 300 mg concentrate for solution for infusion
Therapeutic class:	Natalizumab is a recombinant, humanized form of a murine monoclonal antibody that binds to the α4 subunit of α4β1 (also known as very late antigen 4 [VLA-4] or CD49d-CD29) and α4β7 integrin.

2.2 Does the technology have a UK marketing authorisation for the indications detailed in this submission? If so, please give the date on which authorisation was received. If not, please state current UK regulatory status, with relevant dates (for example, date of application and/or expected approval dates).

Marketing authorisation was received on 27 June 2006. Natalizumab was launched in the UK on 14 July 2006.

2.3 What are the indication(s) in the UK?

Single disease modifying therapy in highly active relapsing remitting multiple sclerosis (HARRMS) for the following patient groups: (1)

Box 1: Natalizumab rapidly evolving severe (RES) indication

Patients with rapidly evolving severe relapsing remitting multiple sclerosis ('rapidly evolving severe', RES)

Patients defined by 2 or more disabling relapses in one year, and with 1 or more Gadolinium-enhancing lesions on brain magnetic resonance imaging (MRI) or a significant increase in T2 lesion load as compared to a previous MRI.

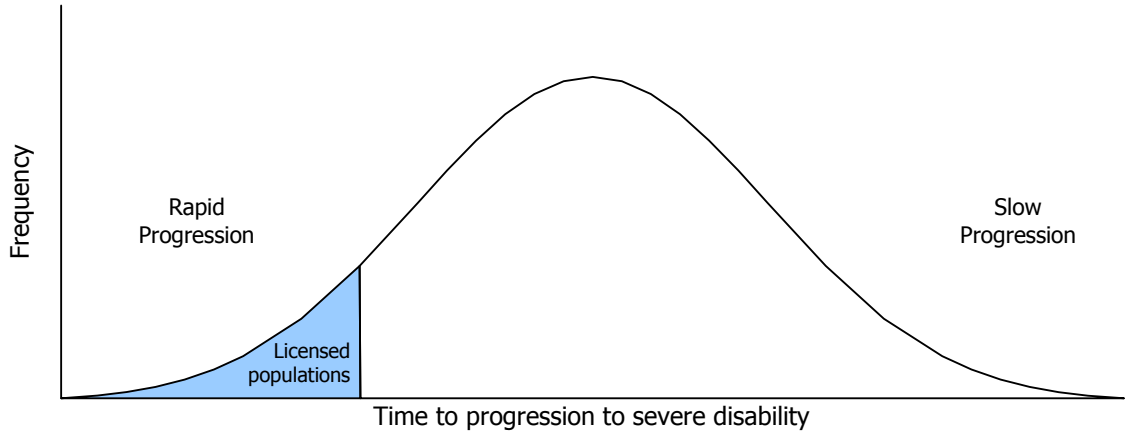
Box 2: Natalizumab sub optimally treated (SOT) indication

Patients with high disease activity despite treatment with an interferon beta ('sub optimal therapy', SOT)

Patients should have had at least 1 relapse in the previous year while on therapy, and have at least 9 T2-hyperintense lesions in brain MRI or at least 1 Gadolinium-enhancing lesion.

These RES and SOT indications should be considered subgroups of relapsing remitting multiple sclerosis (RRMS) that exhibit high disease activity, of a severity that is greater than the typical person with RRMS (see Figure 1). We refer to these subgroups consistently within the dossier as the 'RES subgroup' and the 'SOT subgroup'.

Figure 1 Conceptual framework for positioning prior treatment failure and rapidly evolving severe subgroups within overall RRMS population



Note that the exact profile of the distribution is not known.

A positive NICE opinion is sought for both RES and SOT subgroups. This is supported by the European Medicines Evaluation Agency (EMEA) license above. (1;2)

The licensed populations exhibit disease activity greater than the average person with RRMS.

2.3.1 Genesis of the RES subgroup

The statistical analysis plan within the AFFIRM study specified a number of subgroup analyses and these are shown in Table 1. These subgroups were pre-specified based on the known or inferred influence of the parameters on future disease course, including relapses and disability progression. The subgroup analyses indicate that natalizumab is effective in reducing the rate of relapse regardless of the age, baseline disease activity, prior treatment history, or disability status of the subject. In addition, since the treatment effect is similar in all ranges of body weight studied, the use of a fixed dose of 300 mg natalizumab is justified.

The RES subgroup consisted of patients that had experienced two or more relapses in the prior year and also had one or more gadolinium-enhancing lesions on brain MRI or a significant increase in T2 lesion load as compared to a previous recent MRI. The RES subgroup was defined following an analysis requested by the CHMP as part of their assessment of the natalizumab Marketing Authorisation. Although, strictly speaking, this subgroup analysis was defined 'post-hoc', it is a composite of three subgroup analyses that were pre-specified in the statistical analysis plan. The results of all these pre-specified analyses were statistically significant (Table 2 and Table 3).

Table 1 Pre specified subgroups within the AFFIRM study

Subgroup analysis	Attribute	Contribution to RES subgroup
Number of relapses in the year prior to screening	1, 2, > 2	Y
McDonald criteria	1, >1	
Prior treatment	Y, N	
Baseline Gd-enhancing lesions	Absent, Present	Y
Baseline number of T2 lesions	< 9, ≥ 9	Y
Baseline EDSS	≤ 3.5, > 3.5	
Baseline age (years)	< 40, ≥ 40	
Gender	Male, Female	
Body mass (kg)	*	
Race	White, non-white	
Region	North America, Europe (CEE), Europe (non-CEE), RoW	
Investigational site	Sites with ≥ 17 subjects	

* Attributes varied depending upon outcome.

Table 2 academic / commercial in confidence information removed

Table 3 academic / commercial in confidence information removed

In the placebo group, subjects with more active baseline disease, defined as either a greater number of pre-study relapses, a greater number of Gd-enhancing lesions at baseline or a greater number of T2 hyperintense lesions at baseline, had higher relapse rates and developed more lesions on MRI during the study than those less active disease. Treatment with natalizumab, however, had potent and consistent effects on clinical relapses, new and newly-enlarging T2 lesions, and Gd-enhancing lesions across each of the subgroups, irrespective of baseline MS disease activity. Indeed, subjects with more inflammatory activity at baseline appeared to experience even greater relative reductions in disease activity than those with more quiescent disease. These findings are consistent with the hypothesized mechanism of action of natalizumab, which is thought to exert its therapeutic benefit by inhibition of leukocyte transmigration. Thus, subjects with the highest rates of

inflammatory activity would be expected to exhibit the greatest reduction in the inflammatory lesions that are thought to contribute to acute clinical relapses and subsequent neuropathology.

2.3.2 Genesis of the SOT subgroup

The EMEA granted a license for natalizumab in the SOT indication based upon data from the SENTINEL study, (2;3) which showed that the addition of natalizumab to current IFN-beta therapy significantly reduced relapse frequency and risk of disability progression compared with IFN-beta therapy alone, in patients that were continuing to have relapses despite already being treated with IFN-beta (i.e. sub optimal therapy patients).

It should be noted that baseline characteristics of the patients included in the SENTINEL study and the AFFIRM study were similar. (3;4) In SENTINEL, patients had to have received treatment with IFN-beta for at least 12 months before randomisation; and have had at least 1 relapse during the 12-month period prior to randomisation. This is consistent with the SOT indication approved by the EMEA. (2)

The rationale for the SOT indication is reported in the European Public Assessment Report (EPAR) for natalizumab as follows: (2)

> *For this patient population relevant data could be derived from SENTINEL. Patients had to be on Avonex [IFN-beta 1a] treatment for at least one year (which can be considered a 'full and adequate course') and to show active disease despite this active treatment with an IFN-beta. Unfortunately, there is no data on the efficacy of natalizumab monotherapy in these patients due to the design of the study (add-on). However, the overall efficacy data suggest that efficacy in SENTINEL is mainly driven by natalizumab and not by Avonex, since Avonex by definition was not sufficiently active. Therefore, the efficacy database is considered sufficient to support efficacy in patients being treated in case of failure of interferon beta. The other potential alternatives in the indication wording (e.g. failure of GA) for the SPC are not represented in this SENTINEL population, however, are relevant from a clinical perspective, and it can be assumed that natalizumab will be efficacious.*

2.4 To what extent is the technology currently being used in the NHS for the proposed indication? Include details of use in ongoing clinical studies.

As of 24 November 2006, 11 units (vials) have been distributed in the UK.

Three studies are ongoing although none will produce additional evidence within the next year (Table 4).

Table 4 Summary of ongoing studies of natalizumab in multiple sclerosis

Study Reference	Objective	Study Design	Completion within 12 months?
101-MS-321/322	To evaluate the safety of natalizumab monotherapy following re-exposure to natalizumab. This includes assessing the risk of hypersensitivity and immunogenicity, and	Multicentre, open-label, single-arm, safety extension study for subjects	N

	evaluating the safety of switching from IFN-beta, GA, or other MS therapies to natalizumab.	who completed AFFIRM or SENTINEL and a Dosing Suspension Safety Evaluation.	
TYGRIS 101-MS-403	To determine the incidence and pattern of serious infections, malignancies, and other serious adverse events (SAEs) in patients with MS treated with natalizumab.	Prospective, observational cohort.	N
TOUCH Prescribing Program (US only)	The program was developed to help achieve the following goals: Inform prescribers and patients about the benefits and risks of natalizumab before initiating and while on therapy; assure only appropriate patients are prescribed natalizumab; assure appropriate patients are infused only at sites enrolled in the program; assess the incidence of, and risk factors for, progressive PML and other serious opportunistic infections that may be associated with natalizumab treatment.	Prospective, observational cohort.	N

2.5 Does the technology have regulatory approval outside the UK? If so, please provide details.

Yes. Natalizumab is licensed in all European countries under the EMEA Centralised Licensing Procedure. It is also currently licensed in the USA, Canada and Australia.

2.6 Is the technology subject to any other form of health technology assessment in the UK? If so, what is the timescale for completion?

Yes. A submission was made to the Scottish Medicines Consortium (SMC) on 7th August 2006 and it is anticipated that the SMC will publish guidance on the SMC website on 11th December 2006. The final appraisal determination from the SMC received by Biogen on 10th November 2006 concluded that the economic case had not been demonstrated for natalizumab. This conclusion was based upon an incremental cost effectiveness ratio (ICER) for a comparison with IFN-beta and GA in the RES subgroup of £24 900 and £26 700 respectively (health and personal social services perspective).

2.7 For pharmaceuticals, what formulation(s) (for example, ampoule, vial, sustained-release tablet, strength(s) and pack size(s) will be available?

Strength	Pharmaceutical Form	Route of administration	Packaging	Content (concentration)	Package size
300 mg	Concentrate for solution for infusion	Intravenous use	Vial (glass)	15 ml (20 mg/ml)	1 vial

2.8 What is the proposed course of treatment? For pharmaceuticals, list the dose, dosing frequency, length of course and anticipated frequency of repeat courses of treatment.

Dose	Dosing Frequency	Course Length	Frequency of Repeat Courses
300 mg	Once every 28 days	Chronic treatment	na

2.9 What is the acquisition cost of the technology (excluding VAT)?

The price of natalizumab is £1130 per vial. (1)

2.10 What is the setting for the use of the technology?

Natalizumab will be initiated and supervised by specialised physicians experienced in the diagnosis and treatment of neurological conditions, in centres with timely access to MRI and resources for the management of hypersensitivity reactions.

2.11 For patients being treated with this technology, are there any other aspects that need to be taken into account? For example, are there additional tests or investigations needed for selection, or particular administration requirements, or

is there a need for monitoring of patients over and above usual clinical practice for this condition? What other therapies, if any, are likely to be administered at the same time as the intervention as part of a course of treatment?

It is anticipated that additional safety monitoring will be required:

Immunogenicity: Disease exacerbations or infusion related events might indicate the development of anti-natalizumab antibodies. In the case that either of these events should occur, the presence of antibodies should be evaluated and a confirmatory test should be undertaken after six weeks. (1) Persistent anti-natalizumab antibodies developed in 6% of people in the AFFIRM study.

Hypersensitivity: Patients are to be observed during the infusion and for one hour after completion of the infusion. Resources for the management of hypersensitivity reactions will be available in all treating centres. (1) A total of 4% or patients experienced a hypersensitivity reaction in the AFFIRM study.

Opportunistic Infections: Opportunistic infections have been detected in MS patients treated with natalizumab and should be considered by prescribers in the differential diagnosis of infections. (1)

Progressive Multifocal Leukoencephalopathy (PML): Patients must be evaluated for any new or worsening neurological symptoms or signs that may be suggestive of PML. (1) MRI scans and cerebral-spinal fluid (CSF) testing for JC viral DNA may be required. (5) Following an extensive safety review a rate of PML of 1.0 per 1000 treated patients has been estimated. (6) No cases of PML have been observed in MS patients treated with natalizumab monotherapy, however although a risk of PML associated with natalizumab monotherapy is at present theoretical, it cannot be completely discounted.

3 Statement of the decision problem

Within this submission we address 6 decision problems as shown below.

Best supportive care (i.e. no active treatment) in highly active relapsing remitting multiple sclerosis (HARRMS) patients is inappropriate as these patients have highly active disease and are the group of people with multiple sclerosis (MS) who are likely to progress most rapidly in the absence of active treatment.

The decision problems are described in 3.1 Decision problems. The key parameters that the information in the Evidence Submission will address are summarised in Table 5 on page 27. (7;8)

Following the description of the decision problems, we explain the clear rationale to reject the proposition that mitoxantrone (MTX) is a valid comparator to natalizumab. This section was added at the suggestion of National Institute for Health and Clinical Excellence (NICE) following correspondence and a meeting (on 17th October 2006) relating to the choice of comparator for natalizumab.

3.1 Decision problems

Six decision problems will be reported in this submission, 3 in the sub optimally treated (SOT) subgroup and 3 in the rapidly evolving severe (RES) subgroup.

Based on current treatment practice best supportive care is unlikely and arguably inappropriate in HARRMS patients as these patients have the most active disease course. This means that:

- Their level of disability is likely to progress more rapidly than a RRMS population.
- They will have a high relapse frequency.
- Finally, in an era of increasing constraints on healthcare resources, it is most likely that the patients with highest disease activity will be prioritised to treatment over those with less active disease.

3.1.1 SOT subgroup

- What is the incremental effectiveness and incremental cost-utility of natalizumab compared with glatiramer acetate (GA) in the SOT HARRMS subgroup for patients experiencing disease activity while receiving IFN-beta treatment?
- What is the incremental effectiveness and incremental cost-utility of natalizumab compared with IFN-beta in the SOT HARRMS subgroup for patients experiencing disease activity while receiving GA treatment?
- What is the incremental effectiveness and incremental cost-utility of natalizumab compared with no disease modifying therapy (DMT) in the SOT HARRMS subgroup?

3.1.2 RES subgroup

- What is the incremental effectiveness and incremental cost-utility of natalizumab compared with IFN-beta in the RES HARRMS subgroup?
- What is the incremental effectiveness and incremental cost-utility of natalizumab compared with GA in the RES HARRMS subgroup?
- What is the incremental effectiveness and incremental cost-utility of natalizumab compared with no DMT in the RES HARRMS subgroup?

Please review Sections 2.3.1 and 2.3.2 where the genesis of these subgroups is described.

3.2 Key parameters

Table 5 NICE scope and key parameters

Attribute	Final scope issued by NICE	Key parameters
Population	Adults with highly active RRMS who have: • high disease activity despite treatment with IFN-beta or • rapidly evolving severe RRMS	Identification of a HARRMS population. The natural history of a HARRMS population.
Intervention	Natalizumab 300 mg	-
Comparator(s)	For adults with RRMS and high disease activity despite treatment with a IFN-beta or GA (SOT): • GA, for patients failing on IFN-beta • IFN-beta, for patients failing on GA • best supportive care with no disease modifying treatment (DMT) For adults with rapidly evolving severe RRMS (RES): • IFN-beta • GA • best supportive care with no DMT	Differential effects of natalizumab compared with GA/IFN-beta on outcomes such as disability progression, relapse frequency, adverse events, NHS cost and utility in the SOT subgroup. Differential effects of natalizumab compared with IFN-beta/GA on the above outcomes in the RES subgroup.
Outcomes	The outcome measures to be considered include: • mortality • relapse rate • disability progression • adverse effects of treatment, including PML • health-related quality of life	Derivation of a quality adjusted life year (QALY) for each analysis based on the effect of natalizumab or the comparator on disability progression, relapse frequency and adverse effects.
Special considerations and other issues	If the evidence allows, the appraisal will attempt to identify criteria for selecting patients for whom natalizumab would be particularly appropriate. The intervention will be appraised according to its marketing authorisation.	The RES and SOT subgroups are clearly defined subgroups of RRMS and no additional subgroup analysis has been undertaken. RRMS represents a considerable burden on individuals, caregivers and employers and this impact will also be described.

IFN-beta = interferon beta; GA = glatiramer acetate; RES = rapidly evolving severe; SOT = sub optimal therapy

3.3 Biogen rejects the proposition that mitoxantrone (MTX) is a valid comparator in the UK

In this section we summarise the clear rationale to reject the proposition that MTX is a valid comparator.

3.3.1 Background

MTX is a synthetic anti-neoplastic agent licensed only for use in oncology, which is not licensed for the treatment of MS.

3.3.2 NICE guidelines limit the use of MTX to a study setting

The NICE guideline of 2004 ('Multiple Sclerosis: National clinical guideline for diagnosis and management in primary and secondary care') recommends that MTX should only be used in the following circumstances:

- after full discussion and consideration of all the risks
- **with formal evaluation, preferably in a randomised or other prospective study**
- by an expert in the use of these medicines in MS with close monitoring for adverse events

3.3.3 MTX is not routinely used outside a study setting in the UK

A survey of 2048 people with MS in the UK conducted in 2005 (UK MS Survey 2005, see section 5.8.4) identified no people with RRMS that reported receiving MTX (Table 6). A total of 8 patients reported receiving MTX (6 had secondary progressive MS [SPMS] and 2 had primary progressive MS [PPMS]). Over four hundred (n = 437) reported using a DMT in the survey.

Table 6 Distribution of disease modifying drug treatment in people with MS in the UK

		EDSS										
Disease	**DMT**	**0**	**1**	**2**	**3**	**4**	**5**	**6**	**6.5**	**7**	**8**	**9**	**Total**
PPMS	IFN-beta	0	0	0	0	0	0	0	0	0	0	0	0
	GA	0	0	0	0	0	0	0	0	0	0	0	0
	MTX	0	0	0	0	0	0	0	0	1	1	0	2
RRMS	IFN-beta	6	34	42	17	40	45	26	7	0	2	1	220
	GA	2	11	11	2	19	11	6	5	0	1	0	68
	MTX	0	0	0	0	0	0	0	0	0	0	0	0
SPMS	IFN-beta	0	0	1	1	10	27	52	27	5	0	0	123
	GA	0	0	1	0	3	5	4	5	0	0	0	18
	MTX	0	0	0	0	0	1	3	1	1	0	0	6

DMT = disease modifying therapy; EDSS = Expanded Disability Status Scale; PPMS = primary progressive multiple sclerosis; RRMS = relapsing remitting multiple sclerosis; SPMS = secondary progressive multiple sclerosis; IFN-beta = interferon beta; GA = glatiramer acetate; MTX = mitoxantrone

The UK MS Survey 2005 was conducted by a third-party in collaboration with the MS Trust and was designed to collect contemporary resource data and utility data from people with MS in the UK. The utility and cost analyses are in press.

4 Context

In the large majority of patients multiple sclerosis is a relentlessly progressive chronic disease. Multiple sclerosis is the most common disabling neurological condition affecting young adults. Multiple sclerosis adversely impacts the lives of patients, caregivers and other stakeholders in many ways:

- multiple sclerosis can devastate the quality of life of the individual with the disease, and may lead to a state worse than death in late stages of the disease
- multiple sclerosis necessitates the support of friends and family
- multiple sclerosis impairs the quality of life of caregivers
- multiple sclerosis leads to an increased burden on caregivers
- multiple sclerosis leads to high unemployment
- multiple sclerosis patients require increased nursing care and home help
- multiple sclerosis has a high personal financial cost to sufferers and carers

Highly active relapsing remitting multiple sclerosis patients suffer more frequent relapses and more rapid progression to severe disability than the broader relapsing remitting multiple sclerosis population; therefore one would expect the above consequences to have even greater impact for this group of patients.

There are currently no other treatments that are licensed specifically for patients with highly active relapsing remitting multiple sclerosis and no clear guidelines on initiation of therapy in this patient group, or guidance on what to do in the event of a sub optimal response to current therapy.

It is notable that there are no specific guidelines for patients with highly active relapsing remitting multiple sclerosis. This provides a unique opportunity for NICE to be the first authoritative body to provide much-needed clarity by recognising natalizumab as the most appropriate treatment for highly active relapsing remitting multiple sclerosis patients.

Section 4 describes the landscape into which any new treatment for relapsing remitting multiple sclerosis (RRMS) would be introduced. The landscape is disheartening for patients and other stakeholders. We describe the impact of the disease and, in the absence of any well-publicised treatment pathways in RRMS, we present two simplified pathways: the current position (Figure 2); and a future position after the introduction of natalizumab (Figure 8). We present a summary of the limited treatment options available prior to the launch of natalizumab.

4.1 Please provide a brief overview of the disease/condition for which the technology is being used. Provide details of the treatment pathway and current treatment options at each stage.

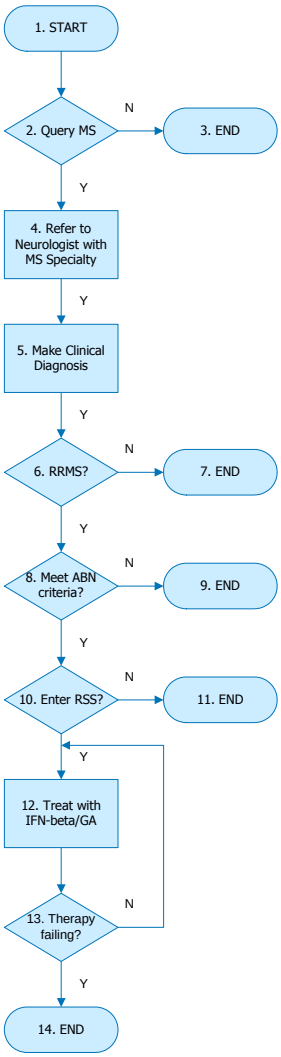
Multiple Sclerosis (MS) is incurable and has increased mortality and morbidity rate compared with the general population.

- Relapsing forms of MS are chronic, disabling conditions resulting in a gradual deterioration of functional status and quality of life, which can result in people living in a health state considered by society to be worse than death (9-21)
- MS is the most common disabling neurological condition affecting young adults. It is most often diagnosed in people between the ages of 20 and 40 – though it can be earlier or later. (22)
- MS is associated with excess mortality compared to the general population (23;24)
- MS causes morbidity and fatigue that increases as the disease progresses (25-27)
- The mean utility of people with MS is worse than the general population and, in the UK, is as bad or worse than the ten most prevalent diseases admitted to a UK inpatient or outpatient department (14;19;28)
- The rate of disability progression is not the same for all patients, with evidence that people in the rapidly evolving severe (RES) subgroup experience more rapid disability progression than the broader RRMS population (29-41)
- The prevalence of MS in England and Wales is approximately 104 per 100,000 on the south coast of England to 155 per 100,000 in the North of England (using the Scottish Borders as a proxy) (29;42-44)
- There are no licensed treatments that provide a cure for MS (42;45)

4.1.1 Treatment pathway in England and Wales

It should be noted in that we were unable to identify a treatment pathway for RRMS (or highly active RRMS [HARRMS]) that is representative of UK practice. Figure 2 was produced after a review of the National Collaborating Centre for Chronic Conditions (NCC-CC) guidelines for MS. (46) It presents a simplified representation of a complex network and concentrates on the areas of the pathway most relevant to RRMS and this submission. It is not known whether this is reflective of routine practice in the UK, although it is thought that the care pathway is often 'broken' at point 4 academic / commercial in confidence information removed. It should also be noted that only a single 'feedback loop' is shown in the pathway (i.e. monitoring patients on treatment), whereas in reality there would be many more. It is possible that the absence of a well-publicised treatment pathway contributed to the stark conclusions drawn as a result of a recent audit of MS services in the NHS (see section 4.6). (48)

Figure 2 RRMS treatment pathway in England and Wales (October 2006)



Notes to the figure

1. Care pathway starts here.
2. Any health care professional should be able to access the rest of the care pathway from this point. The NCC-CC guidelines on the management of MS make recommendations on who should be responsible for this stage. (46)
3. This end node would lead to other diagnoses and treatments, not shown here.
4. A person suspected of having MS should be referred to a specialist. (47)
5. A diagnosis should be made according to the NCC-CC guidelines, which reference the McDonald criteria. (46;49)
6. A diagnosis of RRMS is required to progress further in the care pathway.
7. This end node will lead to other care pathways designed for people with secondary progressive MS (SPMS) or primary progressive MS (PPMS), not shown here.
8. A decision will then be required on whether the to treat RRMS, based on the Association of British Neurologists (ABN)/NCC-CC criteria. (50)
9. This end node will again lead to other care pathways contained within the NCC-CC guidelines, not shown here. (46)
10. The person with RRMS, in conjunction with an experienced clinician, would then make a decision to enter the existing risk-sharing scheme to receive treatment with IFN-beta or GA. (51)
11. This end node is would lead to another pathway of care, not shown here.
12. A person with RRMS would be initiated on treatment with a licensed disease modifying therapy (DMT).
13. Patients on treatment will be monitored until a decision is made that therapy is failing, at which point they will enter a different care pathway, not shown here.

ABN = Association of British Neurologists, IFN-beta = interferon beta, GA = glatiramer acetate, RRMS = relapsing remitting MS, RSS = Risk Sharing Scheme

No specific treatment guidelines exist for people with HARRMS (the licensed population for natalizumab). However, there is considerable evidence that people with highly active disease, characterised by high relapse frequency in the early stages, tend to progress to moderate states of disability more rapidly than a RRMS population.

To our knowledge the economic evaluation in Section 6 is the first to assess the cost-effectiveness of any DMT in HARRMS. Patients with highly active relapsing remitting disease progress more rapidly than the general RRMS population and this is a unique feature of the model we present in the SOT and RES subgroups.

4.1.2 Alternative treatments reflecting current clinical practice in England and Wales

A large survey published by Kobelt et al in 2006 shows that the proportion of people treated with licensed DMTs in England and Wales is the lowest in Europe (20% compared to next lowest country Netherlands 35.5%). (19) The historical factors contributing to this position are multifactorial and include: an inconsistent referral pathway to a neurologist experienced in MS; commissioning practice in the UK, which was reflected in NICE guidance 32; and the establishment of a risk-sharing scheme. (47;51;52) Note that the risk sharing scheme allowed eligible patients equitable access to current DMTs.

4.1.2.1 Licensed disease modifying treatments

The four licensed DMTs are: (53-56)

- Interferon β-1a 0.5 ml 30 μg prefilled syringe for injection once weekly: Avonex (Biogen Idec)
- Interferon β-1a 22 μg prefilled syringe for injection; 44 μg prefilled syringe for injection three times weekly: Rebif (Serono)
- Interferon β-1b powder 250 μg per ml when reconstituted for injection on alternate days: Betaferon (Schering)
- Glatiramer acetate 20 mg/ml solution for injection, pre-filled syringe: Copaxone (TEVA, Sanofi-Aventis)

The current treatment options in the HARRMS populations are limited and unsatisfactory.

- The effect of current DMTs in the RES and SOT subgroups has not been reported.
- None of the currently licensed DMTs were recommended by NICE for routine use in England and Wales. (52)
- The current DMTs may only be provided under the terms of a risk-sharing agreement, established between the Department of Health (DoH) and the manufacturers. (17;42;51;57;58)
- The current ABN and NCC-CC guidelines make no specific reference to treatment of the RES and SOT subgroups. (46;50)
- The effect of current DMTs on disability progression in RRMS is variable and modest at best (compared with placebo, the effect varies from non-significant to significant depending on the choice of drug). (58-73)

- Relapses are the main reason for initiating current DMTs, yet the effect of these treatments on the rate of relapse is modest (approximately 30% reduction compared with placebo in contrast to a reduction in excess of two-thirds for natalizumab). (4;58-72;74)
- Patients treated with IFN-beta who continue to experience disease activity as evidenced by relapses and disability progression do not appear to gain further benefit when switching from one IFN-beta to another. (75)
- There is inconsistent evidence from randomised controlled trials on the effect of current DMTs on quality of life in people with RRMS. (76-84)
- The systemic side effects of IFN-beta are generally more problematic than those for GA. (42)
- Current DMTs require daily, every-other-day or weekly injection, which may deter some patients.

4.1.2.2 Unlicensed medicinal products

Individuals with MS have been treated with methotrexate, cyclophosphamide, cyclosporine, mitoxantrone, intravenous immunoglobulins, or alemtuzumab. None of these drugs are licensed for the treatment of MS in the UK. None of these drugs are recommended within the current ABN guidelines for treatment of MS nor were they considered in the NICE guidance for MS therapy (2003). (50;85)

Alemtuzumab (MabCampath) is licensed for the treatment of patients with chronic lymphocytic leukaemia but it is used, on an experimental basis, in a small number of patients in the UK for treatment of MS. In September 2005, a three-year, phase II study of alemtuzumab given together with IFN-beta in relapsing-remitting multiple sclerosis was suspended after two years due to the emergence of 3 cases (one fatal) of the SAE severe idiopathic thrombocytopenic purpura (ITP). Subsequently a further 3 cases were discovered. (86) Alemtuzumab has also been associated with a 27% incidence of Graves disease (87), and Goodpasture's Syndrome (another antibody-mediated autoimmune disease) has also been reported. (87) Because of the unresolved questions relating to the safety of the product, Genzyme (the manufacturer) discourages patients from using MabCampath for MS outside of a clinical study setting in which procedures are in place for managing ITP risk. (86)

Cyclophosphamide is an alkylating agent, which has been used primarily in oncology. Its cytotoxic effects on DNA synthesis and interference in autoimmune encephalomyelitis led to its use in MS. Positive clinical effects have been found in younger patients with actively progressive disease of short duration. (88)

Intravenous immunoglobulin treatments are not indicated for the treatment of MS and are not recommended in England and Wales. There is no conclusive evidence of their efficacy in MS patients. Some studies have shown reductions in relapse rates compared to placebo and with few side effects but lack of effect has been reported in several studies. (89)

Mitoxantrone (MTX) is a synthetic neoplastic agent used primarily in oncology, which is not licensed for the treatment of MS. MTX is not recommended for use in the UK outside of a study setting and is not used in people with RRMS. MTX is not recommended for use by NICE and NCC-CC outside a study setting in the UK and is not used to treat people with RRMS (see Section 3.3). It has been studied predominantly in a mixed MS population and found to delay relapses but it has shown inconsistent results with respect to disability progression. Only a single,

small (n= 51), randomised, single blinded, placebo controlled study has evaluated its safety and efficacy in a population comprising solely RRMS patients. Caveats regarding the clinical efficacy have been highlighted by the American Academy of Neurology subcommittee on Therapeutics and Technology Assessment. (90) MTX is associated with serious adverse events (SAEs), including potentially fatal congestive heart failure (approximately 1 in 40 patients) and drug-induced acute myeloid leukaemia (AML, approximately 1 in 400 patients). (91) According to a recent review of the use of MTX in MS by Scott 2004 there are no published pharmacokinetic data for intravenous MTX in patients with MS. (92) Novantrone® from Wyeth Pharmaceuticals was discontinued in the UK in early 2006.

4.2 What was the rationale for the development of the new technology?

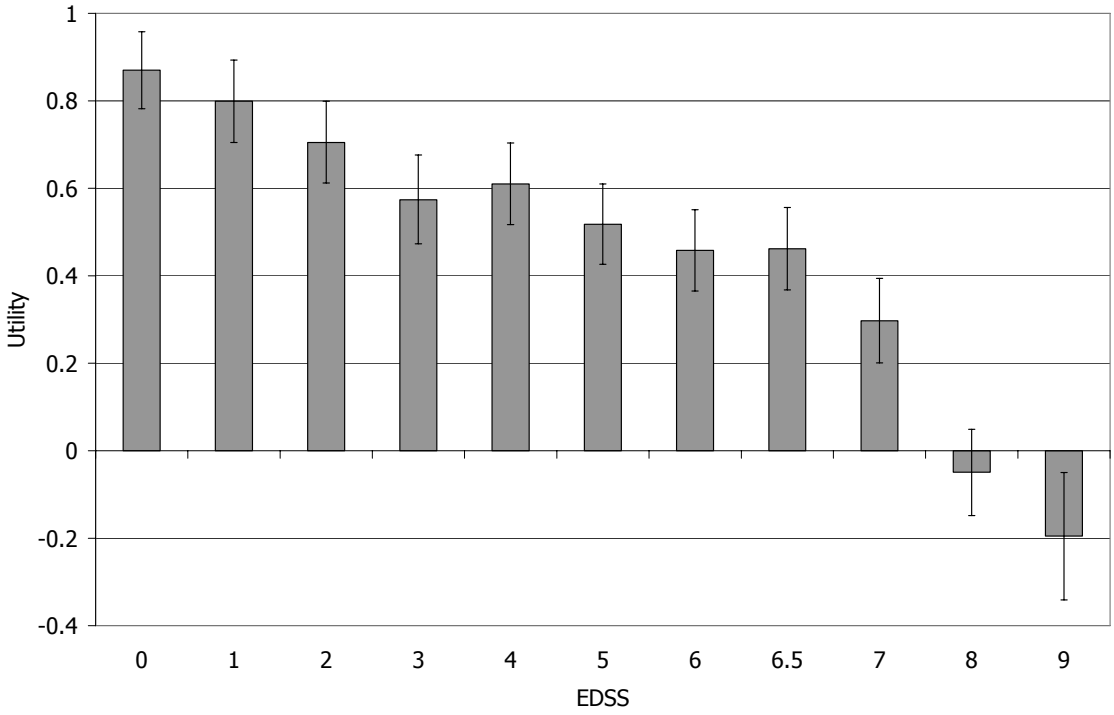
Natalizumab was developed because of the high unmet efficacy need in people with RRMS, despite the availability of licensed treatments with ill-defined mechanisms of action. Natalizumab is the first in a new class of drug for the treatment of HARRMS. It is a selective adhesion-molecule inhibitor. Natalizumab has a unique and specific mechanism of action, which prevents white blood cells, the mediators of inflammation in MS, from entering the brain.

RRMS is a chronic, disabling condition that results in a progressive deterioration of functional status and quality of life, which can result in people living in a health state considered by society to be worse than death. (3-15) There is a clear need to develop treatments that can halt, delay or alleviate the effects of the disease.

MS is a relentlessly progressive chronic disease and the most common disabling neurological condition affecting young adults. As described in this section, MS adversely impacts the lives of patients, caregivers and other stakeholders in many ways:

- MS devastates the quality of life of the individual with the disease, leading to a state worse than death in late stages of the disease
- MS necessitates the support of friends and family
- MS impairs the quality of life of caregivers
- MS leads to an increased burden on caregivers
- MS leads to high unemployment
- MS patients require increased nursing care and home help
- MS has a high financial cost

Figure 3 The effect of MS on quality of life, UK MS Survey 2005, Orme et al in press



The graph presents the utility profile of the MS Survey 2005. The analysis was based on data collected in the MS Survey 2005 (see section 5.8.4) and is currently in press (Orme et al). The utility estimate was derived from EQ-5D using the social tariff published by Dolan et al. (93)

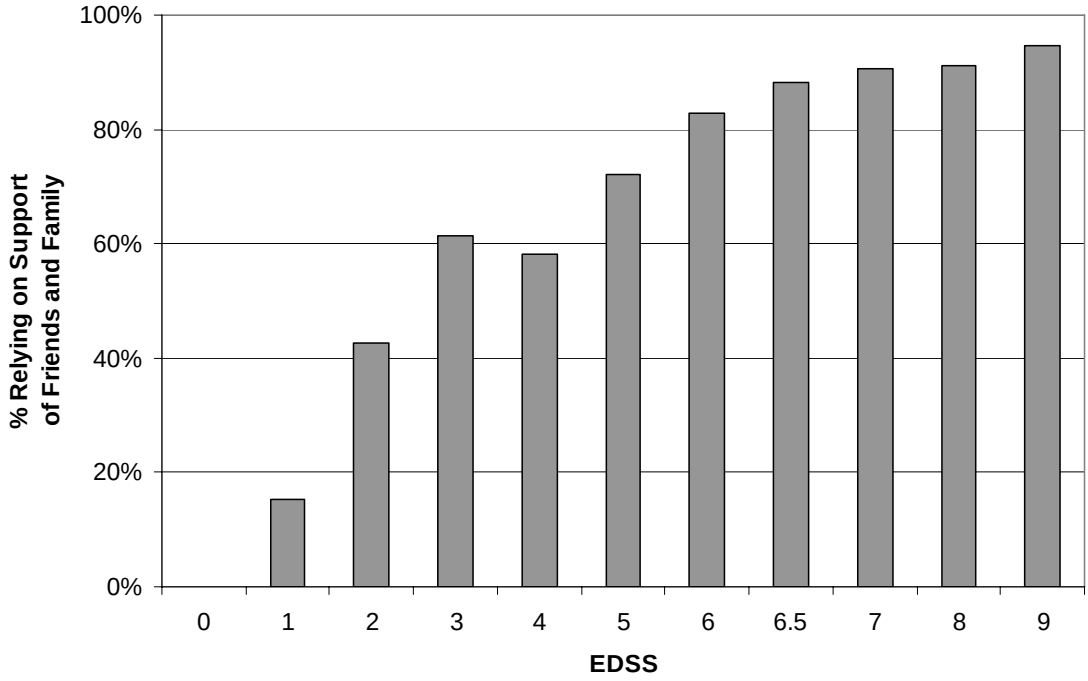
Figure 3 shows the detrimental effect of MS on the utility of people with MS in the UK from the UK MS Survey 2005 (Orme at al, in press). There is a decline in utility that corresponds with an increase in disability as measured by Expanded Disability Status Scale (EDSS). Of particular note is the rapid decline after EDSS 6.5, which culminates in a utility state considered to be worse than death at EDSS 8 and EDSS 9. Orme et al also note that, 'the average utility of people with MS as measured in this study appears to be worse than all but one of the most prevalent conditions assessed by Currie et al in a [UK] hospital setting (people with other rheumatoid arthritis attending a hospital outpatient department)' (Table 7 below). (14;28)

Table 7 A comparison of the utility of people with MS and other prevalent conditions (UK MS Survey 2005)

ICD10	Disease	Mean	SD	N	Setting
N92	Excessive, frequent and irregular menstruation	0.804	0.250	116	OP
K51	Ulcerative colitis	0.787	0.235	61	OP
C44	Other malignant neoplasms of skin	0.726	0.267	273	IP
C61	Malignant neoplasm of prostate	0.718	0.278	83	OP
K80	Cholelithiasis	0.709	0.305	192	IP
N95	Menopausal and other perimenopausal disorders	0.703	0.317	103	OP
I10	Essential (primary) hypertension	0.694	0.306	82	OP
K50	Crohn's disease [regional enteritis]	0.692	0.293	73	OP
E11	Non-insulin-dependent diabetes mellitus	0.674	0.287	159	OP
H26	Other cataract	0.672	0.286	748	IP
K21	Gastro-oesophageal reflux disease	0.671	0.301	216	IP
R10	Abdominal and pelvic pain	0.670	0.325	337	IP
I25	Chronic ischemic heart disease	0.636	0.293	789	IP
I48	Atrial fibrillation and flutter	0.614	0.316	189	IP
I21	Acute myocardial infarction	0.610	0.336	251	IP
R07	Pain in throat and chest	0.589	0.346	472	IP
R10	Abdominal and pelvic pain	0.576	0.350	74	OP
I20	Angina pectoris	0.576	0.306	284	IP
I25	Chronic ischemic heart disease	0.558	0.317	146	OP
-	**Multiple sclerosis (PPMS, RRMS & SPMS)**	**0.491**	**0.320**	**2408**	**-**
M06	Other rheumatoid arthritis	0.432	0.310	120	OP

All conditions other than MS adapted from Currie CJ, McEwan P, Peters JR, et al. The Routine Collation of Health Outcomes Data from Hospital Treated Subjects in the Health Outcomes Data Repository (HODaR): Descriptive Analysis from the First 20,000 Subjects. Value in Health 2005;8:586 (Tables 5 & 6). (28) IP = Inpatient, OP = Outpatient

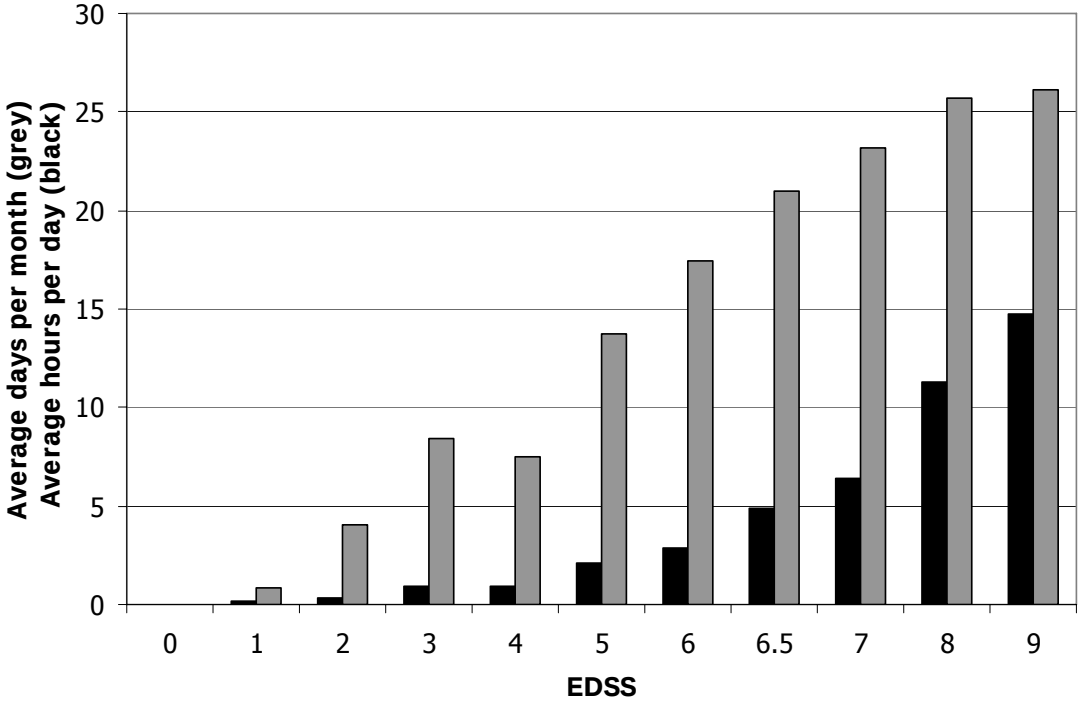
Figure 4 The impact of MS on friends and family, UK MS Survey 2005



The graph presents the proportion of people with MS relying on the support of friends and family by level of disability. Respondents completed a question about their employment status in the UK MS Survey 2005 (see section 5.8.4).

Figure 4 shows the magnitude of the impact of MS on friends and family of people with the disease. By the time someone reaches EDSS 3, 61% of people with MS rely on help from family and friends; by the time the person is unable to walk this increases to 83%. The magnitude of this help varies from a few hours per month to full-time, round the clock care.

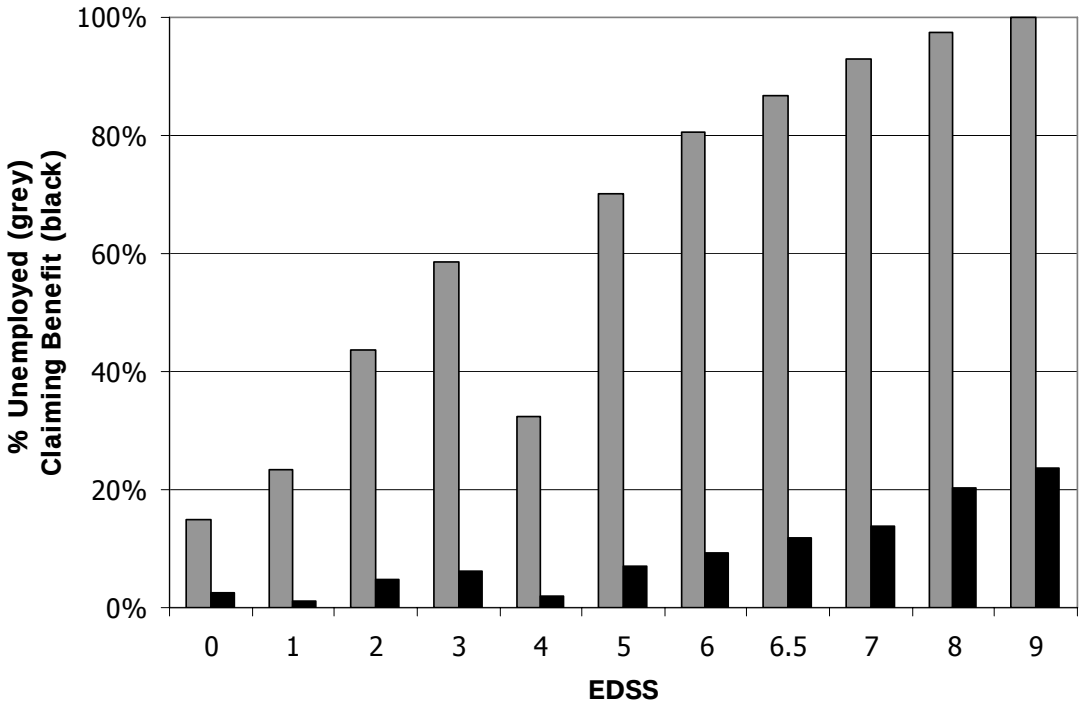
Figure 5 Burden to the caregiver of looking after someone with MS, UK MS Survey 2005



Data presented shows the caregiver burden in mean number of hours per day and mean number of days per month of all respondents who reported that they received care from the UK MS Survey 2005 (see section 5.8.4).

Figure 5 presents data on caregiver burden collected during the UK MS Survey 2005. It shows an inexorable increase in reliance on the support from friends and family as disability increases, both in terms of hours per day and days per month.

Figure 6 The effect of MS on employment, UK MS Survey 2005

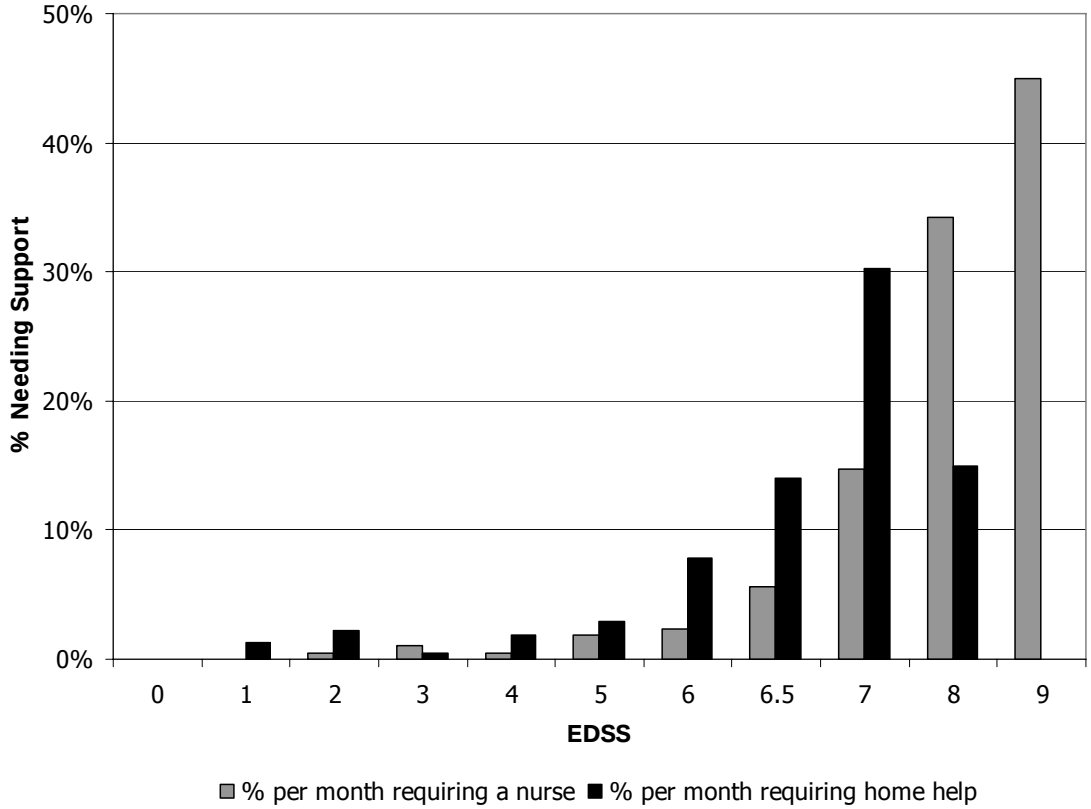


The graph presents the employment status of people of working age with MS from the UK MS Survey 2005 (see section 5.8.4). Grey bars present unemployment rates; black bars represent the rate of incapacity benefit claims.

Figure 6 shows the large effect that MS has on employment prospects for people with the disease (grey bars). Unemployment rates in early stages of disability are greater than 40% by EDSS 2. This increases to more than 80% by EDSS 6.

The black bars depict the rate of benefit claims within the working age population. The profile is similar to the unemployment profile although the majority of those who are unemployed do not claim incapacity benefit.

Figure 7 The effect of MS on nursing and home help, UK MS Survey 2005



The graph presents the nursing and home help requirements of respondents from the UK MS Survey 2005 (see section 5.8.4).

Figure 7 shows that the need for nursing support and home help increases sharply once a person with MS requires a wheel chair (EDSS 6.5). The reduction in home help reported at EDSS 8 could be due to an increase in the proportion of people in the highest states of disability requiring full-time nursing home care.

Table 8 Costs associated with different disease and patient characteristics under different perspectives (UK MS Survey 2005)

		Annual Cost		
Category	**Sub-category**	**NHS & PSS (£)**	**Governmental (£)**	**Societal (£)**
State	EDSS 0	638	2682	16 541
	EDSS 1	927	3242	17 949
	EDSS 2	883	4288	23 176
	EDSS 3	2758	6849	28 958
	EDSS 4	1756	4753	22 657
	EDSS 5	2543	7452	30 598
	EDSS 6	3146	8604	32 166
	EDSS 7	7384	14 217	39 322
	EDSS 8	17 370	27 153	52 686
	EDSS 9	16 307	26 439	52 039
Type	RRMS	†	†	†
	SPMS	56	789	2916
Relapse	No Relapse	†	†	†
	Cost per relapse	228	398	572
Gender	Female	†	†	†
	Male	0	100	1577
DMT (IFN-beta)	No Treatment	†	†	†
	IFN-beta Treatment	8652	8652	8652
DMT (GA)	No Treatment	†	†	†
	GA Treatment	6202	6202	6202
DMT by EDSS State (IFN-beta)	With DMT in EDSS 0-2	†	†	†
	With DMT in EDSS 3-6	236	236	236
DMT by State EDSS (GA)	With DMT in EDSS 0-2	†	†	†
	With DMT in EDSS 3-6	-587	-587	-587
Age	Age	0	-49	-318

* P < 0.01. Reference case (refers to the reference case in the economic evaluation presented in Section 6).
† = reference case. DMG = Direct Medical cost funded by Government. DNMG = Direct Non-Medical cost funded by Government.

The table reports the profile of the direct costs of managing MS in the UK. These costs were collected in the UK MS Survey 2005 (see section 5.8.4).

Table 8 reports the cost of MS for a number of different costs perspectives. These are the NHS & Personal Social Services (PSS), Governmental (i.e. the total cost to the taxpayer), and the societal cost (all relevant costs). Costs increase as disability increases; use of DMTs and relapses add to the cost of care. The average annual direct cost of care increases from a few hundred pounds for someone with mild disability not receiving a DMT to around £10 000 to £13 000 pa for someone with moderate disability receiving a DMT. In addition, the direct medical cost of each relapse is over £200. The full cost of MS to the taxpayer is considerably higher if Department of Work and Pension contributions paid to patients are included. The full societal costs are higher still as these costs account for loss of earnings, (Figure 6) and requirements for care, both being provided by the state and more importantly by friends and family.

4.2.1 Summary

The impact of MS is substantial. These results show that MS affects not only the individual with the disease, but also friends and family, employers and the taxpayer. Most of the severe consequences of the disease are concentrated in higher stages of disability.

The clinical case for any intervention that is able to halt the disease or delay disability progression is well recognised, compelling and imperative. The humanistic and economic grounds for halting the disease or delaying disability progression are equally strong.

4.3 What is the principal mechanism of action of the technology?

Natalizumab is a selective adhesion-molecule inhibitor and binds to the α4 subunit of human integrins, which is highly expressed on the surface of all leukocytes, with the exception of neutrophils. Specifically, natalizumab binds to the α4β1 integrin, blocking the interaction with its cognate receptor, vascular cell adhesion molecule 1, and ligands osteopontin, and an alternatively spliced domain of fibronectin, connecting segment 1. Natalizumab blocks the interaction of α4β7 integrin with the mucosal addressing cell adhesion molecule 1. Disruption of these molecular interactions prevents transmigration of mononuclear leukocytes across the endothelium into inflamed parenchymal tissue. A further mechanism of action of natalizumab may be to suppress ongoing inflammatory reactions in diseased tissues by inhibiting the interaction of α4 expressing leukocytes with their ligands in the extracellular matrix and on parenchymal cells. As such, natalizumab may act to suppress inflammatory activity present at the disease site, and inhibit further recruitment of immune cells into inflamed tissues. (2)

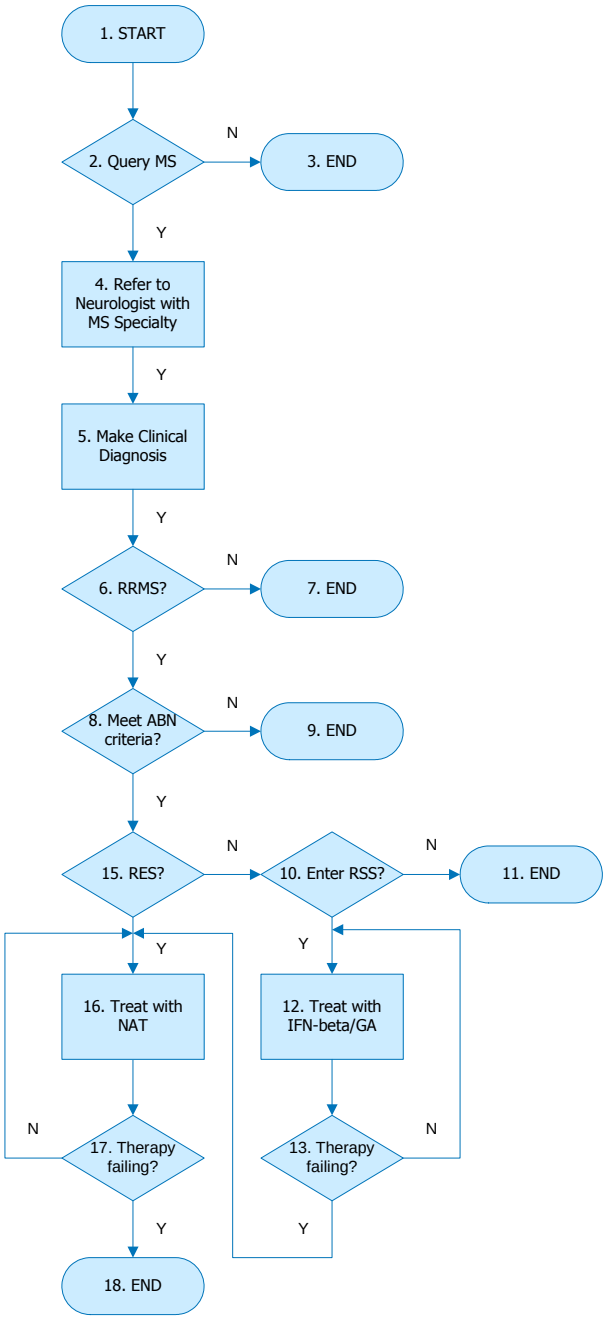
4.4 What is the suggested place for this technology with respect to treatments currently available for managing the disease/condition?

Natalizumab should be available as an active treatment alternative for people with HARRMS (i.e. the RES and SOT subgroups described in Section A). This is because:

- HARRMS patients have a high unmet need
- Natalizumab has a large clinical and statistically significant effect in HARRMS patients

Specifically, natalizumab should be offered to all people that meet the eligibility criteria of RES, and should be offered as an active treatment alternative for the SOT group of patients. The placement of natalizumab within existing care pathway is shown in Figure 8 below (see also previous pathway in Figure 2). It should again be noted that the only 'feedback loops' shown refer to monitoring of treatment.

Figure 8 RRMS treatment pathway in England and Wales after the introduction of natalizumab



Notes to the figure

Natalizumab will provide additional choice for clinicians and patients once an experienced neurologist has confirmed the patient meets the ABN treatment criteria (stage 8 in Figure 8). (50)

Four additional steps are added (stages 15 to 18) and all other parts of the pathway remain the same as the stages shown in Figure 2.

15. At the time that a neurologist assesses a patient against the ABN treatment criteria, they will also consider whether the patient meets the criteria for RES.
16. Patients meeting the criteria for the RES subgroup can be initiated on natalizumab.
17. People would remain on treatment with natalizumab unless therapy is considered to be failing.
18. This node would link to an alternative pathway not shown here.

In contrast with the current pathway, patients failing on IFN-beta or GA and meeting the requirements of the SOT subgroup would become eligible for treatment with natalizumab at stage 13.

IFN-beta = interferon beta, GA = glatiramer acetate, NAT = natalizumab

4.5 Describe any issues relating to current clinical practice, including any variations or uncertainty about best practice

The quality of MS services in the UK falls far short of the guidelines set by NICE and the NCC-CC.

In this section we present information detailing the challenge to the NHS and conclusions from a recent audit, commissioned in July 2006 by the Royal College of Physicians and the MS Trust, of the general quality of MS services.

In 2004, the NCC-CC produced guidelines for the diagnosis and management of MS. These guidelines, which were endorsed and published by NICE, were developed as a result of extensive stakeholder consultation and it is believed that they are the most current in the UK. (46)

The NCC-CC in 2004 summarised the direct challenge facing the NHS in the management of the disease:

> *'The challenge facing both organizations and individual clinicians is major.*
> *… many people with MS are seen by individuals who have relatively little expertise or knowledge, and who cannot find relevant advice easily, and who often are working in isolation away from coordinated services, and the service is sub optimal both for the patient in terms of effectiveness and for society in terms of efficiency and equity.'*

It would appear that nothing has happened substantially in the last two years to change this picture. The Royal College of Physicians and the MS Trust audit concluded: (48)

> *'The main finding of this audit is that the standards set by the seven key recommendations made in the NICE national guideline for the management of multiple sclerosis are not being met, in that they are not being used by:*
>
> - *service providers to guide service delivery*
> - *service commissioners either to commission services or to monitor service delivery*
> - *those responsible for managing health services to monitor that the healthcare needs of their population are being met.*
>
> *A few organisations adhere partially to one or two, but most do not adhere to any. Furthermore, most organisations are not specifically planning to implement any of the recommendations.*
>
> *We draw three major conclusions:*
>
> - *The organisations within the NHS at all levels do not have the*

people, information or structures in place needed to develop and improve services for people with long-term neurologically based disability.

- *Asking patients whether they are satisfied with services is an invalid method for identifying whether service quality is good, even from the point of view of the service user.*

- *The triangulation method we used, obtaining data from several different perspectives, is a powerful and economic way of auditing services nationally.'*

A small proportion of the NCC-CC report (< 11/141 pages) provided guidance on DMTs and the large majority of the document focuses on diagnosis, monitoring and supportive care as opposed to active treatment.

It is notable that there are no specific guidelines for patients with HARRMS. This provides a unique opportunity for NICE to be the first authoritative body to provide much-needed clarity by recognising natalizumab as the most appropriate treatment for HARRMS patients.

The treatment recommendations for IFN-beta and GA reflect the treatment considerations expressed within the risk-sharing scheme. (46;51) These are summarised below:

'R52 People with relapsing-remitting MS, and those with secondary progressive MS in which relapses are the dominant clinical feature, who meet the criteria developed by the Association of British Neurologists are eligible for treatment under the risk-sharing scheme.

R53 People with MS should be advised that linoleic acid 17–23g/day may reduce progression of disability. Rich sources of linoleic acid include sunflower, corn, soya and safflower oils.

R54 The following treatments should not be used except in these specific circumstances:

- *after full discussion and consideration of all the risks*

- *with formal evaluation, preferably in a randomised or other prospective study*

- *by an expert in the use of these medicines in MS with close monitoring for adverse events*

The treatments are:

- *azathioprine*

- *mitoxantrone*

- *intravenous immunoglobulin*

- *plasma exchange, and*

- *intermittent (four-monthly) short (1–9 days) courses of high-dose methylprednisolone'*

4.6 Provide details of any relevant guidelines or protocols

A search was conducted within the Turning Research Into Practice (TRIP) database using the keywords 'multiple sclerosis'. In North America, 35 guidelines were identified, of which 4 focused on multiple sclerosis (see No. 1 to 4 in Table 9). An additional 40 European guidelines were identified, although only 2 concentrated on MS and were included in this review (No. 5 and 6). A total of 5 references were identified from other regions, although none were relevant to this appraisal. Existing NICE guidance on individual technologies was not identified in this search and is not shown in the table.

Table 9 Published International MS Guidelines

No.	Title	Reference	Comments
1	Multiple sclerosis. National clinical guideline for diagnosis and management in primary and secondary care. (46)	National Collaborating Centre for Chronic Conditions. Multiple sclerosis. National clinical guideline for diagnosis and management in primary and secondary care. London (UK): National Institute for Clinical Excellence (NICE); 2004. 197 p.	Most relevant current UK guideline. Described in Section 4.6. Provides limited guidance on the sequencing of interventions.
2	Immunization and multiple sclerosis: a summary of published evidence and recommendations.	Rutschmann OT, McCrory DC, et al, Immunization Panel of the Multiple Sclerosis Council for Clinical Practice Guidelines. Immunization and MS: a summary of published evidence and recommendations. Neurology 2002 Dec 24;59(12):1837-43.	Focus of guidance is on timing of immunisation with respect to relapsing patients.
3	The use of mitoxantrone (Novantrone) for the treatment of multiple sclerosis: report of the Therapeutics and Technology Assessment Subcommittee of the American Academy of Neurology. (90)	Goodin DS, Arnason BG, et al. The use of mitoxantrone (Novantrone) for the treatment of multiple sclerosis: report of the Therapeutics and Technology Assessment Subcommittee of the American Academy of Neurology. Neurology 2003 Nov 25;61(10):1332-8.	Assessed risk-benefit profile of MTX and concluded, 'because the potential clinical benefits on disability progression appear to be only modest, the results of the single phase III study should be replicated in another (and hopefully much larger) clinical study before this agent is widely recommended for the treatment of patients with MS.'
4	Disease modifying therapies in multiple sclerosis: report of the Therapeutics and Technology Assessment Subcommittee of the American Academy of Neurology and the MS Council for Clinical Practice Guidelines. (94)	Goodin DS, Frohman EM, ET AL. Disease modifying therapies in multiple sclerosis: report of the Therapeutics and Technology Assessment Subcommittee of the American Academy of Neurology and the MS Council for Clinical Practice Guidelines. Neurology 2002 Jan 22;58(2):169-78. [55 references]	A summary of clinical evidence. Provides limited guidance of sequencing of interventions.
5	Association of British Neurologists Guidelines for the use of Interferon betas and Glatiramer Acetate in Multiple Sclerosis.	Association of British Neurologists. http://www.theabn.org/documents/msdoc.pdf London 2001	Frequently referred to and provides treatment starting and stopping criteria.

No.	Title	Reference	Comments
	(50)		
6	Multiple sclerosis. Management of multiple sclerosis in primary and secondary care.	Clinical Guideline 8 November 2003 Developed by the National Collaborating Centre for Chronic Conditions	This has been superseded by no. 1 above.
7	The National Service Framework for Longterm Conditions. (95)	Older People and Disability Policy Management Unit Care Services Division Department of Health Room 8E30 Quarry House Quarry Hill, Leeds LS2 7UE www.dh.gov.uk/longtermnsf 10 March 2005	Only treatment references for IFN-beta and GA are to existing NICE guidance and to website sponsored by Medicines Partnership. Guidance for patients appears to be consistent with no. 1 in this table.

The most relevant current UK guidelines are described in Sections 4.4 and 4.5.

We found no treatment algorithms or clinical treatment pathways in the TRIPS search and this is a limitation of current guidelines in MS.

5 Clinical evidence

Based on the results of our indirect comparison, natalizumab is the most effective treatment available for relapsing remitting multiple sclerosis (RRMS). The clinical benefits of natalizumab in the treatment of multiple sclerosis (MS) are unprecedented, highly statistically significant and internally consistent across a broad range of outcome measures.

The five main advantages of natalizumab are:

- slowing disability progression
- reducing relapse frequency
- Adverse Event (AE) profile
- compliance with medication
- the early clinical presentation of immunogenicity

There are currently no other therapies licensed specifically for people with highly active relapsing remitting multiple sclerosis. Highly active relapsing remitting multiple sclerosis patients have more frequent relapses and progress more rapidly to severe disability than the relapsing remitting multiple sclerosis population. The active comparators within this submission are interferon beta and glatiramer acetate. Best supportive care is also considered as a comparator.

Natalizumab is the first in a new class of drug for the treatment of highly active relapsing remitting multiple sclerosis. It is a selective adhesion-molecule inhibitor. Natalizumab has a unique and specific mechanism of action, which prevents white blood cells, the mediators of inflammation in multiple sclerosis, from entering the brain.

Natalizumab is licensed for the treatment of highly active relapsing remitting multiple sclerosis. These patients fall into two subgroups:

Rapidly evolving severe subgroup defined by 2 or more disabling relapses in one year, and with 1 or more Gadolinium-enhancing lesions on brain Magnetic Resonance Image (MRI) or a significant increase in T2 lesion load as compared to a previous MRI.

Sub optimally treated subgroup defined as patients who have had at least 1 relapse in the previous year while on therapy, and have at least 9 T2-hyperintense lesions in brain MRI or at least 1 Gadolinium-enhancing lesion.

Methodology

The AFFIRM and SENTINEL pivotal studies, upon which the licensed indications of natalizumab are based, are the largest prospective, interventional studies to be conducted in relapsing remitting multiple sclerosis to date.

Critical appraisal based upon the key components of the CONSORT statement indicates that the natalizumab pivotal studies were generally better conducted and better reported than equivalent studies of comparator treatments.

Efficacy results of natalizumab pivotal studies:

All clinical and surrogate primary and secondary endpoints, for both AFFIRM and SENTINEL, showed a clinical and statistically significant benefit in favour of natalizumab treated patients.

These benefits were seen early, were sustained throughout the duration of treatment and were typically superior to those observed in clinical studies of other disease modifying therapies in the treatment of relapsing remitting multiple sclerosis. At 2 years, within AFFIRM, compared to placebo natalizumab treated patients experienced a:

- 68% reduction in annualised relapse rate ($p < 0.001$)
- 54% reduction in the hazard ratio for disability progression ($p < 0.001$)
- 81% reduction in annualised relapse rate in the rapidly evolving severe subgroup ($p < 0.001$)
- 64% reduction in the hazard ratio for disability progression in the rapidly evolving severe subgroup ($p = 0.008$)

A large effect on lesions identified by magnetic resonance imaging (MRI) was observed:

- 92% reduction in the mean number of Gd+ lesions ($p < 0.001$)
- 83% reduction in the mean number of new or enlarging T2 hyperintense lesions ($p < 0.001$)
- 76% reduction in the mean number T1 hypointense lesions ($p < 0.001$)

Nearly a third of patients treated with natalizumab remained disease free at 2 years:

- 28% of people were free of all measures of disease activity (disability progression, relapses, Gd+ lesions, new or enlarging T2 lesions or new T1 lesions)

In a 1-year open label extension study, the three-year annualised relapse rate for patients was 0.23. This was consistent with the 0.23 annualised relapse rate observed in the natalizumab arm of the two-year AFFIRM study.

Safety results of natalizumab pivotal studies

All common adverse events, except for fatigue and allergic reaction, were not significantly different from placebo.

The rates of serious adverse events were equivalent to placebo.

A risk of Progressive Multifocal Leukoencephalopathy associated with natalizumab monotherapy cannot be excluded. Progressive Multifocal Leukoencephalopathy has not been reported in patients with multiple sclerosis receiving natalizumab monotherapy.

Indirect comparison:

No head to head trials of natalizumab and the active comparators have

been conducted. An indirect comparison of efficacy and safety outcomes from available clinical trials of disease modifying therapies, using placebo as the common comparator, demonstrated a consistent beneficial effect of natalizumab compared with both interferon beta and glatiramer acetate for disability progression and relapse frequency.

A superior adverse event profile compared to interferon beta and an equivalent profile to glatiramer acetate (except for patterned reaction, which has not been reported in natalizumab treated patients but has a relative risk of 3.29 in patients treated with glatiramer acetate compared with placebo).

Evidence from non-randomised controlled trials shows that:

Highly active relapsing remitting multiple sclerosis patients experience more rapid disability progression and higher relapse frequency than a relapsing remitting multiple sclerosis population, as evidenced by published natural history studies and a new multi state model constructed for this submission. The multi state model estimates that disability progresses approximately twice as fast in an untreated rapidly evolving severe subgroup compared with a relapsing remitting multiple sclerosis population (mean change in Expanded Disability Status Scale (EDSS) of 0.46 and 0.27 respectively over two years).

The standardised mortality rate for people with multiple sclerosis is worse than the general population and increases with disability. Given that disability progresses faster in patients with highly active relapsing remitting multiple sclerosis, it is probable that the standardised mortality rate in highly active relapsing remitting multiple sclerosis patients is higher than the broad population of relapsing remitting multiple sclerosis patients.

In 2005, evidence from the largest population based survey of multiple sclerosis patients conducted in the UK provided information on the effect of multiple sclerosis on:

Direct and indirect resource consumption (resource consumption was directly associated with level of disability).

Utility was inversely associated with disability until a state worse than death was reached in the most severe disability states.

Caregiver disutility is believed to be correlated with disease severity. We estimate that the disutility of being a caregiver reaches a maximum of 0.14 at an EDSS score of 9.

It is probable that compliance with natalizumab will be better than the current disease modifying therapies because natalizumab is dosed less frequently than the current drugs and is delivered in an outpatient setting rather than at home.

Overview

The clinical evidence section of this submission is based on the following data sources:

- The AFFIRM clinical study, comparing natalizumab to placebo in 942 RRMS patients, conducted in 99 centres worldwide, is the main source of clinical data for this submission.
- The similar sized clinical study (SENTINEL, n = 1196) provided the basis for the SOT licensed indication. SENTINEL was an adjunctive study of natalizumab added to IFN-beta. We do not describe SENTINEL in detail in this submission since natalizumab in combination with IFN-beta is contraindicated. (1)
- Two studies (MS 201, MS 231) provide supporting data related to MRI, AEs and some data on efficacy (supportive data is presented in Appendix D).
- A systematic review for IFN-beta contained information from 7 randomised controlled trials (RCTs). We used efficacy data from all RCTs where meta-analysis was possible (n = 3) for indirect analyses of efficacy compared with natalizumab.
- In contrast, a systematic review for glatiramer acetate (GA) contained information from 4 RCTs. In this instance, we used efficacy data from 2 RCTs where meta-analysis was possible for indirect analyses.
- Additionally, substantive data from non-randomised controlled trials used in the submission is summarised in section 5.8.

The AFFIRM study contributes the majority of the clinical data reported in this submission. Additional data from the SENTINEL study supports the sub optimally treated (SOT) indication and is not presented here, since natalizumab in combination with IFN-beta is contraindicated and it is not relevant to the decision problems. Supporting data for natalizumab is also derived from two other studies MS 201 and MS 231; summaries of the study methodology, baseline characteristics and results are provided for these studies (see Appendix D).

There were no studies available that compared natalizumab to the comparators IFN-beta and GA. Information for these two comparators was derived from two systematic reviews (by Rice et al (73) and Munari et al (70) respectively) that we updated and critically appraised. The systematic review for IFN-beta assessed data from 7 studies and the GA evaluated 4 studies.

We used indirect analyses to compare natalizumab with the 2 active comparators. Specifically, data from 3 of the studies in the IFN-beta systematic review and 2 studies in the GA review reported data in a format that enabled an efficacy comparison, whereas, data from all of studies was included in the safety analyses.

The structure of section 5 is summarised in Table 10. Study methodology is reported in 5.1 to 5.3; section 5.4 reports efficacy results of placebo controlled studies; sections 5.5 and 5.6 report results of the meta-analysis and indirect comparison; and section 5.7 reports safety data. Data from non-randomised controlled trials are reported in section 5.8.

Table 10 A summary of clinical evidence by section in this submission

		Natalizumab				IFN-beta	GA
		Main data		Supporting data		Main data	Main data
		AFFIRM	SENTINEL	MS 201	MS 231	Systematic Review (73)	Systematic Review (70)
Study and method summary		5.3	-	Appendix D	Appendix D	Appendix G.1	Appendix G.2
Critical appraisal		Appendix F	Appendix F	Appendix F	Appendix F	Appendix G.1	Appendix G.2
Natalizumab	efficacy	0	-	Appendix D	Appendix D	-	-
	safety	5.7	-	Appendix D	Appendix D	-	-
Comparator	efficacy	-	-	-	-	5.5.2.1	5.5.2.2
	safety	-	-	-	-	5.7.3.1	5.7.3.2
Indirect analyses	efficacy	5.6	-	-	-	5.6	5.6
	safety	5.7.3.1 5.7.3.2	-	-	-	5.7.3.1	5.7.3.2

Section 5.8 reports:

- the natural history of the disease and progression of the SOT and rapidly evolving severe (RES) subgroups (section 5.8.3)
- mortality rates (section 5.8.8)
- estimated relapse rates (section 5.8.5)
- effect of switching IFN-beta treatments (section 5.8.2)
- withdrawal rates from treatment (section 5.8.9)
- a description of the UK MS Survey 2005 (section 5.8.4), details the method used collect the data on which the majority of the costs (section 5.8.6) and utility data (section 5.8.7)

5.1 Identification of studies

To date, there have been no direct head to head comparisons of natalizumab monotherapy with any of the other active comparators. We are confident that all studies of natalizumab, in the indications relevant to this submission, are detailed herein. This is because:

(i) the only studies conducted in MS to date were to support registration and managed by Biogen Idec and those under contract with Biogen Idec

(ii) Biogen Idec has not to date authorised the supply natalizumab to any third party studies

(iii) natalizumab was only recently licensed[1]

5.1.1 Natalizumab

All natalizumab studies relevant to this submission were accessed from an internal Biogen Idec study database and these are detailed further in this submission.

5.1.2 Comparators

We identified Cochrane systematic reviews for the comparators GA and IFN-beta, by Munari et al and Rice et al respectively. (70;73) These systematic reviews form an integral part of the clinical section of this submission, as they draw together data for the comparators to natalizumab from a reputable and independent source. Criticism has been made of the choice of some of the scenarios reported in that publication, although no criticism was made of the reference case (71;96-102). The criticisms focused on: A decision to meta analyse trials of interferon alpha (IFN-alpha) with trials of IFN-beta; and to apply either full benefit or zero benefit to treatment withdrawals within treatment scenarios.

We updated the Cochrane reviews by repeating the Cochrane search strategies in the Medline, Cochrane Central Register of Controlled trials (CENTRAL) and EMBASE databases in late September 2006. The safety and efficacy data for natalizumab, IFN-beta and GA (all versus placebo) were taken respectively from the AFFIRM clinical study report, and the Cochrane reviews of Rice, 2001 (73) and Munari, 2003 (70). The updated systematic reviews of IFN-beta and GA are reported in Appendix B and Appendix C respectively.

A large study of a new oral formulation of GA was identified but excluded from the review as it failed to result in significant benefit compared with placebo in primary or secondary endpoints, and thus was unable to support product registration. (103)

[1] Natalizumab was licensed in the US in November 2004 although was withdrawn voluntarily from the market in February 2005 while concerns regarding PML were investigated; natalizumab was licensed in Europe and relicensed in the US in June 2006.

5.2 Study selection

Sub-section 5.2 summarises the natalizumab trial program and the paucity of data from active comparator RCTs. A list of the current studies available for IFN-beta and GA, together with what they contribute to the submission is presented. Ongoing natalizumab studies are also listed, although they will not contribute anything to the evidence base for natalizumab for at least 12 months.

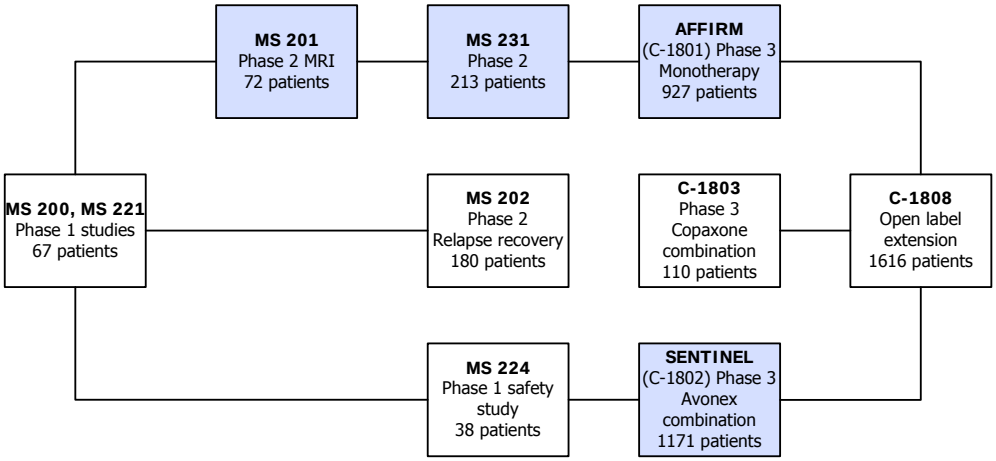
5.2.1 Complete list of RCTs

5.2.1.1 Placebo controlled natalizumab RCTs

An overview of the clinical studies that were pivotal to the development of natalizumab is given in Figure 9. (104) The most relevant of these studies are AFFIRM, SENTINEL, MS 231 and MS 201. The aims of these studies are detailed in the submission. The AFFIRM study contributes the majority of the clinical data given in this submission and forms the main focus of the natalizumab data in section 5. Additional data from SENTINEL study supports the SOT indication but is not presented here since natalizumab in combination with IFN-beta is contraindicated and SENTINEL is not relevant to the decision problems.

- Data for the RES licensed indication comes from a robust subgroup analysis from the AFFIRM study (see section 2.3.1) rather than the intention-to-treat (ITT) population.
- Data supporting the SOT licensed indication comes from the SENTINEL study. SENTINEL has not been described in detail here, because the use of natalizumab in combination with other DMTs is contraindicated, although the study was used by the EMEA to support the SOT license (see section 2.3.2). (2;3)
- MS 231 and MS 201 provide supportive data for MRI and safety endpoints and are reported in Appendix D.

Figure 9: Overview of clinical development of natalizumab in multiple sclerosis



Note: Studies of relevance to the natalizumab license are highlighted.

Table 11 Summary of the relevant natalizumab studies

Study	Treatment group (n)	Type of patients	Outcomes
AFFIRM (Phase III registration study) Once monthly (every 28 days) IV infusions. Two-year study. (4)	Natalizumab 300 mg by IV infusion every 4 weeks (n = 627) Placebo (n = 315)	Adults with RRMS.	**Primary:** Reduction in the rate of clinical relapses at one year Rate of sustained progression of disability at two years (EDSS) **Secondary:** Multiple MRI, progression, relapse and safety outcomes
SENTINEL (Phase III registration study) Once monthly (every 28 days) IV infusions, adjunctive to IFN-beta. Two-year study. (3)	Natalizumab 300mg by IV infusion every 4 weeks interferon β-1a (n = 589) Interferon β-1a (n = 582)	Adults with RRMS.	**Primary:** Reduction in the rate of clinical relapses at one year Rate of sustained progression of disability at two years (EDSS) **Secondary:** Multiple MRI, progression, relapse and safety outcomes
MS 201 (Phase II) Once monthly (every 28 days) IV infusions. Twelve-week study.	Natalizumab 3.0 mg/kg (n = 37) Placebo (n = 35)	Adults with RRMS or SPMS.	**Primary:** The number of new active lesions during the 12 weeks following the first treatment assessed by MRI. **Secondary:** Multiple MRI, progression, relapse and safety outcomes
MS 231 (Phase II) Once monthly (every 28 days) IV infusions. Six-month study.	Natalizumab 3.0 mg/kg (n = 68) Natalizumab 6.0 mg/kg (n = 74) Placebo (n = 71)	Adults with RRMS or SPMS.	**Primary:** Brain lesion activity assessed by magnetic resonance imaging (MRI) **Secondary:** Multiple MRI, progression, relapse and safety outcomes

5.2.1.2 Active comparator RCTs

As noted previously, there are no active comparator studies of natalizumab. We updated the Cochrane systematic reviews to identify relevant placebo-controlled comparator studies (See Appendix B and Appendix C). Details of the criteria used within these previous reviews to identify relevant publications are summarised in Table 12 below. It should be noted that the criteria in our updated review differ (see section 5.5, Appendix B and Appendix C).

Table 12 Summary of systematic reviews (Munari et al, Rice et al (70;73))

	Systematic Review	
	Rice, 2001	**Munari, 2003**
Study criteria	Randomised, double blind, placebo-controlled studies of recombinant interferons	All randomised or quasi-randomised controlled trials comparing GA and placebo in patients with definite MS
Patients	MS patients with established clinical and paraclinical evidence based often on the criteria of Poser. (105) Patients in a relapsing-remitting phase were included.	Definite MS of any severity according to the criteria of Poser. (105) Any patterns of MS course. Patients receiving cytostatics, immuno-modulators or immuno-suppressants 6-months prior to study enrolment were excluded.
Intervention	Studies in which alpa- or beta- recombinant interferons had been compared to placebo. Alpha-interferon studies were excluded from our review.	Any GA administration. Steroids were permitted, provided they were administered without any restriction in both arms.
Outcome measures	Continuing exacerbations; progression during the first two years of treatment; changes in EDSS; ability to walk without aid; time to first exacerbation; time to progression in disability; steroid administration during interferon treatment and follow-up; hospitalisations; side effects or adverse events; effect of treatment on the magnetic resonance imaging.	Progressing patients; Mean EDSS and its standard deviation; Patients experiencing at least one exacerbation; Relapse-free survival; changes in quality of life scores.
Studies included	IFNB MS Group, 1993; The MSCRG, 1996; The PRISMS, 1998; The OWIMS, 1999	Bornstein, 1987; Bornstein, 1991; Johnson, 1995; Comi, 2001

In contrast to the Rice et al systematic review for IFN-beta, which included both beta and alpha interferon studies, we have included only studies relating to IFN-beta. The Munari et al systematic review included MS patients with any MS disease type; we have included only articles relating to the RRMS decision problem. Additionally, we only included studies that reported exacerbations and disability progression outcomes at 2 years. These reviews are reported in Appendix B and Appendix C (search strategies are reported in Appendix E). In addition, we undertook a critical appraisal of the studies reported in the published Cochrane systematic reviews (Appendix G).

The updated systematic review was done in accordance with accepted practises of systematic review and included the appraisal of abstracts in duplicate, by suitable reviewers, according to the criteria for inclusion or exclusion set out in the systematic reviews. The search strategies are detailed in Appendix B and some key characteristics of the pivotal studies for the comparators described in the systematic review are detailed below (see Table 12 and Table 24 to

Table 29 in section 5.5.1). The IFN-beta review was subsequently published in the Lancet in 2003 and was criticised on the choice of some of the scenarios reported in that publication. (64) No criticism was made of the reference case, however, which we use in this indirect comparison. (71;96-102)

Specifically, the two systematic reviews used herein aimed to:

- Assess the efficacy and safety of IFN-beta in adults with RRMS (73)
- Determine the efficacy and safety of the administration of GA in adults with MS (70)

5.2.2 Inclusion and exclusion criteria

The criteria used to identify studies suitable for inclusion for were based on study design, patient characteristics, MS disease type, intervention and outcome measures. A summary of the criteria used in each of the systematic reviews is given above in Table 12. These inclusion criteria were used in the update of these systematic reviews.

The inclusion criteria of the updated review differed in part to those used in the systematic reviews. Specifically, we included only studies of RRMS patients and we did not consider studies of alpha-interferons.

5.2.3 List of relevant RCTs

There were no RCTs that directly compared natalizumab with either IFN-beta or GA. In the absence of relevant active controlled studies, indirect analyses of placebo-controlled studies were used where appropriate to estimate the differential effect of natalizumab and the comparators (section 5.6). The relevant RCTs in this submission are listed in Table 13 and described in detail later in section 5 and in appendices.

Table 13 Summary of trial data included in this submission AFFIRM study (Munari et al, Rice et al)

Study	Active arm	Included in this submission	Included in Cochrane reviews	Comment
AFFIRM (4)	NAT	Efficacy and safety	-	
IFNB MS Group (59)	IFN-beta	Efficacy and safety	Yes	
MSCRG (66)	IFN-beta	Efficacy and safety	Yes	
PRISMS (58)	IFN-beta	Efficacy and safety	Yes	
OWIMS (61)	IFN-beta	Safety	Yes	no relevant efficacy data available
Knobler 1993 (106)	IFN-beta	Safety	Yes	no relevant efficacy data available
Durelli 1994 (107)	IFN-alpha	-	Yes	data not included because this was a trial for alpha interferon
Myhr 1999 (108)	IFN-alpha	-	Yes	data not included because this was a trial for alpha interferon
Bornstein 1987 (109)	GA	-	Yes	included in sensitivity analysis †
Bornstein 1991 (110)	GA	Safety	Yes	efficacy data not included because subgroup was not RR MS.
Johnson 1995 (111)	GA	Efficacy and safety	Yes	
Comi 2001 (63)	GA	Safety	Yes	no relevant efficacy data available

Note that supporting data from MS 201 and MS 231 can be found in Appendix D. IFN-beta, interferon beta; IFN-alpha, interferon alpha; GA, glatiramer acetate; NAT, natalizumab. † Bornstein 1987 was excluded in the ScHARR model on which our model is based (see section 6). (17;109) We report the effect of including and excluding this study in the indirect comparison in section 5.6 and the sensitivity analysis in section 6.3.3.

5.2.4 List of relevant non-randomised controlled studies

There are no non-randomised controlled trials that directly compared natalizumab

with the comparators IFN-beta or GA.

5.2.5 Ongoing studies

Three studies are ongoing, although these will not produce additional evidence within the next 12-months. Details of these studies are given in Table 14 and their context to the overall development of natalizumab for MS treatment is summarised in Figure 9 on page 55.

Table 14 Summary of ongoing studies

Study Reference	Objective	Study Design	Completion within 12 months?
101-MS-321	To evaluate the safety of natalizumab monotherapy following re-exposure to natalizumab. This includes assessing the risk of hypersensitivity and immunogenicity, and evaluating the safety of switching from IFN-beta, GA, or other MS therapies to natalizumab.	Multicentre, open-label, single-arm, safety extension study for subjects who completed AFFIRM or SENTINEL and a Dosing Suspension Safety Evaluation.	N
TYGRIS – ROW 101-MS-403	To determine the incidence and pattern of serious infections, malignancies, and other serious adverse events (SAEs) in patients with MS treated with natalizumab.	Prospective, observational cohort.	N
TOUCH Prescribing Program	The program was developed to help achieve the following goals: Inform prescribers and patients about the benefits and risks of natalizumab before initiating and while on therapy; assure only appropriate patients are prescribed natalizumab; assure appropriate patients are infused only at sites enrolled in the program; assess the incidence of, and risk factors for, progressive PML and other serious opportunistic infections that may be associated with natalizumab treatment.	Prospective, observational cohort.	N

5.3 Summary of methodology of relevant RCTs

The results from the AFFIRM study provides much of the data for this submission and is emphasised in this section. Limited supporting data from MS 201 and MS 231 is referred to in this section and described in more detail in Appendix D.

5.3.1 Methods

AFFIRM was a multicentre, randomised, double-blind, placebo-controlled, parallel-group study (4). It was conducted in Europe (including the UK.), North America, Australia, and New Zealand and enrolled a total of 942 patients beginning on 6th of November, 2001. In total, 99 clinical centres were involved in the study. The study population is likely to reflect the population of Western industrialised countries, which includes England and Wales. Therefore, the results from this study will be relevant to people with HARRMS in England and Wales.

Specifically, the patients were randomly assigned, in a 2:1 ratio, with the use of a computer-generated block randomisation schedule and a multi-digit identification number. A total of 627 patients were assigned to receive IV infusion of 300 mg natalizumab and 315 to an appropriate placebo. This medication regime is the same as that given in the SPC for natalizumab. (1) A summary of the patient numbers throughout the study is given in Figure 10 in section 5.3.3. The randomisation was stratified by site with a centralised randomisation schedule that also balanced the treatment group assignments within sites.

Each subject's treatment assignment was determined by an interactive voice response system. To ensure blinding throughout the study, medication and placebo were provided in identical vials, and labelled to ensure the identity of the treatment remained blinded. The personnel involved in the study, in sponsoring, as investigators and in an advisory capacity were also blinded with respect to assignment of placebo or natalizumab. Additionally, evaluation by MRI, following screening, was conducted by blinded physicians/technicians.

Patients received treatment by infusion once every 4 weeks for up to 116 weeks and were to be in follow-up for an additional 12 weeks after their last dose of study drug. The CHMP specified a RRMS subgroup analysis within AFFIRM that provides data to support the RES indication. The pre specified subgroup analyses are described in Section 5.3.5.

5.3.2 Participants

5.3.2.1 Patients were enrolled if they met the following inclusion criteria:

Consenting male and female subjects between 18 and 50 years of age, inclusive with:

- A diagnosis of relapsing MS as defined by the McDonald criteria (49)
- A baseline EDSS score between 0.0 and 5.0, inclusive
- A brain MRI scan demonstrating lesion(s) consistent with MS

- At least 1 medically documented clinical relapse within the 12 months prior to randomisation

5.3.2.2 Main Exclusion Criteria:

The following criteria were used to exclude specific patients:

- A diagnosis of primary-progressive, secondary-progressive, or progressive-relapsing MS, as defined by Lublin and Reingold (112)
- A relapse within 50 days prior to randomisation and/or had not stabilised from a previous relapse
- A clinically significant infectious illness (e.g., cellulitis, abscess, pneumonia, septicaemia) within 30 days prior to randomisation
- A history of severe allergic or anaphylactic reactions or known drug hypersensitivity
- A history of, or abnormal laboratory results indicative of, significant cardiac, endocrinologic, haematologic, hepatic, immunologic, metabolic, urologic, pulmonary, gastrointestinal, dermatologic, psychiatric, renal, and/or other major disease that would preclude the administration of a recombinant humanised antibody immunomodulating agent for 116 weeks
- An inability to perform the Timed 25-Foot Walk, Nine-Hole Peg Test (9HPT), and 3-Second Paced Auditory Serial Addition Test (PASAT 3)
- An abnormal blood test at Screening exceeding protocol-specified limits for any of the following tests: Alanine transaminase/serum glutamate-pyruvate transaminase (ALT/SGPT), or aspartate transaminase/ serum glutamic-oxaloacetic transaminase (AST/SGOT), total white blood cell (WBC) count, platelet count, creatinine, prothrombin time (PT)
- Treatment with:
  - IFN-beta or GA for a total of 6 months or more, or within 6 months prior to screening
  - Total lymphoid irradiation, cladribine, T-cell or T-cell receptor vaccination, natalizumab, or other therapeutic monoclonal antibodies at any time
  - Mitoxantrone or cyclophosphamide within 1 year prior to randomisation
  - Cyclosporine, azathioprine, methotrexate, subcutaneous GABI β-1bBI β-1a, intravenous immunoglobulin (IVIg), plasmapheresis, or cytapheresis within 6 months prior to randomisation
  - Oral GA within 3 months prior to Screening
  - IV corticosteroids, oral corticosteroids, 4-aminopyridine, or products related to 4-aminopyridine within 50 days prior to randomisation.

Of the 942 patients who participated in the AFFIRM study, 627 were randomised to natalizumab and 315 to placebo. No significant differences in baseline characteristics between the treatment groups were observed. A summary of key baseline characteristics for the patients in the AFFIRM study is given in Table 15. (4) Table 16 presents the baseline characteristics for the RES subgroup from AFFIRM (data on file AFFIRM study). (113)

Table 15 Summary of patient baseline characteristics for the ITT population within the AFFIRM study (adapted from Polman et al 2006 (4))

	Natalizumab (n = 627)	Placebo (n = 315)	Total (n = 942)	P-value
Age — Years				
Mean	35.6 ± 8.5	36.7 ± 7.8	36.0 ± 8.3	0.056
Range	18–50	19–50	18–50	
Sex — no. of patients (%)				
Male	178 (28)	104 (33)	282 (30)	0.144
Female	449 (72)	211 (67)	660 (70)	
Race — no. of patients (%)				
White	603 (96)	296 (94)	899 (95)	0.126
Other	24 (4)	19 (6)	43 (5)	
McDonald criteria — no. of patients (%)‡				
1 (≥ 2 attacks, ≥ 2 lesions)	528 (84)	261 (83)	789 (84)	0.938
2 (≥ 2 attacks, ≥ 1 lesions)	72 (11)	40 (13)	112 (12)	
3 (1 attacks, ≥ 2 lesions)	18 (3)	10 (3)	28 (3)	
4 (1 attack, 1 lesion)	9 (1)	4 (1)	13 (1)	
Disease duration — yr				
Median	5.0	6.0	5.0	0.511
Range	0-34	0-33	0-34	
No. of relapses in past yr — no. of patients (%)				
0	6 (< 1)	6 (2)	12 (1)	
1	368 (59)	180 (57)	548 (58)	
2	197 (31)	102 (32)	299 (32)	
≥ 3	56 (9)	27 (9)	83 (9)	
Mean	1.53 ± 0.91	1.50 ± 0.77	1.52 ± 0.86	0.640
Range	0–12	0–5	0–12	
EDSS score — no. of patients (%)				
0	31 (5)	18 (6)	49 (5)	
1.0–1.5	179 (29)	94 (30)	273 (29)	
2.0–2.5	208 (33)	103 (33)	311 (33)	
3.0–3.5	130 (21)	63 (20)	193 (20)	
4.0–4.5	60 (10)	28 (9)	88 (9)	
5.0	17 (3)	7 (2)	24 (3)	
≥ 5.5	2 (<1)	2 (<1)	4 (<1)	
Mean	2.3 ± 1.2	2.3 ± 1.2	2.3 ± 1.2	0.784
Range	0–6	0–6	0–6	
No. of lesions on gadolinium-enhanced MRI — no. of patients (%)				
0	307 (49)	170 (54)	477 (51)	
1	115 (18)	55 (17)	170 (18)	
2	66 (11)	24 (8)	90 (10)	
3	38 (6)	18 (6)	56 (6)	
≥ 4	100 (16)	46 (15)	146 (15)	
Missing data	1 (< 1)	2 (<1)	3 (<1)	
Mean	2.2 ± 4.7	2.0 ± 4.8	2.2 ± 4.7	
Range	0–36	0–39	0–39	0.511

	Natalizumab (n = 627)	Placebo (n = 315)	Total (n = 942)	P-value
No. of lesions on T2-weighted MRI — no. of patients (%)				
<9	29 (5)	15 (5)	44 (5)	0.921
≥9	597 (95)	299 (95)	896 (95)	
Missing data	1 (< 1)	1 (< 1)	2 (< 1)	

* Plus–minus values are means ± SD. EDSS range of scores, 0 to 10, with higher scores indicating more severe disability. Percentages may not sum to 100, because of rounding. ‡ Criteria are from McDonald et al. (49)

Table 16 Summary of patient baseline characteristics for the RES subgroup (data on file, AFFIRM study (113))

	Natalizumab (n = 148)	Placebo (n = 61)	Total (n = 209)	P-value
Age — Years				
Mean	33.7 ± 8.4	36.4 ± 8.1	34.5 ± 8.4	0.037
Range				
Sex — no. of patients (%)				
Male	37 (25)	10 (16)	47 (22)	0.175
Female	111 (75)	51 (84)	162 (78)	
Race — no. of patients (%)				
White	141 (95)	59 (97)	200 (96)	>0.999
Other	7 (5)	2 (3)	9 (4)	
McDonald criteria — no. of patients (%)‡				
1 (= 2 attacks, = 2 lesions)	133 (90)	53 (87)	186 (89)	0.531
2 (= 2 attacks, = 1 lesions)	15 (10)	8 (13)	23 (11)	
3 (1 attacks, = 2 lesions)	0	0	0	
4 (1 attack, 1 lesion)	0	0	0	
Disease duration — yr				
Median	4.0	5.0	5.0	0.501
Range	0-26	1-31	0-31	
No. of relapses in past yr — no. of patients (%)				
0	0	0	0	0.166
1	0	0	0	
2	110 (74)	47 (77)	157 (75)	
≥ 3	38 (26)	14 (23)	52 (25)	
Mean				
Range				
EDSS score — no. of patients (%)				
0	7 (5)	4 (7)	11 (5)	0.389
1.0–1.5	38 (26)	17 (28)	55 (26)	
2.0–2.5	54 (36)	21 (34)	75 (36)	
3.0–3.5	29 (20)	13 (21)	42 (20)	
4.0–4.5	18 (12)	6 (10)	24 (11)	
5.0	2 (1)	0	2 (<1)	
≥ 5.5	0	0	0	
Mean	2.4 ± 1.1	2.2 ± 1.1	2.3 ± 1.1	
Range	0-5	0-4.5	0-5	
No. of lesions on gadolinium-enhanced MRI — no. of patients (%)				
0	0	0	0	0.891
1	49 (33)	19 (31)	68 (33)	
2	25 (17)	14 (23)	39 (19)	
3	14 (9)	7 (11)	21 (10)	
≥ 4	60 (41)	21 (34)	81 (39)	
Missing data	0	0	0	
Mean	5.3 ± 6.3	5.4 ± 7.8	5.3 ± 6.8	
Range	1-34	1-39	1-39	
No. of lesions on T2-weighted MRI — no. of patients (%)				
<9	3 (2)	1 (2)	4 (2)	>0.999
≥9	145 (98)	60 (98)	205 (98)	
Missing data	0	0	0	

* Plus–minus values are means ± SD. EDSS range of scores, 0 to 10, with higher scores indicating more severe disability. Percentages may not sum to 100, because of rounding. ‡ Criteria are from McDonald et al. (49)

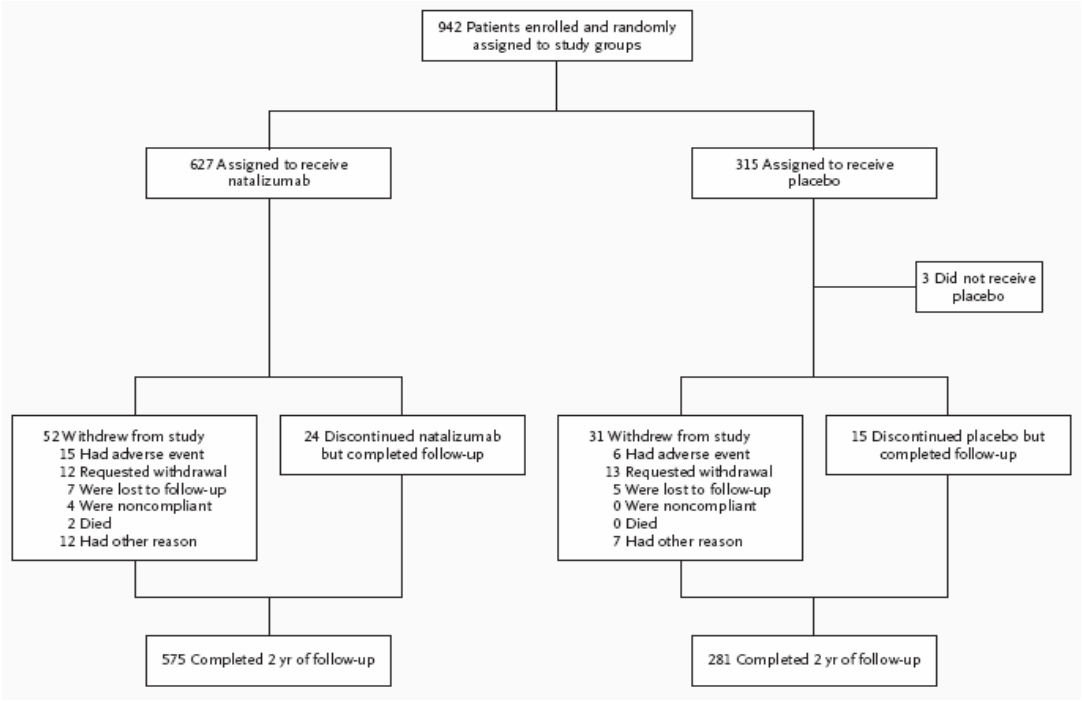
The only significant difference in the baseline characteristics of the RES subgroup is in the age of the two arms. The mean age of the natalizumab arm was 33.7 years, whereas it was 36.4 years for the placebo arm (p = 0.037); the standard deviation age for both arms was similar, however, at 8.1 and 8.4 years respectively.

5.3.3 Patient numbers

A summary of the patients entering the AFFIRM study, follow-up and completing patients is given in Figure 10.

Missing data was accounted for using the principle of last observation carried forward (LOCF).

Figure 10 Summary of patient flow through the AFFIRM study, Polman et al 2006 (4)



5.3.4 Outcomes

The primary endpoints evaluated in the AFFIRM study are consistent with other studies of DMTs and EMEA recommendations for studies in the disease. (114) These were:

- At 1 year to determine whether natalizumab, when compared with placebo, was effective in reducing the rate of clinical relapses.
- At two years, determine whether natalizumab, when compared with placebo, was effective in slowing the progression of disability. This was measured as a greater than 1.0 point increase in EDSS from baseline EDSS ≥1.0 that was sustained for 12 weeks, or at least a 1.5 point increase on the EDSS from baseline EDSS 0 that was sustained for 12 weeks. A pre specified sensitivity analysis was performed using a more stringent endpoint of disability progression sustained for 24 weeks (see Table 18 on page 69). (115)

The secondary endpoints at 1 year were to determine whether natalizumab, when compared with placebo, was effective in:

- Reducing the number of new or enlarging T2 hyperintense lesions on brain magnetic resonance imaging (MRI) scans.
- Reducing the number of gadolinium (Gd)-enhancing lesions on brain MRI scans.
- Increasing the proportion of relapse-free subjects.

The secondary endpoints at 2 years were to determine whether natalizumab, when compared with placebo, was effective in:

- Reducing the rate of clinical relapses.
- Attenuating the increase in T2 hyperintense lesion volume on brain MRI scans.
- Attenuating the increase in T1 hypointense lesion number on brain MRI scans.
- Slowing the progression of disability, as determined by the change in the Multiple Sclerosis Functional Composite Scale (MSFC) in each treatment group.
- Sustaining quality of life as measured by the MS Quality of Life Inventory/SF-36 Health Survey (MSQLI/SF-36).

5.3.4.1 Description of endpoints

Efficacy measures included EDSS, relapse assessment, MSFC, Visual Function Test (VFT), MRI measures, MSQLI/SF-36, Visual Analogue Scale (VAS), rate of relapses requiring IV steroid use, and the rate of hospitalisation.

Safety was assessed by physical examination, vital signs, AE monitoring, blood chemistry, haematology, urinalysis, and pregnancy tests.

- Clinical relapses were defined as new or recurrent neurological symptoms, not associated with fever or infection, lasting for at least 24 hours, and accompanied by new objective neurological findings upon examination by the examining neurologist at unscheduled visits. Please note that in the submission relapse is synonymous with exacerbation.
- The EDSS evolved from the Disability Status Scale (DSS) and, when used in conjunction with signs coded to eight Functional Systems (FS), is the preferred method to assess changes in disability associated with MS. (114;116;117)
- MSFC consists of the Timed 25-Foot Walk, 9HPT, and PASAT 3. (118)
- The MSQLI is a validated outcomes assessment inventory developed by the Consortium of Multiple Sclerosis Centres Health Services Research Subcommittee. (119) The MSQLI, consists of 10 scales including the SF-36 Health Survey. The MSQLI is available for English-speaking subjects only.
- The SF-36 is one of the most widely accepted generic health status measures. It is a brief (36-item) scale developed by Steward, Hayes, and Ware. (120) The SF-36 was to be completed by all subjects for whom a validated translation in the local language was available.
- VFT was measured using the low-contrast Sloan letter chart. (121)

5.3.5 Statistical analysis and definition of study groups

This section describes the statistical methodology of the AFFIRM study, which are in line with methodology from the earlier trials of DMTs. Supportive data from studies MS 201 and MS 231 are presented in Appendix D.

The hypotheses used to test for the primary outcome measures in AFFIRM were:

H_0: The hazard ratio for disease progression or for disease relapse in patients treated with natalizumab rather than placebo is 1

H_A: The hazard ratio is not equal to 1

Disease progression was defined as the time to disability progression. This was measured by at least a one point increase in the EDSS from a baseline EDSS (≥ 1.0), or at least a 1.5 point increase on the EDSS from baseline (EDSS = 0). Both of these increases were to be sustained for 12 weeks. The two sided test comparison between treatment groups used a Cox proportional hazards model that adjusted for the baseline EDSS score and age group (<40 versus ≥ 40). Gd+ lesion number at baseline and T2-hyperintense lesion number at baseline were also assessed in the model, but did not significantly impact upon the model results, and were excluded by backward selection.

Sample size estimates were made using data from the natalizumab phase II study, MS 231 (relapse rate), and the Avonex phase III study, (disability progression rate). (66) Two-sided tests with an experiment-wise α = 0.05 and approximately 90% power were used for sample size calculations. Additional detail on the calculations for sample size is given in Polman et al 2006. (4) The annualised rate of relapse at one year was predicted to be 0.6 with natalizumab and 0.9 with placebo. A likelihood-ratio test was subsequently used to estimate the sample size required for

90% power with a 2:1 ratio of natalizumab to placebo. The sample size calculated for 90% power was 765. A dropout rate of 15 percent was assumed and, with rounding, the number of patients needed was estimated to be 900. In order to power the study for the two-year end point of disability progression, progression rates at the end of two years were assumed to be 34.9% for the placebo group and 22.7% for the natalizumab group. Simulations of the log-rank test for survival were run with 60% of the accrual in the first 24 weeks and the remainder in the next 24 weeks, assuming a 20% dropout rate over the 2-year study. The sample size of 900 provided 90% power with the use of a Bonferroni adjustment for multiple end points, maintaining the type 1 error rate of 0.05.

Categorical outcomes were modelled by logistic regression, multiple logistic regression, or Poisson regression (log-likelihood ratio test assuming response variable follows a Poisson distribution). Continuous responses were modelled by analysis of variance (ANOVA) or analysis of covariance (ANCOVA). Time to event responses were analysed with Cox proportional hazards regression models.

For natalizumab we use the hazard ratio calculated from the Cox proportional hazard model as a measure of relative risk of disability progression rather than the relative risk ratio. Lyman et al describe the hazard ratio is a more robust measure of relative risk as it is, 'particularly designed for comparing two survival curves by allowing for both censoring and time to an event'. (122)

Primary analysis was based on an ITT population, defined as all subjects who were randomised. At the request of the EMEA, a subgroup analysis was also undertaken in RES subjects defined by two or more disabling relapses in one year and with one or more Gd-enhancing lesions on brain MRI or a significant increase in T2 lesion load compared to a previous MRI (for more detail please refer to Section 2.3.1 on page 20).

5.3.6 Critical appraisal of relevant RCTs

Relevant natalizumab studies are summarised in Table 17. Similar tables for IFN-beta and GA appear in section 5.5. We also critically appraised AFFIRM, SENTINEL, MS 201 and MS 231 studies from which information was taken for this submission (see Appendix F starting on page 226). A health outcomes analyst, who was not actively involved in drafting this submission, performed the critical appraisal. All of the studies for natalizumab were considered to be of comparable or better quality to the comparator studies detailed in the Cochrane systematic reviews. For example, they all achieved the maximum Jadad [2] score of five, which is used as a measure of study quality. This is not surprising given that clinical study reports were available for all natalizumab studies, whereas the critical appraisal of comparator studies relied on data from publications.

[2] The Jadad score is widely used to assess the quality of clinical studies and is based on five questions: 1) Is the study randomized? 2) Is the study double blinded? 3) Is there a description of withdrawals? 4) Is the randomization adequately described? 5) Is the blindness adequately described?

Table 17 Summary of the trials included in this submission for natalizumab.

	Trial			
	AFFIRM	**SENTINEL**	**MS 201**	**MS 231**
Analysis	ITT mentioned	ITT mentioned	ITT mentioned	ITT mentioned
Study country	Europe, North America, Australia and New Zealand; 99 centres	USA and Europe; 124 centres	UK; 9 centres	USA, Canada and UK; multi-centre
Patients n (n active, n comparator)	942 (627, 315)	1171 (589, 582)	72 (37, 35)	214 (68 3mg, 74 6mg, 71)
Patient age	18-50	18-55	18-55	18-65
Number of patients lost to follow up	47 (86 withdrawals of which 39 completed through to follow-up)	total withdrawals was 168 patients	4 (69 completed study)	16
Treatment period	up to 116 weeks	116 weeks (discontinued one month early due to SAE (PML))	2 injections 4 weeks apart	6 months
Follow up period	128 weeks	2 years	28 weeks	12 months
Allocation concealment	A - adequate	A - adequate	A – adequate	A - adequate
Jadad score[+]	5	5	5	5

5.4 Results from relevant comparative RCTs

The efficacy results from the AFFIRM study that are most pertinent to this submission are summarised in Table 18. Safety results are reported subsequently in Section 5.7, starting on page 85.

All clinical and surrogate primary and secondary endpoints for AFFIRM showed a clinical and statistically significant benefit in favour of natalizumab treated patients. These benefits were seen early and were sustained throughout the duration of treatment.

5.4.1 Primary endpoints from AFFIRM

Table 18 Pertinent primary efficacy results from AFFIRM (Polman et al 2006 and data on file AFFIRM study (4;113))

ITT Population				
Outcome	**Natalizumab (n = 627)**	**Placebo (n = 315)**	**Absolute risk reduction**	**Hazard ratio (95% CI)**
Probability of sustained disability progression (defined as an increase in EDSS sustained for 12 weeks) at two years †	0.17	0.29	0.12	0.58 (0.43, 0.77)
Probability of sustained disability progression (defined as an increase in EDSS sustained for 24 weeks) at two years † ‡ §	0.11	0.23	0.12	0.46 (0.33, 0.64)
Annualised relapse rate at one year	0.26	0.81	0.55	0.68 (0.59, 0.74) *
Annualised relapse rate at two years §	0.24	0.73	0.50	0.68 (0.60, 0.74) *

RES Subgroup				
Outcome	**Natalizumab (n=148)**	**Placebo (n=61)**	**Absolute risk reduction**	**Hazard ratio (95% CI)**
Probability of sustained disability progression (defined as an increase in EDSS sustained for 12 weeks) at two years †	0.14	0.29	0.15	0.47 (0.24, 0.93)
Probability of sustained disability progression (defined as an increase in EDSS sustained for 24 weeks) at two years † ‡ §	0.10	0.26	0.16	0.36 (0.17, 0.76)
Annualised relapse rate at two years §	0.28	1.46	1.17	0.81 (0.70, 0.88) *

† Based on the Kaplan-Meier product limit method; ‡ Disability progression sustained for 24 weeks is recognised by Rio et al as an alternative measure of efficacy than progression sustained for 12 weeks. (115) Rio et al concluded that progression sustained for six months was, 'the best criterion for reducing noise in this group of patients', and, 'had the best correlations with outcome disability measures at 4 years'. § Used in the economic evaluation in Section 6. * Relative risk reduction. Note that the absolute risk reduction may not equate to the difference in individual analyses due to rounding.

5.4.2 Secondary endpoints from AFFIRM

We present data on the following secondary endpoints:

- MRI
- MSFC
- Health Related Quality of Life
- Visual function test
- Hospitalisations

5.4.2.1 MRI outcomes

Natalizumab resulted in large significant benefit compared with placebo on all MRI outcomes (Table 19).

Table 19 Pertinent MRI efficacy results from AFFIRM (data on file AFFIRM study (113))

Outcome (ITT Population)	Natalizumab (n = 627)	Placebo (n = 315)	Absolute risk difference	Relative risk reduction (95% CI)
MRI: Free of Gd-enhancing lesions at two years	608 (97%)	227 (72%)	25%	1.35 (1.26, 1.45)
MRI: Free of new or enlarging T2 lesions at two years	360 (57%)	46 (15%)	42%	3.93 (3.00, 5.20)
MRI: Free of new T1 lesions at two years	396 (63%)	84 (27%)	36%	2.37 (1.96 2.89)

Note that the outcomes presented are prefaced by 'Free of…', which means that an increase in relative risk reduction is beneficial, rather than a decrease.

5.4.2.2 MSFC outcomes

Natalizumab resulted in significant benefit compared with placebo on all three domains of the MSFC (Timed 25-Foot Walk, 9HPT, and PASAT 3) (Table 20).

Table 20 Pertinent MSFC efficacy results from AFFIRM (data on file AFFIRM study (113))

	Placebo (315)	Natalizumab (627)	p-value (a)
25-Foot Walk Z-Score Mean (sd)	-0.50 (1.73)	-0.20 (1.91)	< 0.001
9 HPT Z-Score Mean (sd)	-0.13 (0.71)	0.09 (0.61)	< 0.001
PASAT 3 Z-Score Mean (sd)	0.13 (0.63)	0.22 (0.53)	0.005
MSFC Composite Z-Score Mean (sd)	-0.16 (0.72)	0.04 (0.71)	< 0.001

NOTE: Z-scores were calculated based on a reference population mean of 5.33 and a standard deviation of 2.01 for the 25-foot Walk, a mean of 0.05 and a standard deviation of 0.01 for the 9 Hole Peg Test, and a mean of 50.82 and a standard deviation of 10.30 for the PASAT 3.

(a) P-value for comparison between the treated and placebo groups, based on Friedman's analysis of covariance (ranked data), adjusted for the baseline MSFC corresponding component score.

5.4.2.3 Health related quality of life outcomes

Natalizumab resulted in significant benefit compared with placebo on the mental and physical scales of SF-36. Due to the limited availability of validated translations, a subset of 118 placebo subjects and 241 natalizumab subjects completed the MSQLI subscales in addition to the SF-36 at 1 or more post baseline visits; no significant effect was noted for MSQLI (data on file AFFIRM study (113)).

A total of 929 subjects completed the SF-36 at 1 or more visits in addition to baseline. The mean change from baseline to 2 years in the SF-36 physical component score and the SF-36 mental component score is shown in Table 26.

Table 21 Pertinent SF-36 efficacy results from AFFIRM (data on file, AFFIRM study (113))

	Placebo (264)	Natalizumab (536)	p-value (a)
SF-36 Mental Component Scale (b)			
Mean (sd)	-0.53 (10.52)	2.00 (10.91)	0.011
SF-36 Physical Component Scale (b)			
Mean (sd)	-1.34 (8.47)	0.67 (8.05)	0.003

NOTE: SF-36 is available for all subjects where a validated translation in the local language is available. Change from baseline to Week 104 scores are presented.

(a) P-value for comparison between the treated and placebo groups was based on analysis of covariance adjusted for the corresponding baseline SF-36 component score.

(b) A higher score indicates a better QOL.

After 2 years of treatment, there were statistically significant increases in the mean scores on the SF-36 mental and physical components in subjects in the natalizumab group, indicating an improved QOL versus placebo. Subjects in the natalizumab group had a mean increase of 2.00 (improvement) on the mental component scale at 2 years compared to a mean decrease of 0.53 (worsening) in the placebo group ($p = 0.011$). A similar difference was seen on the physical component scale where subjects in the natalizumab group had a mean increase of 0.67 (improvement) compared to a mean decrease of 1.34 (worsening) in the placebo group ($p = 0.003$).

Due to the limited availability of validated translations, a subset of 118 placebo subjects and 241 natalizumab subjects completed the MSQLI subscales in addition to the SF-36 at 1 or more post baseline visits. No significant effect was noted for MSQLI (data on file AFFIRM study (113)).

A number of factors underlie the discrepancy between the SF-36 and MSQLI results. Perhaps most importantly, the development of the SF-36 was guided by rigorous scale development methodology. The psychometric properties of the scales have been widely validated and the scaling of final scores minimizes floor and ceiling effects in most clinical populations. The baseline MSQLI scores of the current population indicate that patients in this study had minimal pre-existing deficits related to many of the physical areas evaluated by the MSQLI subscales. This finding suggests a significant ceiling effect in the MSQLI instrument in this cohort, which limits its responsiveness and ability to detect change over time. This was confirmed by the observation that there was minimal change in the mean subscale scores over time. Finally, the MSQLI subscales were acquired from a smaller group of patients, which reduced the power of statistical tests to detect an actual difference. It is, therefore, not surprising that there were few significant differences between the groups when quality of life was assessed using this scale.

5.4.2.4 Visual function test

There was no difference between treatment groups in the change on the VFT 100% contrast chart. However, a highly statistically significant treatment effect was seen on both the 2.5% and 1.25% charts (Table 22).

Table 22 Pertinent Visual Function Test results from AFFIRM (data on file AFFIRM study (113))

	Placebo (n = 283)	Natalizumab (n = 586)	p-value *
100% Chart Mean (sd)	0.5 (6.7) †	0.6 (6.4)	0.874
2.5% Chart Mean (sd)	-1.2 (8.7)	0.4 (8.8)	0.005
1.25% Chart Mean (sd)	-0.4 (10.9)	0.9 (10.8)	0.019

NOTE: Visual Function Test Scores are expressed as the number of letters correctly identified on the Low-contrast Sloan Letter Chart (LCSLC). Three different contrast level charts (100%, 2.5% and 1.25%) were used. Changes from baseline scores are analysed.

* P-value for comparison between the treated and placebo groups, based on the analysis of covariance, adjusted for the baseline VFT score.

† n = 284 for this comparison.

5.4.2.5 Hospitalisations

Natalizumab resulted in significant benefit compared with placebo on the rate of MS-related hospitalisations (data on file, AFFIRM study (113)).

There were 125 hospitalizations involving 77 subjects (24%) in the placebo group, compared to 156 in 114 subjects (18%) in the natalizumab group. The annualised hospitalisation rates were 0.183 in the placebo group compared with 0.112 in the natalizumab group, a relative reduction of 39% (p = 0.005).

For each hospitalisation, the primary reason was categorized as MS relapse, other MS-related complication, elective surgery, or 'other'. A further analysis of hospitalisations was carried out including only those hospitalisations for MS relapse or other MS-related complications. MS-related hospitalisations followed a similar pattern to all hospitalisations. There were 66 MS-related hospitalisations involving 41 subjects (13%) in the placebo group, compared to 48 in 37 subjects (6%) in the natalizumab group. The annualised MS-related hospitalisation rates were 0.097 in the placebo group compared with 0.034 in the natalizumab group, a relative reduction of 65% (p < 0.001).

5.4.3 Supplemental post-hoc analyses from AFFIRM

5.4.3.1 Proportion of patients free of all measures of disease activity

The number of patients that remained disease free for the duration of AFFIRM is an important measure of the overall efficacy of natalizumab in the treatment of RRMS. For the purposes of this analysis, patients were deemed to be disease free if they fulfilled all of the following pre-specified criteria (see Table 23):

1. free of relapses
2. free of sustained disability progression
3. free of Gd enhancing lesions
4. free of T2 hyperintense lesions
5. free of T1 hypointense lesions

In the natalizumab treated arm 28% (n = 177) remained disease free compared to 6% (n = 18) in the placebo arm.

Table 23 Patients free of disease in the ITT population of the AFFIRM trial (data on file)

Measure	Placebo n (%)	Natalizumab n (%)	p
Number of subjects randomised	315 (100)	627 (100)	
Number of subjects relapse free			
Yes	129 (41)	418 (67)	< 0.001
No	170 (54)	176 (28)	
Unknown	16 (5)	33 (5)	
Number of subjects free of disability progression			
Yes	231 (73)	523 (83)	< 0.001
No	84 (27)	104 (17)	
Number of subjects free of Gd+ lesions *			
No Gd+ lesions	170 (54)	576 (92)	< 0.001
Gd+ lesion present	145 (46)	51 (8)	
Number of subjects free of T1 hypointense lesions *			
No T1 Hypointense Lesions	84 (27)	396 (63)	< 0.001
T1 Hypointense Lesions	231 (73)	231 (37)	
Number of subjects free of T2 hyperintense lesions *			
No T2 hyperintense lesions	46 (15)	360 (57)	< 0.001
T2 hyperintense lesions	269 (85)	267 (43)	
Number of patients free of disease	18 (6)	177 (28)	< 0.001

* In the analysis, patients with missing MRIs were considered to have a lesion

5.4.3.2 Relapse severity

Overall, the results of two analyses of relapse suggest that natalizumab may also reduce the severity of a relapse. Specifically, the results that support this conclusion were:

- Of the 345 relapses in the placebo group, 244 (71%) required steroid treatment, whereas only 157 (63%) of the 248 relapses that occurred in the natalizumab group required steroid treatment ($p < 0.001$). (113)
- Significantly fewer relapses in the natalizumab arm required hospitalisation compared with placebo-relates relapses (3.4% and 9.7% respectively, $p < 0.001$). (113)
- A post-hoc analysis of SF-36 data revealed that among those who had a relapse during the study period, natalizumab was associated with significantly higher physical component summary scores at the end of the study compared with placebo. (data on file)

It should be noted that despite these observations, the economic model we present in Section 6 assumes no differential effect for natalizumab on relapse severity. The cost-effectiveness estimates for natalizumab are therefore conservative in this respect.

5.4.3.3 One year open label extension to AFFIRM and SENTINEL

Patients who participated in the phase III natalizumab program were eligible to enrol in an open-label extension study that evaluated the long-term effects of natalizumab (data on file). Patients previously receiving placebo were received natalizumab in the extension study. The annualised relapse rate for these patients over the three-year period was 0.23. This was consistent with the 0.23 annualised relapse rate seen in the natalizumab arm of the two-year AFFIRM study.

5.4.4 Supporting data from MS 231 and MS 201

The main results of studies MS 201 and MS 231 can be found in Appendix D starting on page 217.

5.5 Meta-analysis

There was a single relevant study for natalizumab; hence, a meta-analysis was not required. Prior to describing the results of the meta-analyses of comparators, we report the methods and results of the trials from which the data was first reported.

5.5.1 Methods of the relevant placebo controlled studies of the comparators

All of the publications in the systematic reviews for the comparators IFN-beta and GA were summarised as part of the review process and are reported in Appendix B and Appendix C. (70;73) A summary of the key points from the RCTs reported in Table 24 and Table 25 for IFN-beta and GA respectively. Additionally, we undertook independent critical appraisals of the study publications in the IFN-beta and GA systematic reviews and these are given in Appendix G. There was a large difference in the size of the studies, and the number of centres and countries where they were performed.

In the IFN-beta studies reviewed by Rice et al (73) allocation concealment was considered adequate in two of the studies but unclear in the remaining three (Table 24). Patients were reported to be clinically stable at study entry, except in the PRISMS 1998 study where this was not reported. All studies were intended to be double-blinded, however, the authors raised doubts as to the extent of successful blinding on account of the side effects caused by treatment with IFN-beta.

Table 24 Summary data for IFN-beta versus placebo studies evaluated in systematic review by Rice et al (73)

	Publication (RCT) *				
	IFNB MS Group, 1993	**Knobler, 1993**	**MSCRG, 1996**	**Owims, 1999**	**PRISMS, 1998**
Analysis	ITT mentioned	ITT not mentioned	ITT mentioned	ITT mentioned	ITT mentioned
Study country	USA & Canada, 11 centres	USA, 3 centres	USA, 4 centres	International, 11 centres	International, 22 centres
Patients (n)	372	31	301	293	560
Patient age	18-50	18-50	18-55	18-50	NA
Patients lost to follow up	8	7	5	14	26
Treatment period	2 years	3 years	2 years	24 weeks	2 years
Follow up period	2 years	3 years	2 years	48 weeks	2 years
Allocation concealment	B - unclear	B - unclear	B - unclear	A - adequate	A - adequate
Jadad score+	4	2-3	4	5	5

* All studies included patients of both sexes; all studies included patients with definite RRMS
+ Jadad scores were not given in the review, but were inferred from the critical appraisals given in the review.

Allocation concealment was considered adequate in three of the four GA studies reviewed (Table 25). All studies were double blind in design, but the reviewers raised concerns about the ability to ensure masking of treatment because of side effects such as injection site and skin reactions. The review also considered that the researchers in the publication of Bornstein 1987 violated the ITT analysis principles

in their analyses. The Jadad scores were calculated for each study in this review and only one study obtained the maximum score of five. The study of Bornstein scored only three in the Jadad because of unclear allocation concealment and insufficient details on withdrawn patients.

Table 25 Summary data for GA versus placebo studies evaluated in systematic review by Munari et al (70)

	Publication (RCT) *			
	Bornstein, 1987	**Bornstein, 1991**	**Comi, 2001**	**Johnson, 1995**
Analysis	ITT	ITT	ITT	ITT
Study country	Israel, 1 centre	Israel & USA, 2 centres	Europe & Canada, 29 centres	USA, 11 centres
Patients (n)	50	106	239	251
Patient age	20-35	20-60	18-50	18-45
patients lost to follow up	NA	NA	NA	NA
treatment period	24 months	24 months	9 months	24 months
follow up period	24 months	24 months	9 months	24 months
Allocation concealment	B - unclear	A - adequate	A - adequate	A - adequate
Jadad score	3	4	4	5

* All studies included patients of both sexes

5.5.2 Results of the relevant placebo controlled studies of the comparators

We could identify no reason, based on issues related to study quality or design, to warrant concern about the results and conclusions drawn in the published systematic reviews.

Since we found no published data to the contrary, both of our review updates found that the data and conclusions of the reviews were valid up to September 2006. However it is noteworthy to add that a study on the effects of GA in patients with RRMS (103) was included in our updated systematic review of GA. This study failed to achieve statistical significance on any primary, secondary or tertiary endpoints. This substantiates the conclusions of Munari et al. (70)

The studies that were identified for IFN-beta and GA in the systematic reviews (see section 5.2.1) included placebo as comparator. As recommended by the EMEA, the primary outcome measures of MS studies should assess the likelihood of disability progression on EDSS and the reduction in the number of clinical relapses over a defined period of time. (114) We have summarised the results from clinical studies of IFN-beta and GA, which were taken from systematic reviews, with an emphasis on these primary outcome measures and the authors' conclusions. However, this discussion is by no means exhaustive and the appropriate systematic reviews should be consulted for more detail.

5.5.2.1 Randomised placebo controlled trials of IFN-beta

The baseline characteristic and efficacy data for patients with at least one exacerbation at 2 years and patients who progressed at 2 years for studies with relevant outcome data are given in Table 26 and Table 27. These data were taken from the systematic review of Rice et al 2001 and from published study data.

Table 26 Baseline relapse characteristics of patients enrolled in studies of IFN-beta

Study	Baseline relapse characteristics
IFNB MS Study Group 1993 (59)	Mean (SEM) relapses in previous 2 years = 3.6 (0.1) and 3.4 (0.2) for placebo and 8.0 MIU respectively
MSCRG 1996 (66)	Mean (SEM) annualised relapses rate = 1.2 (0.05) for both active and placebo
PRISMS 1998 (58)	Mean (SD) relapses in previous two years = 3.0 (1.1) % of patients with 2 relapses, 3 relapses, ≥ 4 relapses = 41, 33, 26 respectively

Information relating to the number of patients that continued to experience exacerbations during the first year of treatment was given in 3 of the 7 studies assessed by the systematic review of Rice et al 2001. (73) There was a lack of data available specifically for the RES and SOT subgroups of RRMS.

The authors of the systematic review concluded that there was a modest effect in patients with RRMS when treated with IFN-beta. The effect observed was a reduction in the relative risk of relapse and in the progression of disability.

Table 27 Comparison of IFN-beta versus placebo: disability progression and relapse at 2 years

	Treatment (r/N)	Control (r/N)	Relative risk (95% CI)
Patients with at least one relapse at 2 years			
IFNB MS Group 1993 (59)	97/124	94/123	0.83 (0.71, 0.98)
MSCRG 1996 (66)	53/158	64/143	0.75 (0.56, 1.00)
PRISMS 1998 (58)	125/184	157/187	0.81 (0.72, 0.91)
Total	275/466	315/453	0.80 (0.73, 0.88)
Patients who progressed at 2 years			
IFNB MS Group, 1993 (59)	25/124	34/123	0.73 (0.46, 1.15)
MSCRG, 1996 (66)	18/158	29/143	0.56 (0.33, 0.97)
PRISMS, 1998 (58)	49/184	68/187	0.73 (0.54, 0.99)
Total	92/466	131/453	0.69 (0.55, 0.87)

5.5.2.2 Randomised placebo controlled trials of GA

Two of the four studies included in the systematic review of Munari et al contained information that was of relevance to the updated review. (70) The authors concluded that, 'glatiramer acetate seems to have no beneficial effect on the main outcome measures in this disease, i.e. disease progression, and it does not substantially affect the risk of clinical relapses over time', and ... 'there is at present insufficient evidence to support its routine use in clinical practice and more data from randomised clinical studies are needed'. The baseline characteristics and efficacy data at 2 years for studies with relevant outcome data are given in Table 28 and

Table 29 respectively. These data support the conclusions of the reviewers.

Table 28 Baseline relapse characteristics of patients enrolled in studies of GA

Study	Baseline relapse characteristics
Bornstein 1987 (109)	Mean relapses in previous 2 years = 3.9, 3.8 for placebo, GA respectively
Johnson 1995 (111)	Mean (SD) relapses in previous 2 years = 2.9 (1.1), 2.9 (1.3) for placebo, GA respectively

Table 29 Comparison of GA versus placebo: disability progression and relapse at 2 years

	Treatment (n/N)	Control (n/N)	Relative risk (95% CI)
Patients with at least one relapse at 2 years			
Bornstein, 1987 (109)	11/25	17/25	0.65 (0.39, 1.09)
Johnson, 1995 (111)	83/125	92/126	0.91 (0.77, 1.07)
Total	94/150	109/151	0.87 (0.74, 1.02)
Patients who progressed at 2 years			
Bornstein, 1987 (109)	5/25	11/25	0.45 (0.18, 1.12)
Johnson, 1995 (111)	27/125	31/126	0.88 (0.56, 1.38)
Total	32/150	43/151	0.77 (0.51, 1.14)

Bornstein 1987 was excluded from the ScHARR MS cost-effectiveness model that forms the basis for the health economic model for the evaluation of natalizumab (see section 6). (17;109) We report the effect of including and excluding this study in the indirect comparison in section 5.6 and the sensitivity analysis in section 6.3.3.

5.6 Indirect / mixed treatment comparisons

The decision problems require comparisons of natalizumab with best supportive care, GA and IFN-beta. Comparison with best supportive care can be made directly (using placebo as a proxy) although we believe that best supportive care is inappropriate in patients with HARRMS (see section 3.1). Comparisons with GA and IFN-beta must be made indirectly as no direct comparator evidence is available, hence indirect comparisons have been used to estimate the efficacy of natalizumab compared with IFN-beta and GA.

The efficacy outcomes assessed are the most relevant to the economic evaluation in Section 6 and are presented in this section. Indirect safety analyses are reported subsequently in section 5.7.

Evidence for the efficacy and safety of natalizumab, GA and IFN-beta was taken from RCTs of these treatments, identified in our update to the Cochrane systematic reviews. All identified studies had a placebo control group, which provides a simple evidence network for this assessment. (123) Sophisticated methods have been developed by Ades et al to facilitate indirect treatment comparisons in generalised evidence networks. (124) However, in the setting of this assessment, where the network is straightforward and all studies are placebo controlled, we believe the simpler methods of Song et al are appropriate and equivalent. (125;126) This enables the comparison of two treatments against a common comparator even though they follow a frequentist rather than Bayesian approach.

The statistic chosen to make comparisons between treatments was the (logarithm of the) risk ratio, which has a clear interpretation. As recommended by Song et al, the Cochrane review meta-analyses were recalculated using a random-effects model. Statistical significance was assessed at the 5% level and all tests and confidence intervals were two-sided, unless stated. The software used was the metan command written for Stata. (Bradburn 1999) (70;125;126)

Efficacy data were pooled only from studies that included patients with RRMS or that reported on such patients as a separate subgroup. This was done on the assumption that efficacy of the DMTs will be associated with disease type. However, there were no suitable RES or SOT subgroups available for analysis. In the absence of evidence to the contrary, it was assumed that there was no difference in efficacy for IFN-beta or GA between an ITT population (i.e. a RRMS population) and the RES subgroup. No subgroup analyses of current DMTs in the populations covered by the natalizumab license have been reported. It is not known whether the treatment effects observed for the current DMTs would differ in the natalizumab licensed populations. For both the RES and SOT comparisons it has been assumed that the effect size for the DMTs is consistent with a RRMS population. We believe that this is the most robust assumption because:

In the case of the RES subgroup:

- The exact mechanism of action of both IFN-beta and GA in people with MS has not been defined. (53-56) For example, in the Avonex SPC it states, 'whether the mechanism of action of Avonex in MS is mediated by the same pathway as the biological effects is not known because the pathophysiology of MS is not well established.' In the GA SPC it states, 'the mechanism(s) by which glatiramer acetate exerts its effects in patients with MS is (are) not fully elucidated'. In the absence of a known mechanism of action, there is no specific reason to expect that the efficacy of IFN-beta or GA (relative to placebo) in a RES subgroup would be greater than or less than that observed in a RRMS population. This is in contrast to natalizumab where a precise mechanism of action is known – it is the first molecule in a new class of 'selective adhesion molecule inhibitors'. (1)
- Although no comparable subgroup analyses were performed in clinical studies of the current DMTs, relapse frequency immediately prior to enrolment has been reported in the DMT studies, and it is clear that a significant proportion of subjects in these studies could be classified as RES (Table 26 and Table 28 above). Hence the results from these studies are likely to be broadly representative of those of a RES subgroup

In the case of the SOT indication:

- Evidence has been reported in the Quality Assessment in Multiple Sclerosis study (QUASIMS) that switching IFN-beta in people with continuing active disease would offer no additional benefit (see section 5.8.2). (75) QUASIMS was a large retrospective, controlled observational cohort study of the efficacy and tolerability of IFN-beta products in relapsing forms of MS.

When interpreting the results of these indirect comparisons, two active treatments will be significantly different if:

- The comparison statistic differs greatly from the value associated with no treatment difference (i.e. differs greatly from one in the case of the risk ratio, or from zero in the case of the log risk ratio)
- The standard errors of comparison statistic is small

Therefore, the power of this approach is higher if there are numerous, large studies and the difference in the underlying treatment effect is substantial.

Our conclusions from these analyses are that natalizumab has a consistent beneficial effect on disability progression and relapse rate compared with IFN-beta and GA that is highly significant for comparison of relapse rate, and a significantly better AE profile compared with IFN-beta. Indirect comparisons of the two important efficacy measures used in the economic evaluation in section 6 and of AEs are presented.

- The indirect comparisons performed demonstrate that natalizumab significantly reduces the frequency of relapse compared with current DMTs and has a consistent effect on slowing disease progression.
- In addition, natalizumab has an AE profile that is the same as or more favourable than IFN-beta for all AEs reported in the Cochrane systematic review of Rice et al (70;73)
- No significant differences were noted in safety between natalizumab and GA.

The indirect comparison is described below in sections 5.6.1 and 5.6.2.

5.6.1 Disability progression

academic / commercial in confidence information removed

Table 30 academic / commercial in confidence information removed

Table 31 academic / commercial in confidence information removed

5.6.2 Relapse frequency

The indirect comparison of relapses at two years resulted in a risk ratio of relapses significantly favouring natalizumab compared to both IFN-beta and GA (Table 32 and Table 33). This is despite the paucity of relevant studies with which to undertake the comparison. The point estimate for relative risk ranged from 0.47 to 0.63. GA was reported in the Cochrane review to have a significant effect on relapse at one year, but this effect did not extend to two years.

These results suggest that a sufficiently powered direct comparison would result in significant differences in the numbers of relapse between natalizumab and both IFN-beta and GA.

Table 32 Results of the indirect comparison of relapse for natalizumab and IFN-beta

ITT population													
Cochrane endpoints (73)	**AFFIRM endpoints**	**Cochrane (n = 919): IFN-beta vs. placebo**				**AFFIRM (n = 942): NAT vs. placebo**				**Indirect: NAT vs. IFN-beta**			
		RR	**Lcl**	**ucl**	**p**	**RR**	**lcl**	**ucl**	**p**	**RR**	**lcl**	**ucl**	**p**
All patients with at least one exacerbation at 2 years	All patients with at least one exacerbation at 2 years	0.81	0.74	0.89	*	0.51	0.44	0.61	*	0.63	0.53	0.77	*
RES subgroup													
Cochrane endpoints	**AFFIRM endpoints**	**Cochrane (n = 919): IFN-beta vs. placebo**				**AFFIRM (n = 209): NAT vs. placebo**				**Indirect: NAT vs. IFN-beta**			
		RR	**Lcl**	**ucl**	**p**	**RR**	**lcl**	**ucl**	**p**	**RR**	**lcl**	**ucl**	**p**
All patients with at least one exacerbation at 2 years	RES patients with at least one exacerbation at 2 years	0.81	0.74	0.89	*	0.39	0.29	0.53	*	0.49	0.36	0.66	*

* p < 0.01; IFN-beta, interferon beta; NAT, natalizumab; RES, rapidly evolving severe subgroup; RR, risk ratio; lcl, lower confidence limit (95%); ucl, upper confidence limit (95%)

Table 33 Results of the indirect comparison of relapse for natalizumab and GA

ITT population													
Cochrane endpoints (70)	**AFFIRM endpoints**	**Cochrane (n = 251): GA vs. placebo**				**AFFIRM (n = 942): NAT vs. placebo**				**Indirect: NAT vs. GA**			
		RR	**Lcl**	**ucl**	**p**	**RR**	**lcl**	**ucl**	**p**	**RR**	**lcl**	**ucl**	**p**
All patients with at least one exacerbation at 2 years	All patients with at least one exacerbation at 2 years	0.91	0.77	1.07	0.26	0.51	0.44	0.61	*	0.57	0.45	0.71	*
RES subgroup													
Cochrane endpoints	**AFFIRM endpoints**	**Cochrane (n = 251): GA vs. placebo**				**AFFIRM (n = 209): NAT vs. placebo**				**Indirect: NAT vs. GA**			
		RR	**Lcl**	**ucl**	**p**	**RR**	**lcl**	**ucl**	**p**	**RR**	**lcl**	**ucl**	**p**
All patients with at least one exacerbation at 2 years	RES patients with at least one exacerbation at 2 years	0.91	0.77	1.07	0.26	0.39	0.29	0.53	*	0.43	0.31	0.6	*

* p < 0.01; GA, glatiramer acetate; NAT, natalizumab; RES, rapidly evolving severe subgroup; RR, risk ratio; lcl, lower confidence limit (95%); ucl, upper confidence limit (95%)

5.6.3 A note on compliance with medication

It is probable that compliance with natalizumab will be better than the current DMTs because natalizumab is dosed less frequently than the current drugs and is delivered in an outpatient setting rather than at home. In a large systematic review conducted in 2001, Claxton et al demonstrated an inverse relationship between dose frequency and compliance, and found compliance rates were higher with weekly regimens, compared with daily regimens. (127) The compliance effect of monthly natalizumab administration compared with more frequent regimens required of the current DMTs is not known.

The compliance rates of natalizumab are likely to be equal to the clinic attendance rates of recipients (i.e. as long as the recipient attends their outpatient appointment, they will receive their correct dose on time). In addition, the benefit of knowing exactly what the compliance profile is for each recipient should not be

overlooked. Non-attendees at outpatient clinics can be easily identified and followed up, whereas the compliance rates with current DMTs, which are self-administered at home, are not known, cannot easily be assessed, and are more difficult to influence.

Compliance has been defined by the International Society of Pharmacoeconomics and Outcomes Research (ISPOR) as:

> 'Medication Compliance (Synonym: Adherence) [is] the extent to which a patient acts in accordance with the prescribed interval and dose of and dosing regime. The unit of measure for compliance is administered doses per defined period of time, reported as a proportion (%) of prescribed doses (D) taken at the prescribed time interval (T) as measured by the period of time, i.e., % of TD, measured by percentage.' (128)

ISPOR defines persistence as:

> 'The accumulation of time from initiation to discontinuation of therapy. Measured by time metric.' (128)

Withdrawal rates for the current DMTs and natalizumab are known and represent a good proxy for persistence.

5.7 Safety

The safety population in AFFIRM comprises of patients who received at least one dose of natalizumab or placebo. In addition to the results from the AFFIRM study, we have also included in this section the results from the indirect analyses (section 5.7.3.).

5.7.1 Adverse events

Overall, treatment with natalizumab was well tolerated by patients. The incidence of any treatment emergent AE was not different between the group receiving natalizumab (95%) and the group receiving placebo (96%). (4) The only AEs that were significantly more common in the natalizumab group were fatigue and allergic reaction. Moderate AEs were reported by 55% and 56% of patients receiving natalizumab and placebo respectively, and severe AEs were reported by 23% and 27%. (4) These results are summarised in Table 34.

Table 34 Incidence of treatment emergent adverse events in AFFIRM*

	NAT (627)	Placebo (312)	P Value		NAT (627)	Placebo (312)	P Value
	% of patients				% of patients		
General condition				Menstrual disorder †			
Headache	38	33	0.137	Irreg. menstru. dysmenorrhoea	7	4	0.102
Fatigue	27	21	0.048	Amenorrhea	2	1	0.405
Arthralgia	19	14	0.106	Neurological condition			
Urinary urgency or frequency	9	7	0.365	Vertigo	6	5	0.779
Allergic reaction	9	4	0.012	Tremor	3	3	0.566
Chest discomfort	5	3	0.169	Serious adverse event ‡			
Local bleeding	3	2	0.386	Relapse of multiple sclerosis	6	13	<0.001
Rigors	3	1	0.080	Cholelithiasis	<1	<1	0.435
Syncope	3	3	0.895	Need for rehabilitation therapy	<1	<1	0.999
Infection				Urinary tract infection, NOS	<1	0	0.308
Urinary tract	20	17	0.257	Depression	<1	<1	0.669
Lower respiratory tract	17	16	0.644	Anaphylactic reaction	<1	0	0.555
Gastroenteritis	11	9	0.328	Hypersensitivity reaction	<1	0	0.555
Vaginitis †	10	6	0.133	Fall	<1	<1	0.999
Tonsillitis	7	5	0.291	Breast cancer, NOS	<1	0	0.999
Psychiatric condition (depression)	19	16	0.197	Anaphylactoid reaction	<1	0	0.999
Gastrointestinal condition				Convulsion, NOS	<1	<1	0.604
Abdominal discomfort	11	10	0.561	Gastritis, NOS	<1	0	0.999
Abnormal liver-function results	5	4	0.406	Cervical dysplasia	<1	0	0.999
Skin				Alcohol poisoning	<1	<1	0.999
Rash	11	9	0.301	Head injury	<1	<1	0.999
Dermatitis	7	4	0.053	Thermal burn	<1	0	0.999
Pruritus	4	2	0.090				

*This table is reproduced from Polman 2006 (4). NOS denotes not otherwise specified.†, the percentage and P value calculated on the basis of the number of female patients; ‡, SAEs are listed only if they occur in two or more patients in the natalizumab group.

Serious adverse events (SAEs) were observed in 19% of patients receiving

natalizumab and 24% of patients receiving placebo (p = 0.06). The most common SAE, relapse of multiple sclerosis (that was also a primary outcome measure), was significantly less common in the natalizumab group (6% compared with 13%, p < 0.001). (4) When relapse was excluded from the SAE analysis the rates of SAEs were not found to be significantly different, at 14% for each arm (p > 0.999) (data on file, AFFIRM study (113)).

The most common clinically significant AE associated with natalizumab therapy was acute hypersensitivity reaction. These events occurred in up to 4% of patients, of which 1.1% was considered serious and 0.8% was reported as anaphylactic or anaphylactoid (serious systemic hypersensitivity). Hypersensitivity reactions were generally associated with the presence of anti-natalizumab antibodies. Any patients who experienced these events were to permanently discontinue natalizumab. During the clinical studies, no cardio-pulmonary compromise-related events occurred.

5.7.2 Rare SAEs

An increased risk of PML in people administered natalizumab has been reported (6) and two cases were identified in the MS clinical studies (1). Both cases were exposed to concomitant IFN-beta during the study and had received over 2 years of dosing. A third case, previously misdiagnosed as malignant astrocytoma, was identified in a patient in a Crohn's disease study. This patient had received 8 infusions of natalizumab and had had a long history of treatment with immunosuppressants and associated lymphopenia.

Based on the discovery of the two cases, an extensive safety review was undertaken. A total of 3116 out of 3417 (91%) of people who had received natalizumab for a mean of 17.9 months, while participating in clinical studies underwent evaluation for PML and no new cases were confirmed (total confirmed 1.0 per 1000 treated patients; 95% CI 0.2 to 2.8 per 1000). Although each case of PML occurred in patients concomitantly using immune modulating drugs or with evidence of immunosuppression, a risk of PML associated with natalizumab monotherapy cannot be excluded.

No cases of PML have been reported in people with RRMS receiving natalizumab monotherapy.

Other opportunistic infections have been reported with use of natalizumab, primarily in people with Crohn's disease who were immuno-compromised or where significant co-morbidity existed (1). The increased risk of other opportunistic infections with use of natalizumab in people without these co-morbidities cannot be excluded.

5.7.3 Indirect comparison with included comparator studies

Natalizumab was observed to have a more favourable AE profile than IFN-beta when used in monotherapy in the treatment of RRMS. Indirect comparisons were conducted, limited to AEs reported in the Cochrane review.

Specifically, natalizumab was associated with fewer incidences of flu-like symptoms and myalgia/arthralgia compared with IFN-beta.

The AE profile of natalizumab did not appear to be substantially different to that of GA.

5.7.3.1 Indirect safety comparison of natalizumab compared with IFN-beta

The results of indirect comparisons of safety for natalizumab and IFN-beta, which includes all treatment emergent AEs reported in the IFN-beta Cochrane review (73), are given in Table 35. Where possible, the AE descriptions in the AFFIRM, MS 201 and MS 231 studies report were matched to descriptions reported in the Cochrane systematic reviews. For each AE where indirect comparison was possible, we first meta-analysed available data from the three natalizumab studies AFFIRM, MS 201 and MS 231.

The majority of possible indirect comparisons of AEs (7/9) resulted in a reduced incidence of AE for natalizumab compared with IFN-beta. The results were significant in 2 comparisons:

- The incidence of flu-like or influenza-like symptoms for natalizumab was significantly less than that observed with IFN-beta. In the included studies, the total numbers of patients experiencing flu-like symptoms on IFN-beta and placebo were 269/564 (48%) and 157/553 (28%) respectively. The difference in terms of risk ratio, favouring natalizumab, was significant with a p-value of 0.01 (Table 35).
- The incidence of Myalgia/arthralgia for natalizumab was significantly less than that observed with IFN-beta. Of the 6 included studies, the total numbers of patients experiencing fever on IFN-beta and placebo were 149/564 (26%) and 77/553 (14%). The difference in terms of risk ratio, favouring natalizumab, was significant with a p-value of 0.04 (Table 35).

A trend favouring natalizumab treatment over IFN-beta treatment was also observed in the incidence of nausea and vomiting (p = 0.12). No notable differences were seen in any other AEs analysed.

Table 35 Results of the indirect comparison of safety for natalizumab and IFN-beta

Cochrane endpoints (n) (73)	Endpoints from NAT trials (n)	Cochrane: IFN-beta vs. placebo				AFFIRM, MS 201, MS231: NAT vs. placebo				Indirect: NAT vs. IFN-beta			
		RR	lcl	ucl	p	RR	lcl	ucl	p	RR	lcl	ucl	p
Committed or attempted suicide (919)	Suicidal ideation (939)	1.98	0.41	9.56	0.39	2.49	0.12	51.75	0.56	1.26	0.04	38.29	0.90
Fatigue (870)	Fatigue (1011)	1.34	0.96	1.87	0.08	1.62	0.80	3.28	0.18	1.21	0.55	2.64	0.63
Fever (1117)	Pyrexia (1152)	1.85	1.48	2.32	*	1.49	0.34	6.63	0.60	0.81	0.18	3.64	0.78
Flu-like symptoms (1117)	Influenza-like illness (1011)	1.70	1.23	2.37	*	0.79	0.50	1.25	0.32	0.47	0.26	0.82	0.01
Headache (870)	Headache (1224)	1.18	1.03	1.34	0.02	1.07	0.91	1.26	0.44	0.91	0.74	1.12	0.37
Injection site reaction (816)	Infusion site reaction (1152)	5.57	2.33	13.29	*	2.29	0.59	8.96	0.23	0.41	0.08	2.07	0.28
Major psychic disorders (1117)	Psychiatric disorders (939)	0.95	0.74	1.23	0.69	0.57	0.21	1.55	0.27	0.60	0.21	1.69	0.33
Myalgias / Arthralgia (1117)	Myalgias / Arthralgia (939)	1.87	1.46	2.38	*	1.26	0.95	1.68	0.11	0.68	0.47	0.98	0.04
Nausea and vomiting (301)	Nausea / vomiting (939)	1.39	0.94	2.03	0.10	0.94	0.70	1.26	0.69	0.68	0.42	1.10	0.12

* p < 0.01; IFN-beta, interferon beta; NAT, natalizumab; NOS, not otherwise specified; RR, relative risk; lcl, lower confidence limit (95%); ucl, upper confidence limit (95%)

5.7.3.2 Indirect safety comparison of natalizumab compared with GA

The results of the indirect comparison of natalizumab and GA for safety outcomes (treatment emergent AEs) are shown in Table 36. A greater number of AEs were reported in the Cochrane review of GA than the IFN-beta review. No significant differences between natalizumab and GA in any AE were noted. Patterned reaction was not reported for any patient in the AFFIRM study, whereas a significantly increased incidence was observed for GA compared to placebo.

Table 36 Results of the indirect comparison of safety for natalizumab and GA

Cochrane endpoints (n) (70)	Endpoints from NAT trials (n)	Cochrane: GA vs. placebo				AFFIRM, MS 201, MS231: NAT vs. placebo				Indirect: NAT vs. GA			
		RR	lcl	ucl	p	RR	lcl	ucl	p	RR	lcl	ucl	p
Abdominal discomfort (154)	Abdominal discomfort (1152)	0.63	0.32	1.25	0.19	1.96	0.22	17.69	0.55	3.11	0.31	31.02	0.33
AEs causing treatment withdrawal (538)	AEs causing treatment withdrawal (1224)	2.75	0.80	9.51	0.11	1.54	0.85	2.81	0.16	0.56	0.14	2.22	0.41
Anxiety (356)	Anxiety (1152)	1.32	0.69	2.54	0.40	0.70	0.44	1.11	0.13	0.53	0.24	1.18	0.12
Appetite loss (154)	Appetite decreased NOS (939)	0.81	0.41	1.60	0.54	0.50	0.13	1.98	0.32	0.62	0.13	2.88	0.54
Constipation (154)	Constipation (1224)	0.89	0.48	1.67	0.72	0.88	0.55	1.40	0.58	0.98	0.45	2.14	0.96
Cramps (154)	Muscle contraction, involuntary (1152)	1.23	0.59	2.57	0.58	0.80	0.10	6.44	0.83	0.65	0.07	5.93	0.70
Dizziness (154)	Dizziness (1224)	1.44	0.38	5.48	0.59	0.94	0.67	1.32	0.71	0.65	0.16	2.57	0.54
Drowsiness (154)	Somnolence (1152)	0.75	0.41	1.39	0.37	2.46	0.63	9.55	0.19	3.26	0.73	14.47	0.12
Dyspnoea (356)	Dyspnoea (1152)	0.69	0.42	1.13	0.14	1.13	0.47	2.73	0.79	1.65	0.60	4.55	0.34
Faintness (154)	Syncope (1152)	1.47	0.67	3.24	0.34	0.77	0.22	2.67	0.68	0.52	0.12	2.28	0.39
Headache (154)	Headache (1224)	1.02	0.61	1.69	0.94	1.07	0.91	1.26	0.44	1.05	0.62	1.78	0.86
Itching localised to injection site (407)	Infusion site erythema (939)	4.69	2.44	9.03	0.00	1.49	0.16	14.29	0.73	0.32	0.03	3.34	0.34
Joint pain (154)	Joint stiffness (939)	1.09	0.68	1.76	0.71	0.83	0.20	3.45	0.80	0.76	0.17	3.40	0.72
Nausea (154)	Nausea (1224)	1.29	0.63	2.66	0.49	0.65	0.32	1.33	0.24	0.51	0.18	1.40	0.19
Pain localised to injection site (646)	Infusion site pain (1152)	1.85	1.53	2.23	0.00	2.16	0.33	14.20	0.42	1.17	0.18	7.77	0.87
Palpitations (407)	Convulsions (1152)	1.95	0.97	3.92	0.06	0.67	0.13	3.57	0.64	0.35	0.06	2.11	0.25
Patterned reaction (646)	† (0)	3.29	2.15	5.04	0.00								
Rash (154)	Rash NOS (1152)	0.82	0.14	4.69	0.83	1.21	0.80	1.83	0.37	1.47	0.25	8.82	0.67
Redness localised to injection site (407)	Infusion site pruritus (939)	2.63	1.42	4.90	0.00	1.00	0.09	10.93	1.00	0.38	0.03	4.49	0.44
Swelling localised to injection site (407)	Infusion site swelling (1152)	3.65	2.54	5.24	0.00	1.23	0.16	9.27	0.84	0.34	0.04	2.63	0.30
Vomiting (154)	Vomiting (939)	0.62	0.08	4.87	0.65	0.65	0.42	1.02	0.06	1.06	0.13	8.71	0.96

* $p < 0.01$; IFN-beta, interferon beta; NAT, natalizumab; NOS, not otherwise specified; RR, relative risk; lcl, lower confidence limit (95%); ucl, upper confidence limit (95%); †, AE not reported for natalizumab

5.7.3.3 A note on hypersensitivity

Persistent anti-natalizumab antibodies are associated with a substantial decrease in effectiveness. (1) Neutralising antibodies are also produced to IFN-beta (typically 15-40%). In the case of both natalizumab and IFN-beta, significant attenuation of treatment effect is observed in patients that have developed neutralising antibodies. The majority (approximately two thirds) of patients that develop anti-natalizumab antibodies suffer a hypersensitivity reaction. This means that the presence of anti-natalizumab antibodies is likely to be almost immediately obvious in most patients. This is not the case for IFN-beta where the presence of neutralising antibodies tends to remain clinically silent for some time and is typically only manifested (in the absence of routine screening) by increased relapses and/or disability progression. Hence, in those patients that develop neutralising antibodies on IFN-beta, these antibodies may not be detected for some time with the consequence that the patient may continue to receive a therapy whose efficacy is attenuated.

5.7.4 Supportive data from MS 201 and MS 231

The phase II studies, MS 201 (129) and MS 231 (130), provided further supportive

safety data.

Study MS 201 (129) treated patients randomised to natalizumab to two infusions at a dose of 3 mg/kg, 4 weeks apart. Study MS 231 (130) treated patients randomised to natalizumab to monthly infusions for 6 months at doses of either 3 mg/kg or 6 mg/kg. By comparison, in the AFFIRM study, treatment was given every 4 weeks for more than two years, at a dose in the natalizumab arm of 300 mg (regardless of patient weight).

The phase II studies reported similar safety outcome data as AFFIRM. Data from these two studies was meta-analysed with data from AFFIRM to inform the indirect comparisons conducted in sections 5.7.3.1 and 5.7.3.2 above.

5.7.4.1 Study MS 201 (129)

The only significant difference in any AE or SAE between natalizumab and placebo noted in the MS 201 study was for fatigue. The difference for natalizumab versus placebo was 32% compared with 11% ($p = 0.047$).

5.7.4.2 Study MS 231 (130)

In the study MS 231, approximately 98% of subjects in each treatment group experienced AEs during the study. There was no significant difference in the incidence of AEs between treatment groups and the majority of AEs, in each treatment group, were reported as mild or moderate in severity and not related to the study drug.

Overall, 24 patients experienced SAEs during the study. These comprised 9 (13%), 11 (16%) and 4 (5%) patients in the placebo, 3 mg/kg natalizumab, and 6 mg/kg natalizumab treatment arms respectively. One patient in the placebo group died.

Overall, 10 patients discontinued study drug due to AEs and this comprised 4 (6%), 3 (4%) and 3 (4%) patients in the placebo, 3 mg/kg natalizumab and 6 mg/kg natalizumab treatment arms respectively.

5.8 Non-RCT evidence

This section describes substantive non-RCT evidence used in the economic evaluation reported in section 6.

Section 5.8 breaks down into 9 sub sections as follows:

5.8.1 Natural history of HARRMS
5.8.2 Effect of switching IFN-beta treatments
5.8.3 Estimating transition probabilities in RES and SOT subgroups
5.8.4 UK MS Survey 2005
5.8.5 Estimating relapse rates by EDSS state and disease type
5.8.6 Estimating health state costs using a seemingly unrelated regression (SUR)
5.8.7 Estimating Utility
5.8.8 Adjustments to standardised mortality rate for people with MS
5.8.9 Withdrawal from active treatment

5.8.1 Natural history of HARRMS

5.8.1.1 London Ontario RRMS dataset

The London Ontario dataset has been used extensively in the analysis of the natural history of MS. (34) The dataset contains annual data collected from over 1000 patients followed for a mean of 25 years. This dataset is particularly useful as it was collected before the widespread use of DMTs and therefore is often used as a reference case against which the effects of DMTs can be measured. Patients in the dataset are broken down by disease type into RRMS, SPMS and PPMS but the RRMS patients are not further subdivided into SOT or RES subgroups, which are the subject of this analysis.

HE Europe provided the analysis of the London Ontario dataset for this submission (personal communication). The London Ontario dataset contains data on a RRMS and SPMS population and was used in the ScHARR model on which our model is based (the ScHARR model was commissioned by NICE and is described in section 6.1).

5.8.1.2 A comparison of RRMS with HARRMS

Richards et al, in their review of natural history and epidemiology of MS for the NHS R&D HTA Program, identified seven predictive variables that have been found by most epidemiological studies to predict more rapid disability progression: Male; older age; motor symptoms at onset; incomplete recovery [between relapses]; short inter-attack interval; high relapse rate in first years; and rapid progression to EDSS 3. (29) The last four of these factors coincide with the RES subgroup within the AFFIRM study, and arguably the SOT subgroup, and provide clear evidence that this group experiences more rapid disability progression than other people with RRMS. An analysis of disability progression within AFFIRM is presented in section 5.8.3.

It is probable that patients in the SOT subgroup have a similar disease profile as patients in the RES subgroup, although some disease activity is 'masked' by the

effect of their failing treatment with IFN-beta or GA.

Table 37 Clinical predictors of rapid disability progression (31;33;34;41)

Variable	Median time from onset of MS to EDSS 4 (years)	Median time from onset of MS to EDSS 6 (years)	Median time from onset of MS to EDSS 7 (years)
No. relapses during the first 5 years of the disease (Confraveux 2003) (33)			
n = 1	15.1 Reference	25.3 Reference	34.5 Reference
n = 2	11.1 (p < 0.001)	21.9 (p = 0.01)	33.3 (p = 0.20)
n ≥ 3	9.5 (p < 0.001)	24.7 (p < 0.001)	26.1 (p < 0.001)
No. relapses during the first 2 years of the disease (Weinshenker 1989) (41)			
n = 0-1	nr	19 *	nr
n = 2-4	nr	15 *	nr
n ≥ 5	nr	7 *	nr
No. relapses during the first 2 years of the disease (Ebers 2001) (34)			
n = 1	13 (median time to EDSS 3)	20	nr
n = 2	8 (median time to EDSS 3)	17	nr
n = 3	9 (median time to EDSS 3)	18	nr
n = 4	8 (median time to EDSS 3)	14	nr
n ≥ 5	3 (median time to EDSS 3)	7	nr
Time from second relapse to DSS 6 (Weinshenker 1989) (41)			
First inter-attack interval ≥ 6 years	nr	19 *	nr
First inter-attack interval 3-5 years	nr	16 *	nr
First inter-attack interval 0-2 years	nr	12 *	nr
Time from onset of MS to EDSS 4 (Confraveux 2003) (33)			
≥ 5		20.7 (p < 0.001)	30.1 (p < 0.001)
2-5		8.1 (p = 0.003)	15.3 (p = 0.30)
< 2		6.3 Reference	13.2 Reference
Time from onset of MS to DSS 6 (Weinshenker 1989) (41)			
Reached DSS 3 in ≥ 8 years	nr	18 *	nr
Reached DSS 3 in 3-7 years	nr	9 *	nr
Reached DSS 3 in 0-2 years	nr	4 *	nr
Time from DSS 3 to DSS 8 (years) (Cottrell 1999) (31)			
Reached DSS 3 in > 2 years		nr	15.2 (median time from DSS 3 to DSS 8)
Reached DSS 3 in < 2 years		nr	11.2 (median time from DSS 3 to DSS 8)

* Estimated from survival curve. Disability that had developed before enrolment into this study was determined historically for most patients, based on patient interviews and chart reviews and is not true time from onset; this data should be treated with caution.

Table 37 confirms the predictors reported by Richards, that early markers of active disease have a large significant impact on the speed of disability progression. A high relapse rate early in the course of the disease and a rapid progression to DSS 3 or EDSS 4 are associated with rapid progression to severe states of disability.

In addition to the data reported in Table 37, Ebers also reports that the time between first and second relapse increases the risk of reaching DSS 6, DSS 8 or DSS 10. (34) Runmarker also confirms that the number of functional systems affected after five years has a, 'high prognostic significance' on disability progression. (131)

Lublin helps quantify the effect of residual EDSS deficit after relapse on disability progression (42.4% increase by 0.5 or more on EDSS after a relapse; 28.1% increase by 1 or more). (37) Lublin concludes that 'acute exacerbations of MS have a measurable and sustained effect on the accrued impairment/disability in MS'. Runmarker also reports that the prognosis for patients having a complete or near complete remission after their first relapse is significantly better compared with patients with a significant degree of remaining symptoms. (131)

These studies support the hypothesis that a high relapse frequency leads to higher residual EDSS deficit and hence a more rapid rate of progression compared with a

low relapse frequency.

5.8.2 Effect of switching IFN-beta treatments

One study that may be pertinent to this submission is the Quality Assessment in Multiple Sclerosis Therapy (QUASIMS) study that compared the 3 IFN-betas:

- Interferon beta-1a (Avonex) 30 mcg IM once weekly)
- Interferon beta-1b (Betaferon/Betaseron) 8 MIU SC every other day)
- Interferon beta-1a (Rebif) 22 mcg SC 3 times weekly)
- Interferon beta-1a (Rebif) 44 mcg SC 3 times weekly)

This was a retrospective, open-label, observational cohort study in which the available IFN-beta products were compared in 4754 MS patients in a wide range of clinical practice settings. (75)

The results of this study showed that:

- There were no significant differences among IFN-beta products when used as initial or follow-up therapy on almost all outcome variables.
- 895 (18.8%) patients switched therapy in the observation period and the commonest reason for switching (38%) was lack of efficacy
- The results suggest that patients do not benefit in terms of disease outcome from switching between IFN-beta preparations/dosing regimens.

Based on the fact that a significant number of therapy switches are for the reason of 'lack of efficacy', data from this study is used to justify the rationale for an active comparator in the SOT subgroup.

5.8.3 Estimating transition probabilities in RES and SOT subgroups

Overview

It was recognised that available disability transition rates derived from the London Ontario dataset are not appropriate since they are not applicable to a HARRMS population academic / commercial in confidence information removed. On account of these problems, alternative sources of evidence on the natural history of highly active RRMS were sought. Transition rates were derived using data from the placebo arm of the AFFIRM study by fitting a multi-state model (MSM) to the data. (132)

The MSM method estimates the progression rates between distinct disability states. It uses longitudinal individual patient data from patients with degenerative conditions. Each observation is treated independently using degeneration over a period of time to predict progression. Previous applications of MSM have included modelling HIV and AIDS, (133;134) diabetes (135) and cancer screening. (136) The

method was implemented using the statistical software package, R. (3) [3]

The model makes the following assumptions:

- transition rates are similar across studies
- the probability of transition from one state to another is constant and independent of the time spent within the state. However, the model approximates the observed mean time spent in each state.

Below we describe the method by which the progression rates were derived from RCT data for:

- the SOT subgroup (using placebo data from the ITT population from AFFIRM as a proxy)
- the RES subgroup (using placebo data from the RES subgroup from AFFIRM)

One can also question, in the SOT group of patients, whether the assumption that efficacy is the same as in the ITT population from the AFFIRM study is valid. It is probable that SOT patients merely represent the RES subgroup at a later point in time, after they have tried and experience break-through disease activity on IFN-beta or GA. The possibility that RES patients are more likely to fail to respond adequately to IFN-beta is plausible given that IFN-beta does not seem to have a specific mechanism of action in MS. If this is the case then it might be more appropriate to use the RES subgroup efficacy values and then adjust the ICER for the effects of age (assuming that SOT patients are likely to be slightly older that RES patients). This analysis is reported as a sensitivity analysis in section 6.2.11.

We list the underlying assumptions in the model, including assumptions relating to the method by which we exclude the impact of relapses on the underlying EDSS scores. This was produced using the MSM package in R. This analysis has been reproduced and verified by an independent statistician familiar with the techniques and software used to derive these transition matrices (Dr Chris Jackson, Imperial College London).

Source data

The transition probabilities for the base case analysis and the sensitivity analysis (with the exception of the London Ontario sensitivity analysis) were derived from the placebo arm of the AFFIRM study, for both the ITT and RES subgroups. This was the only clinical study data available to us for RRMS patients for whom EDSS was optionally measured at the date of relapse.

For each patient, the observations recorded were EDSS score taken at different times from baseline, and dates of relapse during the study. The data contained observations from 315 patients from the ITT placebo arm of the AFFIRM study, and

[3] The MSM model is fitted to the data using R. R is a statistical package available from http://www.r-project.org/. Further details can be found on the website. R can be downloaded from the website, installed and used free of charge. Once installed, an additional package may be required. These can be installed by opening the R interface, selecting 'Packages' from the menu toolbar, then setting the CRAN mirror to a local site. Then, again in Packages, select 'Install package(s)...' and, from the pop-up menu, select the desired package. The package used here is called 'msm'. Once selected it is added to your local copy.
To perform the analyses in R, commands should be written in a text editor and copied and pasted directly into the R console window, where each command will be executed. This model has been frequently used to estimate transition probabilities for patients with degenerative conditions, and details of the model and its implementation in R can also be found at http://www.stats.bris.ac.uk/R/src/contrib/Descriptions/msm.html. The R code used to generate the MSM analysis may be found in the appendix.

from 61 patients in the RES subgroup. Two core datasets (ITT data and RES data) were created by making the following censoring assumptions:

- all observations defined as being taken at the date of first symptoms were removed, as accurate dates and EDSS measurement for these were not available
- all EDSS scores were rounded up to minimise the number of states to which the MSM model was fitted and to enable the transition matrix to be consistent with the economic model. For example, EDSS 4 was made up of EDSS 3.5 and EDSS 4
- all EDSS scores greater than 7 were added to EDSS 7. This creates a 'most severe disease' state whilst not discarding any data due to low numbers of observations
- all patients with only one observation were removed

Following censoring there were 5019 observations from 526 patients in the ITT dataset and 688 observations from 60 RES patients. This is equivalent to 4493 transition events for the ITT population and 628 for the RES subgroup. These are shown in by EDSS state in Table 38 for the ITT population and in Table 39 for the RES subgroup.

Table 38: Number of transition events between EDSS states for the ITT population (AFFIRM Study)

		To EDSS State							
		0	1	2	3	4	5	6	7
From EDSS State	0	124	32	27	1	1	0	0	0
	1	33	216	108	15	6	1	0	0
	2	28	111	1142	188	54	11	8	3
	3	4	11	186	494	158	19	12	1
	4	0	4	52	129	572	62	37	7
	5	0	0	6	13	60	130	38	5
	6	0	1	1	10	18	23	193	25
	7	0	0	2	0	5	2	15	89

Table 39: Number of transition events between EDSS states for RES subgroup (AFFIRM Study)

		To EDSS State						
		0	1	2	3	4	5	6
From EDSS State	0	22	4	4	0	1	0	0
	1	4	31	22	5	2	1	0
	2	2	17	203	30	7	3	1
	3	1	2	31	48	17	5	0
	4	0	2	4	16	85	10	2
	5	0	0	1	5	7	18	3
	6	0	0	0	1	0	2	9

Assumptions for deriving the transition matrices

In the base case scenario we fitted the MSM model to the ITT data with the exception that EDSS scores collected during unscheduled visits (i.e. relapse visits) were removed from the dataset. This was necessary as relapses were included separately in the economic model, therefore a transition matrix to estimate underlying progression was needed, excluding the effect of relapse. This was repeated for the RES subgroup.

The first sensitivity analysis was derived by fitting all of the ITT data, including unscheduled visits. For the next set of transition matrices for the sensitivity analyses, we replace any EDSS observation recorded within either 1, 3 or 6 months of a relapse with the next point that does not occur within 1, 3 or 6 months of a relapse respectively. This was repeated with the RES data.

Implementation of the MSM

We make similar assumptions in the MSM to those made in the ScHARR model. For this analysis we assume that transition rates are similar across studies. Another assumption in the model is the Markov assumption that the probability of transition from one state to another is constant and independent of the time spent within the state. The model approximates the observed mean time spent in each state. The code used to implement the MSM can be found in Appendix I on page 256.

MSM transition matrices

The values from the MSM for the ITT population with the 95% confidence intervals are given in Table 40; the values from the MSM fitted to the data from the RES subgroup are given in Table 41. Confidence intervals were calculated using a bootstrapping routine written in R (personal communication, , Imperial College London).

Table 40: Transition probabilities (95% CI) generated by the MSM model fitted to the placebo arm ITT group from the AFFIRM Study

		To EDSS state							
		0	1	2	3	4	5	6	7
From EDSS state	0	0.268 (0.191, 0.362)	0.257 (0.223, 0.292)	0.358 (0.301, 0.420)	0.085 (0.066, 0.104)	0.028 (0.020, 0.036)	0.004 (0.003,0.006)	0.001 (0.001, 0.002)	1e-04 (1e-04, 2e-04)
	1	0.139 (0.101, 0.180)	0.198 (0.166, 0.233)	0.452 (0.415, 0.495)	0.139 (0.119, 0.161)	0.058 (0.048, 0.070)	0.010 (0.007, 0.013)	0.004 (0.002,0.005)	4e-04 (2e-04, 8e-04)
	2	0.055 (0.040, 0.072)	0.129 (0.1072,0.15)	0.487 (0.455, 0.523)	0.194 (0.170, 0.219)	0.104 (0.087, 0.119)	0.022 (0.016, 0.028)	0.009 (0.006, 0.013)	0.001 (5e-04, 0.002)
	3	0.024 (0.016, 0.031)	0.071 (0.058, 0.086)	0.349 (0.313, 0.385)	0.240 (0.213, 0.271)	0.214 (0.188, 0.244)	0.061 (0.046, 0.076)	0.035 (0.024, 0.051)	0.006 (0.003, 0.010)
	4	0.008 (0.005, 0.011)	0.031 (0.024, 0.038)	0.191 (0.162, 0.222)	0.219 (0.189, 0.249)	0.313 (0.278, 0.361)	0.121 (0.095, 0.148)	0.098 (0.070, 0.130)	0.020 (0.009, 0.033)
	5	0.003 (0.002, 0.004)	0.012 (0.009, 0.016)	0.091 (0.069, 0.114)	0.142 (0.110, 0.172)	0.274 (0.230, 0.322)	0.175 (0.134, 0.221)	0.242 (0.179, 0.324)	0.061 (0.028, 0.103)
	6	6e-04 (3e-04, 0.001)	0.003 (0.002, 0.005)	0.030 (0.016, 0.046)	0.066 (0.038, 0.097)	0.179 (0.112, 0.241)	0.195 (0.131, 0.241)	0.407 (0.299, 0.551)	0.119 (0.057, 0.218)
	7	3e-04 (1e-04, 6e-04)	0.002 (6e-04, 0.003)	0.016 (0.007, 0.032)	0.043 (0.020, 0.075)	0.139 (0.070, 0.206)	0.188 (0.106, 0.240)	0.458 (0.331, 0.583)	0.153 (0.067, 0.406)

Table 41: Transition probabilities (95% CI) generated by the MSM model fitted to the placebo arm RES subgroup of the AFFIRM Study

		To EDSS state						
		0	1	2	3	4	5	6
From EDSS state	0	0.230 (0.084, 0.557)	0.167 (0.108, 0.224)	0.425 (0.221, 0.525)	0.104 (0.052, 0.149)	0.060 (0.024, 0.097)	0.012 (0.004, 0.022)	0.002 (5e-04, 0.006)
	1	0.070 (0.024, 0.146)	0.110 (0.072, 0.163)	0.511 (0.442, 0.577)	0.156 (0.117, 0.199)	0.119 (0.077, 0.163)	0.028 (0.013, 0.046)	0.007 (0.002, 0.015)
	2	0.030 (0.011, 0.061)	0.086 (0.056, 0.122)	0.503 (0.433, 0.572)	0.173 (0.136, 0.216)	0.156 (0.108, 0.207)	0.042 (0.022, 0.065)	0.011 (0.004, 0.024)
	3	0.017 (0.006, 0.033)	0.060 (0.036, 0.087)	0.393 (0.311, 0.472)	0.177 (0.141, 0.233)	0.241 (0.174, 0.314)	0.082 (0.044, 0.128)	0.031 (0.009, 0.063)
	4	0.007 (0.002, 0.015)	0.032 (0.018, 0.050)	0.253 (0.176, 0.321)	0.171 (0.1240, 0.228)	0.333 (0.255, 0.430)	0.136 (0.079, 0.216)	0.068 (0.020, 0.138)
	5	0.003 (0.001, 0.008)	0.0120 (0.009, 0.033)	0.171 (0.094, 0.251)	0.148 (0.090, 0.211)	0.346 (0.238, 0.438)	0.176 (0.093, 0.294)	0.136 (0.035, 0.330)
	6	0.001 (0.000, 0.003)	0.007 (0.000, 0.016)	0.076 (0.000, 0.155)	0.093 (0.000, 0.169)	0.283 (0.000, 0.426)	0.221 (0.000, 0.329)	0.319 (0.086, 1.000)

The estimated average annual rate of disability progression from the MSM for the placebo arm ITT population of the AFFIRM trial is estimated to be 0.27 EDSS states (95% CIs: 0.11, 0.43); for the RES subgroup, the mean annual rate of disability progression is 0.46 (0.16, 0.79).

Comparing the fit of the model to the data

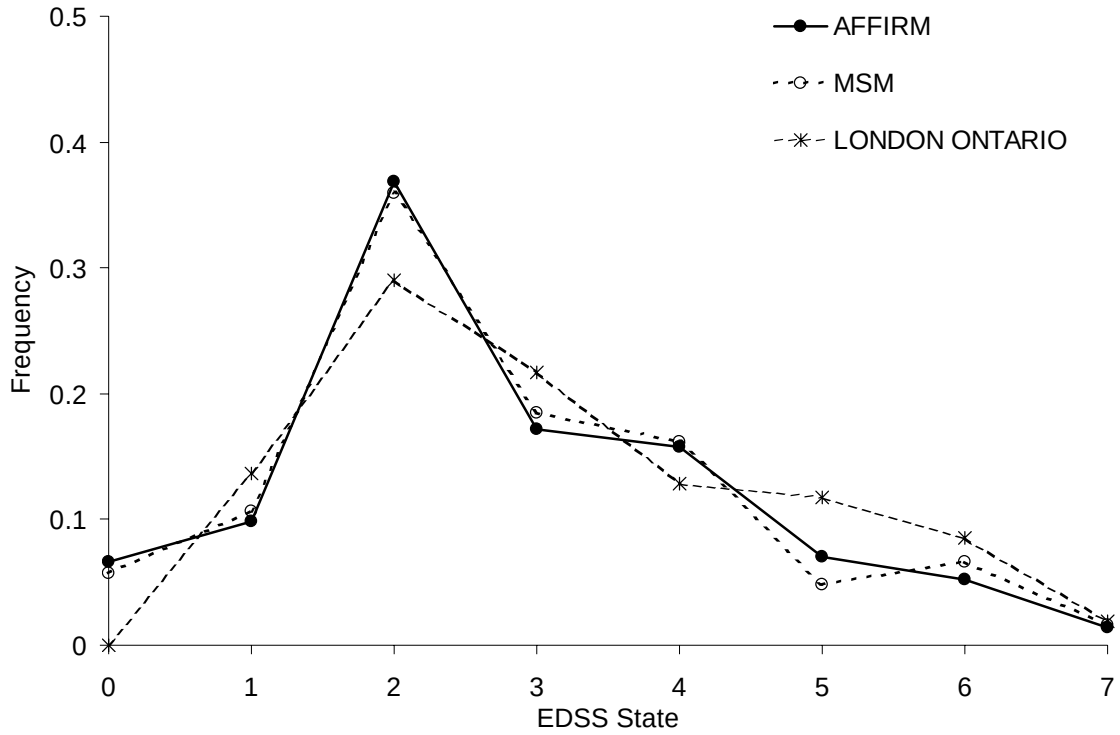
In order to assess how well the model fits to the AFFIRM data, we used the baseline EDSS data from patients randomised to placebo within the AFFIRM study as initial conditions in the model for:

(i) the ITT placebo arm

(ii) the RES subgroup.

We then used the MSM model to estimate the distribution of cases at the AFFIRM endpoint (i.e. at 2 years) using data from the ITT placebo arm (i). This was also done using the London Ontario transition matrix and is shown in Figure 11. The actual endpoint profile of EDSS and the modelled profile are very similar, which indicates that the predictive power of the MSM model is high. The London Ontario dataset predicted a different EDSS profile at study endpoint and appears to over-estimate the frequency of people in higher states (EDSS >5), while underestimating people in EDSS 2.

Figure 11 Comparison between the endpoint data from the ITT population in the AFFIRM study with predictions by EDSS state based on the MSM applied to the AFFIRM data and transition probabilities derived from the London Ontario dataset

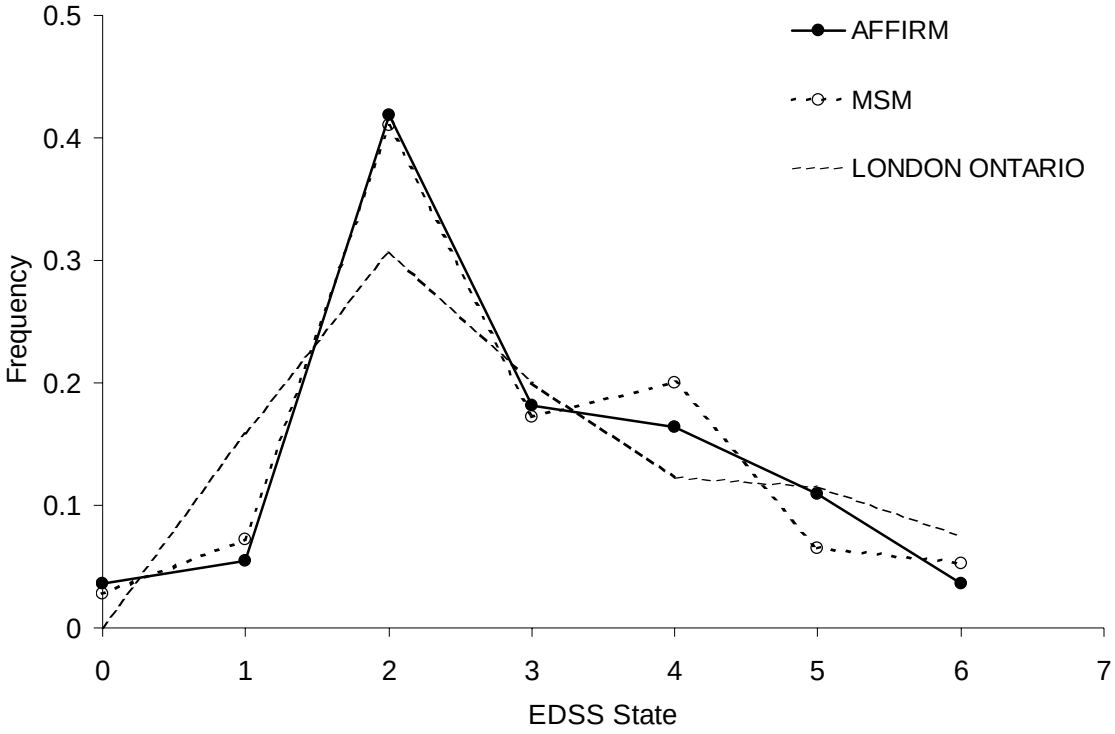


Note that no transition probabilities were available for the London Ontario dataset from EDSS 0 so here in the initial conditions EDSS 0 was pooled with EDSS 1

This process was repeated using the RES matrix (ii) using the baseline EDSS distribution from the AFFIRM RES subgroup to predict EDSS distribution at endpoint. A comparison between the modelled prediction and the actual distribution of these patients at endpoint is shown in Figure 12. The London Ontario prediction is also shown. The predictive power of the model in the RES subgroup is still good. Fewer observations were available for the RES subgroup, however, and this means

that the fit is not quite as accurate as that observed for the ITT population from the AFFIRM study. The London Ontario dataset does not appear to be able to accurately predict RES EDSS distribution. When comparing between the London Ontario and MSM transition matrices, a better fit is observed using the MSM transition matrix derived from the AFFIRM data.

Figure 12 Comparison between the endpoint data from the RES subgroup in the AFFIRM study with predictions by EDSS state based on the MSM applied to the AFFIRM data and transition probabilities derived from the London Ontario dataset



Note that no transition probabilities were available for the London Ontario dataset from EDSS 0 so here in the initial conditions: EDSS 0 was pooled with EDSS 1

In these simulations for baseline and endpoint data, and endpoint predictions from the MSM model, patients in EDSS 0 and EDSS 1 are pooled in EDSS 1, as no data on transition to or from EDSS 0 is available from the London Ontario dataset.

The London Ontario transition matrix only allows patients to either remain within a state or to progress to a more severe state. This may explain why the fit is less good than the data from AFFIRM, which also allows regression (i.e. a reduction in disability over time). The MSM allows transition between both higher and lower states as observed in the data. In the full economic model, the transition matrix contains data from the MSM and, where there was a paucity of data, from the London Ontario data, as described below.

Comparisons with observations in the literature

The estimates of progression using the MSM model are comparable to progression data found in the literature collected from patients with high disease activity. Table 42 tabulates the median time to progression from less severe to more severe states of disability using the transition matrices from the London Ontario data set and the two MSM models. Table 37 on page 91 presents median times to progression from the literature by way of comparison.

Table 42 Median time to disability progression derived from MSM

	From EDSS 1 to EDSS 3	From EDSS 1 to EDSS 4	From EDSS 1 to EDSS 6	From EDSS 1 to EDSS 7	From EDSS 3 to EDSS 8
London Ontario Data	11-12 yrs	14-15 yrs	18-19 yrs	22-23 yrs	13-14 yrs
ITT population (AFFIRM)	3-4 yrs	6-7 yrs	10-11 yrs	14-15 yrs	16-17 yrs
RES subgroup (AFFIRM)	2-3 yrs	4-5 yrs	8-9 yrs	11-12 yrs	13-14 yrs

In Table 37, the start point for time to different EDSS states was often the time of onset of MS. However, as we were using the London Ontario dataset, which does not provide transition to or from EDSS 0, we set the start point of the estimates in Table 42 above to EDSS 1. Therefore the duration in Table 42 and Table 37 are not directly comparable and one would expect those in Table 42 to be shorter.

These tables illustrate that disability progression of people with higher relapse rates is faster, and that the progression of the higher relapsing groups is more comparable with the rates derived from the AFFIRM data than those estimated from the London Ontario data. Conversely, the London Ontario data is more comparable with slower progressing less frequently relapsing patients.

The ITT and the RES datasets are used to calculate transition matrices for the SOT and RES base case analyses respectively.

Sensitivity analysis

We varied a number of the censoring assumptions for relapse to assess their sensitivity to the calculated transition matrices. Changes to the base case assumptions are described in Table 43.

Table 43 Variations from the base case used during the sensitivity analysis (data on file AFFIRM study, 315 patients for ITT population, 61 for RES subgroup)

Scenario	Observations		Mean Progression		Change from base case	
	ITT	RES	ITT	RES	ITT	RES
Reference case	3584	689	0.272	0.463	-	-
Fit to all data including unscheduled visits	3968	820	0.266	0.454	-0.006	-0.009
Replace observations within one month of relapse by next valid observation*	3934	804	0.239	0.418	-0.034	-0.045
Replace observations within three month of relapse by next valid observation*	3845	761	0.234	0.412	-0.038	-0.051
Replace observations within six month of relapse by next valid observation*	3598	638	0.246	0.441	-0.026	-0.022

* Observations lost where no non-relapse observations occur before the end of the study

Using the MSM within the economic model

Before being used in the model to predict progression, the following changes are needed. The matrices derived by the MSM only represent transitions between EDSS states 0 to 7, and between states 0 to 6 for the RES subgroup, due to a paucity of

data at higher states of disability. In order to model RRMS patients from EDSS 0 to 9.5, we use additional data from the London Ontario dataset for the missing states. In addition, we use transition probabilities taken from the London Ontario dataset to estimate transition between RRMS to SPMS and between SPMS states, as no other comparable data is available. The transition matrices derived from this analysis are reported in section 6.2.6.1. Uncertainty is modelled explicitly within the probabilistic sensitivity analysis (see section 6.3.3.2).

5.8.4 UK MS Survey 2005

In 2005 an extensive survey was undertaken in the UK by Heron Evidence Development Ltd to assess the resource requirements of people with MS and the utility associated with the disease. This cross-sectional study was undertaken via a postal survey and was part of a European-wide study by Kobelt et al. (19) The UK-specific questionnaire used in the survey was based upon an established instrument developed by Kobelt et al. This formed the basis of previous cost-of-illness studies and includes a comprehensive range of questions on resource use to estimate both direct and indirect costs. (9;137) The questionnaire was amended and adapted to the UK setting following consultation with MS nurses, neurologists and experts at the MS Trust and MS Society, and a copy is shown in Appendix J. The questionnaire was checked to ensure it met the reporting requirements of the Medicines and Healthcare products Regulatory Agency (MHRA). (138)

Questionnaires were distributed by the MS Trust to people in its database to ensure names and addresses remained anonymous. No personal data that would allow the respondent to be identified was collected on the questionnaire. The questionnaire was sent as an insert to the February 2005 edition of the UK MS Trust quarterly newsletter 'Open Door' (circulation of 12 968). A covering letter explained the details of the study, and the circumstances in which the data was to be used. The respondent was required to sign a consent statement to indicate they had read and agreed with the terms of the study. It is recognised that some people with MS would be unable to complete a questionnaire themselves. Therefore, the instructions indicated that a caregiver could complete the questionnaire on behalf of the person with MS provided they had authority to do so, in which case the caregiver was required to sign the consent statement to indicate this.

The completed questionnaire was returned to the investigators using a pre-addressed envelope. The number of questionnaires returned was 2708 (20.9%) and 2048 (15.8%) were suitable for analysis. The main reasons for excluding responses from the analysis were: Type of MS not reported (n = 315); questionnaire unsigned or received after the deadline (n = 200); EQ-5D questionnaire incorrectly completed (n = 130); and other reasons (n = 15). A number of variables were collected. Utility data was collected using EQ-5D. (139) Utilities were assigned using the EQ-5D UK value set, which was obtained from a representative sample of the UK population using the time-trade-off method. (93) Resource data was also collected from patients.

Upon receipt, the questionnaire identifier was logged in an MS Access database (Microsoft Inc.) and the questionnaire checked to ensure the consent statement had been signed. The questionnaire was processed using specialised Optical Character Recognition (OCR) and Form Reading software called FormReader 6.0 (ABBYY Europe GmbH). A sample of original questionnaire pages was compared with the OCR output and adjustments made to eliminate character recognition errors. Incoming questionnaires were scanned and batch processed in FormReader and an investigator reviewed any data point that failed the established validation rules. Inter and intra-field validation was again performed within the Access database using queries to flag illogical or ambiguous data entries. These were

checked against the original questionnaire to rule out data entry error and records containing invalid data were marked as censored and excluded from the analysis.

The demographic and disease information is presented in Table 44.

Table 44 Demographic and disease information (UK MS Survey 2005)

Demographics	Proportion or mean	Disease information	Proportion or mean
Gender		Diagnosis	
Male	24.7%	Mean age at first diagnosis	38.8 years
Female	74.5%		
Missing	0.8%	Type of MS	
		RRMS	35.5%
Age		SPMS	37.2%
Mean age	51.4 years	PPMS	27.3%
18 - 29 years	1.4%		
30 - 39 years	13.8%	EDSS level (disease severity)	
40 - 49 years	27.0%	EDSS 0 - 3	21.3%
50 - 59 years	35.3%	EDSS 4 – 6.5	59.6%
60 - 69 years	18.0%	EDSS 7 – 9.5	19.1%
70 - 79 years	4.2%		
80+ years	0.3%	Relapses during last 3 months	
		yes	28.9%
Education		no	71.1%
Secondary school	32.2%		
College or sixth form	26.5%		
University or polytechnic degree	29.7%		
Post graduate degree	10.1%		
No answer	1.6%		

Two analyses from this survey have been accepted for publication by Value in Health; in particular estimates of utility by Orme et al in press and estimated cost by Tyas et al in press. Data and analysis from this survey is used through out the economic evaluation and will be referred to as the UK MS Survey 2005.

5.8.5 Estimating relapse rates by EDSS state and disease type

Relapse rates per person by year since diagnosis are available from Patzold and Pocklington 1982. (140) In addition, the distribution of patients experiencing relapse by EDSS state by time since diagnosis is available from the UK MS Survey 2005. These data can be used to derive the annual relapse rates per EDSS state used in the economic evaluation. Data from Patzold and Pocklington 1982 on the number of relapses since year of diagnosis are shown in Table 45. The trend in the data is clear, despite some anomalies.

Table 45 Number of relapse by year since diagnosis (Patzold and Pocklington 1982)

Years since diagnosis	Relapse rate per person
1	1.85
2	1.10
3	1.00
4	0.85
5	0.65
6-7	0.75
8-9	0.25
10-11	0.60
12-13	0.28
14-15	0.30
16+	0.20

Data from the UK MS Survey 2005 for RRMS patients and for SPMS patients is

shown in Table 46 and Table 47 respectively. Owing to the small number of records in EDSS states 7, 8 and 9, these have been pooled together such that the relapse rate for states 7, 8 and 9 are the same.

Table 46 Number of relapses per RRMS EDSS group by time from diagnosis (UK MS Survey 2005)

EDSS	Years since diagnosis: data obtained from UK MS cohort										
	1	2	3	4	5	6-7	8-9	10-11	12-13	14-15	16+
0	2	2	1	2	6	6	3	2	0	1	3
1	11	16	18	11	16	22	15	10	3	10	18
2	11	16	7	17	14	13	19	19	9	5	22
3	6	4	4	5	7	9	4	1	5	6	6
4	6	15	7	12	13	24	8	13	6	2	17
5	2	5	12	9	13	18	11	10	4	7	23
6	2	3	3	5	2	6	11	2	2	6	20
6.5	1	0	2	0	3	3	4	1	2	2	9
7	1	0	0	0	0	0	1	1	1	0	3
8	0	0	0	0	1	2	1	0	0	0	1
9	1	0	0	0	0	0	0	0	0	0	1

Table 47 Number of relapses per SPMS EDSS group by time from diagnosis (UK MS Survey 2005)

EDSS	Years since diagnosis: data obtained from UK MS cohort										
	1	2	3	4	5	6-7	8-9	10-11	12-13	14-15	16+
2	0	0	0	1	2	2	0	0	0	0	5
3	2	0	1	1	0	4	0	1	1	0	1
4	1	2	3	3	0	6	6	2	6	1	7
5	6	6	5	6	7	14	17	15	10	11	35
6	3	5	8	14	11	20	23	21	17	14	74
6.5	2	1	3	4	5	18	16	11	19	12	78
7	0	1	0	0	3	8	10	9	7	8	63
8	0	0	0	0	3	5	4	7	4	5	46
9	0	0	0	0	0	1	2	1	2	0	2

These values are then multiplied by the relative relapse rates from Patzold and Pocklington 1982 resulting in the mean number of relapses per patient per EDSS state. When modelling the RES subgroup, the number of relapses per patient is multiplied by 1.98 to reflect the higher relapse rates observed in the RES subgroup during the AFFIRM study. During the AFFIRM study, the average relapse rate in the placebo groups for ITT placebo patients was 0.733 and in the RES subgroup was 1.455. The final estimated relapse rates for the different patients by disease type and EDSS state is given in Table 48.

Table 48 Mean number of relapses per patient for SOT and RES subgroups for RRMS and SPMS patients by EDSS state (Patzold and Pocklington 1982, UK MS Survey 2005, AFFIRM)

	SOT Subgroup (AFFIRM ITT population used as proxy)		AFFIRM RES Subgroup	
EDSS	RRMS	SPMS	RRMS	SPMS
0	0.709	na	1.407	na
1	0.729	na	1.448	na
2	0.676	0.465	1.343	0.923
3	0.720	0.875	1.430	1.738
4	0.705	0.545	1.400	1.083
5	0.591	0.524	1.173	1.041
6	0.490	0.453	0.972	0.900
7	0.508	0.340	1.009	0.676
8	0.508	0.340	1.009	0.676
9	0.508	0.340	1.009	0.676

5.8.6 Estimating health state costs using a seemingly unrelated regression (SUR)

The 2005 UK MS survey questionnaire included 115 different resources. The results of the survey were used to provide an estimate of the quantity of each resource used per person based on a number of relevant covariates including type of MS, EDSS state, sex and presence of relapse. These quantities were multiplied by the unit costs for each to find the mean cost of each resource per person. In addition, since most data were collected for less than a year, the resource use per person was adjusted to 12 months. Unit costs for the resources used in this analysis are provided in Table 49.

Table 49 Unit cost for resources used in the economic evaluation (UK MS Survey 2005, unit cost sources)

Cost Def.	Type	Description	Period	Ref *	Unit cost for England and Wales
1	Inpatient admission	Neurology	per day	3	£222.00
1	Inpatient admission	Other	per day	3	£237.86
1	Nursing home	inpatient days	per day	3	£98.28
1	Nursing home	outpatient visits	per day	3	£59.73
1	Day admission	Neurology	per visit	3	£156.80
1	Day admission	Other	per visit	3	£141.87
1	REHAB	inpatient days	per day	3	£252.80
1	REHAB	outpatient visits	per visit	3	£252.80
1	Visits to specialist	Neurologist visits	per consultation	3	£222.13
1	Visits to specialist	Junior doctor	per consultation	3	£19.00
1	Visits to specialist	Urologist	per consultation	4	£128.71
1	Visits to specialist	Ophthalmologist	per consultation	3	£92.38
1	Visits to specialist	Psychiatrist	per consultation	3	£22.40
1	Visits to specialist	GP	per consultation	3	£30.00
1	Visits to specialist	Nurse	per consultation	3	£23.00
1	Other health care specialists	Physiotherapist	per consultation	3	£20.00
1	Other health care specialists	Social Worker	per consultation	3	£115.00
1	Other health care specialists	Occupational therapist	per consultation	3	£54.00
1	Other health care specialists	Speech therapist	per consultation	3	£18.00
1	Other health care specialists	Acupuncturist	per consultation	Average of private *	£35.95
1	Other health care specialists	Chiropractor/ Osteopath	per consultation	Average of private *	£19.43
1	Other health care specialists	Counsellor/ Psychologist	per consultation	Average of private *	£28.22
1	Other health care specialists	Chiropodist	per consultation	3	£11.00
1	Other health care specialists	Reflexologist	per consultation	Average of private *	£24.04
1	Investigations, Tests	MRI (brain)	per test	1	£313.00
1	Investigations, Tests	MRI (spine)	per test	1	£313.00
1	Investigations, Tests	CT scan	per test	1	£160.00
1	Investigations, Tests	Lumbar puncture (LP)	per test	2	£89.15
1	Investigations, Tests	Evoked potential	per test	1	£43.73
1	Investigations, Tests	Ultrasound	per test	1	£67.00
1	Investigations, Tests	Electrocardiogram (ECG)	per test	1	£25.00
1	Investigations, Tests	Blood test	per test	1	£2.93
1	MS drugs	AIMSPRO	Month	8	£0.00
1	MS drugs	AVONEX	Month	12	£708.50
1	MS drugs	BETAFERON	Month	12	£604.92
1	MS drugs	COPAXONE	Month	12	£485.25
1	MS drugs	IMURAN	Month	4	£3.56
1	MS drugs	IVIG	Month	4	£0.00
1	MS drugs	METHOTREXATE	Month	4	£1.48
1	MS drugs	NOVANTRONE	Month	4	£11.87
1	MS drugs	REBIF22	Month	12	£626.08
1	MS drugs	REBIF44	Month	12	£745.17
1	MS drugs	STEROID	Month	4	£51.90
1	MS drugs	NATALIZUMAB	4 weeks	SPC	£1130
1	Other Prescription drugs	Baclofen	Daily cost	4	£0.41
1	Other Prescription drugs	Clonazepam	Daily cost	4	£0.16
1	Other Prescription drugs	Dantrolene	Daily cost	4	£1.72
1	Other Prescription drugs	Diazepam	Daily cost	4	£0.12
1	Other Prescription drugs	Gabapentin	Daily cost	4	£1.41
1	Other Prescription drugs	Tizanidine	Daily cost	4	£3.62
1	Other Prescription drugs	Amitriptyline	Daily cost	4	£0.29
1	Other Prescription drugs	Citalopram	Daily cost	4	£0.33
1	Other Prescription drugs	Escitalopram	Daily cost	4	£0.80
1	Other Prescription drugs	Fluoxetine	Daily cost	4	£0.12
1	Other Prescription drugs	Fluvoxamine	Daily cost	4	£0.70
1	Other Prescription drugs	Imipramine	Daily cost	4	£0.54
1	Other Prescription drugs	Mianserin	Daily cost	4	£0.22
1	Other Prescription drugs	Mirtazapine	Daily cost	4	£0.37
1	Other Prescription drugs	Nortriptyline	Daily cost	4	£0.98
1	Other Prescription drugs	Paroxetine	Daily cost	4	£0.19
1	Other Prescription drugs	Sertaline	Daily cost	4	£0.50

Cost Def.	Type	Description	Period	Ref *	Unit cost for England and Wales
1	Other Prescription drugs	Venlafaxine	Daily cost	4	£1.39
1	Other Prescription drugs	Amantadine	Daily cost	4	£0.60
1	Other Prescription drugs	Methylphenidate	Daily cost	4	£0.14
1	Other Prescription drugs	Modafinil	Daily cost	4	£4.00
1	Other Prescription drugs	Prochlorperazine	Daily cost	4	£0.44
1	Other Prescription drugs	Bisacodyl	Daily cost	4	£0.03
1	Other Prescription drugs	Docusate	Daily cost	4	£0.22
1	Other Prescription drugs	Glycerol	Daily cost	4	£0.15
1	Other Prescription drugs	Ispaghula husk	Daily cost	4	£0.14
1	Other Prescription drugs	Lactulose	Daily cost	4	£0.13
1	Other Prescription drugs	Milk of Magnesia	Daily cost	5	£0.16
1	Other Prescription drugs	Nitrofurantoin	Daily cost	4	£0.36
1	Other Prescription drugs	Oxybutynin	Daily cost	4	£0.48
1	Other Prescription drugs	Senna	Daily cost	4	£0.14
1	Other Prescription drugs	Sildenafil	Daily cost	4	£4.84
1	Other Prescription drugs	Tolterodine	Daily cost	4	£1.09
1	Other Prescription drugs	Botulinum toxin A	Daily cost	4	£128.93
1	Other Prescription drugs	Carbamazepine	Daily cost	4	£0.26
1	Other Prescription drugs	Phenyton	Daily cost	4	£0.10
1	Nurse home visit	Nurse home visit	per visit	3	£23.00
1	Nurse home visit	Nurse home visit	per hour on visit	3	£64.00
2	Long term sick leave	Incapacity benefit	Quarter	9	£1,020.50
2	Permanent sick leave	Incapacity benefit	Quarter	9	£1,020.50
2	Age addition (3)	Incapacity benefit top up	Quarter	9	£214.50
2	Help from friends and family	Care and disability allowance (4)	Quarter	9	£1,716.65
2	Short term sick leave	SSP benefit	Daily	9	£10.00
3	Community and social services	Transportation	Per mile	Assumed Values *	£1.04
3	Community and social services	Social care worker	Per visit	3	£21.33
4	Inpatient admission	Neurology	per day	3	£222.00
4	Inpatient admission	Other	per day	3	£237.86
4	Nursing home	inpatient days	per day	3	£98.28
4	Nursing home	outpatient visits	per day	3	£59.73
4	Day admission	Neurology	per visit	3	£156.80
4	Day admission	Other	per visit	3	£141.87
4	REHAB	inpatient days	per day	3	£252.80
4	REHAB	outpatient visits	per visit	3	£252.80
4	Visits to specialist	Neurologist visits	per consultation	3	£222.13
4	Visits to specialist	Junior doctor	per consultation	3	£19.00
4	Visits to specialist	Urologist	per consultation	3	£128.71
4	Visits to specialist	Ophthalmologist	per consultation	3	£92.38
4	Visits to specialist	Psychiatrist	per consultation	3	£22.40
4	Visits to specialist	GP	per consultation	3	£30.00
4	Visits to specialist	Nurse	per consultation	3	£23.00
4	Other health care specialists	Physiotherapist	per consultation	3	£20.00
4	Other health care specialists	Social Worker	per consultation	3	£115.00
4	Other health care specialists	Occupational therapist	per consultation	3	£54.00
4	Other health care specialists	Speech therapist	per consultation	3	£18.00
4	Other health care specialists	Acupuncturist	per consultation	Average of private *	£35.95
4	Other health care specialists	Chiropractor/ Osteopath	per consultation	Average of private *	£19.43
4	Other health care specialists	Counsellor/ Psychologist	per consultation	Average of private *	£28.22
4	Other health care specialists	Chiropodist	per consultation	3	£11.00
4	Other health care specialists	Reflexologist	per consultation	Average of private *	£24.04
5	Income	National wage in UK 2004 (1)	Hr	10	£9.88
5	Loss of income	National wage in UK 2004 (2)	per month	10	£1,486.47
6	Aids and appliances	Multiple resources	per year	As reported *	-
7	Other Prescription drugs	Antihistamines (Piriton 4mg)	for 20	4	£0.19
7	Investigations, Tests	JC viral DNA test	per test	11	£46.87
7	Other Prescription drugs	ciprofloxacin 750mg one per day	for 10	4	£3.00
7	Other Prescription drugs	Promethazaine Hydrochloride IV	50mg	4	£0.58
7	Admin for natalizumab	Day admission to neurol. clinic	per visit	3	£162.76
7	Anaphylactic reaction	Non elective IP HRG Data: S26	per event	1	£471.79
7	Investigations, Tests	NAB Test	per test	11 (5)	£46.87

Where current prices could not be found, costs were taken from a previous version and inflated to 2006 prices assuming the inflation rate is the same as for 2004/05 of 3.8%. (141) * References without numbers are taken from UK MS Survey 2005. IP = Inpatient, HRG = Health related group, NAB = neutralising antibody.

References to the Table

1 - NHS reference Costs 2004/05 (2006); 2 - Parkin D, McNamee P, Jacoby A, Miller P, Thomsa S, Bates D. A cost-utility analysis of interferon beta for multiple sclerosis. Health Technol Assessment 1998; 2(4); 3 - Curtis L, Netten A. Unit Costs of Health and Social Care 2005. Personal Social Services Unit, Canterbury, 2006; 4 - British National Formulary, 52; 5 - Boots Group PLC, Nottingham UK 2005; 6 - Denniston K, Pithouse A, Bloor M (2001) An economic analysis of Best Value for discharging patients into community care: a pilot study of social worker time costs. Research Policy and Planning. 18(1); 7 - De Broe S, Christopher F, Waugh N (2001) The role of specialist nurses in multiple sclerosis: a rapid and systematic review. Health Technol Assess. 2001;5(17):1-47; 8 - Daval International Ltd (Manufacturer of Aimspro); 9 - Department for Work and Pensions; 10 - Official for national statistics; 11 - Health Protection Agency for England and Wales; 12 - Risk sharing scheme (51)

These unit costs have been divided into categories for use with different cost

perspectives, with the definitions for the cost categories provided in Table 50.

Table 50 Cost categories used in economic evaluation

Cost definition	Description
1	Direct medical (NHS) unit costs
2	Direct non-medical non-social care costs
3	Direct non-medical (social care) cost
4	Direct out of pocket costs
5	Indirect costs
6	Aids and appliances costs
7	Adverse events costs

NOTE: cost reference 7 was not derived from the UK MS Survey 2005. A derivation is reported in 6.2.6.1.

For the NHS and social services perspective (NHS & PSS), cost definitions 1 and 3 are used in addition to cost definition 6, aids and appliances. The cost of aids and appliances was provided by the patients and defined by who pays (either the patient or the government). In the NHS & PSS perspective, only the proportion paid by the state is included.

The second perspective is the Direct Government (DG) perspective, which includes all state costs and comprises NHS & PSS and cost definition 2.

The final perspective is societal, which comprises Government costs, out-of pocket expenses defined in cost definitions 4, aids and appliances paid for by the patient, and cost category 5 which is loss of income.

Cost category 7 comprises costs due to adverse events associated with natalizumab treatment.

Costs associated with the different cost perspectives for a given person are unlikely to be independent (e.g. a person with high NHS & PSS costs may also have high DG costs) the data were modelled using a seemingly unrelated regression (SUR). (142) The SUR accounts for correlation between costs. Also, instead of the error terms in the two regression models being independent of each other, both within and between people, the error term for each person is sampled from a multivariate normal distribution. In this way there is now dependence in costs within a person, but still independence between people. The model fitting is achieved using the SUR package in R.

The SUR produces a cost for a reference case, which defines each of the predictive variables described above. Any alteration in one or more of the predictive variables from the reference case alters the value of one or more of the cost categories. The reference case is a 0 year old woman with RRMS at EDSS 0 with no recent relapse and not receiving a DMT. It may seem unexpected for the reference case for age to be zero, however, the cohort age is multiplied by the coefficient for age and added to other coefficients to derive the cost estimate. For example the expected annual NHS & PSS cost of a 47 year old male at EDSS 5 with RRMS treated with IFN-beta would be £11 431.

The SUR generates coefficients for each of the predictive variables and are shown in Table 8 on page 42 above. These allow cost estimations to be undertaken for the different cost perspectives and for numerous permutations of the predictive variables. A manuscript describing the cost model has been accepted for publication. (143)

5.8.7 Estimating Utility

5.8.7.1 Utility of MS patients

Utilities by EDSS state were derived from data collected in the UK MS Survey 2005. The ED-5Q scores taken from patients were fitted using a multivariate regression for EDSS states 0 to 9 for MS patients, in addition to disease type (either SPMS or PPMS), relapse and year since diagnosis. This is similar to the model derived from these data by Orme et al (in press). We excluded the education variable in this model, as it is not relevant to the decision problem. These utilities are provided in Table 51.

Table 51 Utility for different EDSS states, UK MS Survey 2005

	No relapse	
EDSS State	**RRMS**	**SPMS**
0	0.91	0.87
0.5 to 1	0.84	0.80
1.5 to 2	0.74	0.70
2.5 to 3	0.61	0.57
3.5 to 4	0.65	0.61
4.5 to 5	0.56	0.51
5.5 to 6	0.49	0.45
6.5 to 7	0.44	0.39
7.5 to 8	-0.01	-0.05
8.5 to 9.5	-0.15	-0.19
Disutility associated with year since diagnosis	-0.00167 per year	

The disutility due to relapse estimated in this regression could be applied across all EDSS states. This was considered to be inappropriate as the disutility of relapses from different starting EDSS states is likely to be different. This relationship was investigated using data on relapses collected during the AFFIRM study, displayed in Table 52.

Table 52 Data for severity of relapse in patients, data on file AFFIRM study

		EDSS within five days after relapse												
		n	**1**	**1.5**	**2**	**2.5**	**3**	**3.5**	**4**	**4.5**	**5**	**5.5**	**6**	**6.5**	**7**
EDSS prior to relapse	**0**	6	2	1	2	0	0	0	1	0	0	0	0	0	0
	0.5-1	22	1	2	9	4	3	2	0	0	0	0	1	0	0
	1.5-2	90	1	2	22	15	18	13	7	5	2	1	4	0	0
	2.5-3	65	0	1	2	6	15	14	12	7	1	1	5	1	0
	3.5-4	61	0	0	0	0	1	7	20	16	10	3	4	0	0
	4.5-5	25	0	0	0	0	0	0	1	4	5	6	7	2	0
	5.5-6	7	0	0	0	0	0	0	0	1	0	2	3	1	0
	6.5-7	3	0	0	0	0	0	0	0	0	0	0	0	1	2

In Table 52, the estimated EDSS states were collected within five days of the start of a relapse. This allowed us to calculate the average change in EDSS for all patients that relapsed from the same initial EDSS state. Given that in Table 51 we have estimates for the utility for each EDSS state, we could then estimate the disutility associated with the average change in EDSS for relapse from each EDSS state. Any relapse disutilities recording a post relapse utility higher than that observed prior to relapse were excluded from the analysis and due to low number, relapses from patients with an EDSS of greater than 4 were pooled together, and

utilities for the 0.5 intervals between EDSS scores was calculated by interpolating utilities across EDSS scores. The disutilities by EDSS state for relapse are shown in Table 53.

Table 53 The utility loss associated with each relapse for different EDSS states, UK MS Survey 2005, AFFIRM Study

Initial EDSS State	Utility change associated with relapse
0	-0.138
1	-0.142
2	-0.086
3	-0.014
4	-0.048
5+	-0.024

The analysis undertaken here represents a more conservative estimate of utility loss associated with relapse compared with earlier estimates by Parkin 2000 and disutilities used in the ScHARR model. These report a change as great as -0.468. (12) As a consequence, natalizumab would appear less cost-effective in this analysis compared to these other analyses, since natalizumab has a greater effect on reducing the rate of relapse than either comparator.

The duration of the average relapse is assumed to be 46 days, the duration that was used in the ScHARR model. The disutility of relapse is applied over this duration.

5.8.7.2 Disutility from DMT Adverse Events

IFN-beta and GA

Disutility from adverse events for IFN-beta and GA were estimated as part of a study by Prosser 2003, using the standard gamble technique. (144) These data have since been used to parameterise economic evaluations by Prosser 2004 and the previous ScHARR model commissioned by NICE.

A description of the treatment types considered by Prosser 2003 is given in Table 54, and the calculated disutilities for the treatment types were -0.115 for treatment A, -0.204 for treatment B and -0.066 for treatment C. From these we derived a disutility per patient with adverse events on IFN-beta of -0.160, as the average of treatments A and B. For glatiramer acetate we use the reported value of -0.066.

Table 54 Description of MS treatment states for utility assessment, reproduced from Prosser 2003 (144)

Treatment A:

- Imagine that you take an injectable drug once per week. This requires first mixing the powered drug with the liquid, drawing it into a syringe, and injecting it into your thigh.
- Often you will feel feverish and achy for about 24 hours after the injection – just as if you had the flu.
- The injection itself is not very painful, but sometimes the skin around the injection site will get sore. A doctor can prescribe medication to ease the soreness. Occasionally it will get infected.

Treatment B:

- Imagine that you take an injectable drug every other day. This requires first mixing the powered drug with the liquid, drawing it into a syringe, and injecting it into your thigh.
- Often you will feel feverish and achy for about 24 hours after the injection – just as if you had the flu.
- The injection itself is not very painful, but sometimes the skin around the injection site will get sore. A doctor can prescribe medication to ease the soreness. Occasionally it will get infected.

Treatment C:

- Imagine that you take an injectable drug every day. This requires first mixing the powered drug with the liquid, drawing it into a syringe, and injecting it into your thigh.
- The injection itself is not very painful, but sometimes the skin around the injection site will get sore. A doctor can prescribe medication to ease the soreness. Occasionally it will get infected.

We next assume only a proportion of patients taking each treatment option experience the disutility derived above. Estimated adverse event rates for IFN-beta are typically high (see indirect comparison in Section 5.7.3, and also Herndon 2005 and Jacobs 1996). (66;145) However we assume that only 30% of IFN-beta patients will experience disutility due to adverse events, which is the same assumption as the rate used in the first year of the ScHARR model. This produces an average disutility of -0.048 per patient receiving treatment with IFN-beta. We assume a lower rate of adverse events for patients receiving GA since the incidence of adverse events is expected to be lower (again see indirect comparison in Section 5.7.3) and assume that 20% of patients experience a disutility, which results in an average disutility per patient of -0.013. The values used are therefore likely to represent a conservative assumption, though it should be noted that each of the treatments in Table 54 no longer requires the patient to prepare the medication himself or herself and they now come in a pre filled syringe. (146) In addition to the adverse events rates described above, we assume the disutility for patients on natalizumab is at half the rate for GA, with the same disutility of -0.066 per event. This lower rate reflects the lower frequency of administration of natalizumab, at once every four weeks, as opposed to every day with GA. This increases the disutility per patient on natalizumab in the reference case by 0.007, giving an overall disutility per patient on natalizumab of -0.008 per year. [4]

Table 55 Disutility for treatment, Prosser 2003, (144) ScHARR model (147)

	glatiramer acetate (n = 19) †	**interferon beta (n = 38) †**	**natalizumab* -**
Disutility per event	0.066 (144)	0.156 (144)	0.066 *
Frequency of event	0.20	0.30 (147)	0.5 × GA *
Disutility per patient	0.013	0.047	0.007
Distribution	beta	beta	beta

† sample size from Prosser 2003. * note the disutility reported here for natalizumab is in addition to disutility estimated due to rare SAEs on page 127.

In the ScHARR model, adverse events for IFN-beta were only applied during the first year. However, since the ScHARR model was developed in 2001, substantial evidence has been collected that suggests that adverse events persist over the long term. (145;148;149) Adverse events for patients using IFN-beta were documented by Herndon 2005 as part of a six-year open-label extension study following a IFN-beta phase III clinical study. (145) Herndon reported that adverse event rates over the extension study were similar to those observed in the original study. Gold 2005 stated that the adverse event profiles for two different IFN beta-1a doses at four years were comparable to those observed in the initial phase of the study. (148) Rio 2005 observed that during an eight-year study adverse events were in accordance with those previously associated with IFN-beta. (150) We therefore apply these disutility rates to the treated groups in the model beyond the first year (i.e. for all years in the model).

[4] Note that this figure includes a disutility estimate due to serious AEs reported in Table 62 on page 127. These AEs for natalizumab are urticaria, hypersensitivity, anaphylactic and anaphylactoid reactions, urinary tract infection and nasopharyngitis. The disutility estimates in Table 75 are applied in addition to the disutility reported in Table 55.

5.8.7.3 Disutility of caregivers

It is well recognised that there is a significant burden on the caregivers of people with MS (151-153). The burden in terms of hours per day and days per month, estimated during the UK MS Survey 2005, is illustrated in Figure 4 on page 38. Previous submissions to NICE have accepted an effect of treatment on the utility of caregivers as a valid benefit of treatment. (154)

Whilst literature exists on the effect of disease on the quality of life of caregivers, only one study was found that estimated the quality of life of caregivers in people with MS. (155) In this study 29 caregivers of people with MS receiving best supportive care (mean EDSS = 7.24) had their quality of life assessed by SF-36. Caregivers experienced deterioration in general health and two domains of SF-36 over the two years of the study (Role, physical and Social function). Insufficient detail is provided in this study to enable an estimation of utility.

However, estimates for the disutility of caregivers or people with Alzheimer's disease are available. A mean caregiver utility of 0.86 has been quoted in the NICE assessment of treatments for Alzheimer's Disease, and here we assume the maximum disutility for a caregiver of a person with MS to be 0.14. (154)

We expect caregiver disutility to be correlated with disease severity, and this has been observed for caregivers of MS patients, (an increase in depression of caregivers with disability severity of people with MS). (152) The percentage of time spent by friends and family caring for a person with MS is available from the UK MS Survey 2005 (Figure 5). These data are available per patient by EDSS score, which enabled us to weight the assumed maximum disutility of caregivers by time spent providing care. These values are shown in Table 56 by EDSS state, along with percentage of time spent caring for patients by friends and family. The disutility of caregivers is estimated to increase from 0.00 at EDSS 0 to 0.14 at EDSS 9.

Table 56: Utilities of caregivers by EDSS (UK MS Survey 2005, Alzheimer's disease - donepezil, rivastigmine, galantamine and memantine (review) (154))

EDSS	Average hours of care per patient per day across all patients	Average % of 24-hour day that friends/family spends providing care per patient	Weighting relative to maximum disutility	Maximum disutility	Disutility for caregivers per patient
0	0.0	0%	0%	0.14	0.00
1	0.1	1%	1%	0.14	0.00
2	0.3	1%	2%	0.14	0.00
3	1.0	4%	7%	0.14	0.01
4	1.0	4%	6%	0.14	0.01
5	2.1	9%	14%	0.14	0.02
6	2.9	12%	19%	0.14	0.03
7 *	5.6	23%	38%	0.14	0.05
8	11.3	47%	76%	0.14	0.11
9	14.8	61%	100%	0.14	0.14

* Average across EDSS 6.5 and EDSS 7

5.8.8 Adjustments to standardised mortality rate for people with MS

Adjustments to the standard mortality rate were made on the basis of an epidemiological study by Pokorski 1997. (156) Pokorski 1997 reported an assessment of the long-term survival of 6727 patients with MS based on data included in the Danish MS registry. This registry was constructed from a prospective survey that included virtually everyone diagnosed with definite, probable or possible MS in Denmark since 1948. An adjustment to the standard mortality ratio was reported by level of disability (Table 67). These values are used in the model.

Table 57 Multiplier to standard mortality rate (Pokorski 1997 (156))

Description	EDSS Range	Multiplier on Standard Mortality Rate
Mild	0-3	1.60
Moderate	4-6	1.84
Severe	7-9	4.44

5.8.9 Withdrawal from active treatment

Withdrawal rates were derived from all active treatment arms for the evaluation. We assume that after 10 years of treatment, no more patients on either natalizumab or other active comparators will drop off treatment. The reference values are 6.4% per annum for natalizumab and 5.5% for other active comparators.

5.8.9.1 Natalizumab withdrawal rate

Data from the AFFIRM study was used to estimate the annual withdrawal rate for natalizumab (Table 58). We assume that the annual withdrawal rate is constant and derive the withdrawal rate per year by fitting an exponential curve (i.e. $\exp(-r/t)$ where r is the rate and t is time) by minimising the sum of the squared errors (SSE). The derived rate per month is 0.55% and the derived annual discontinuation rate is 6.4%.

Table 58 Natalizumab withdrawal rate, data on file AFFIRM

Month	Discontinuing	% on treatment	Fitted exponential model (minimised the SSE)
Baseline	0	100%	100%
0-6	31	95%	97%
7-12	12	93%	94%
13-18	16	91%	91%
18-24	14	88%	88%

SOURCE: AFFIRM data on file, from 627 patients at baseline

5.8.9.2 IFN-beta/GA withdrawal rate

Data from Herndon were used to estimate withdrawal rates over a 6-year period. (145) Within this study, the annual withdrawal rate was reported to be 5.5% per year, which is calculated in Table 59. We assume that the dropout rates for both IFN-beta and GA are the same; this assumption is in line with the assumptions employed within the earlier ScHARR MS cost-effectiveness model.

Table 59 IFN-beta and GA withdrawal rates, adapted from Herndon 2005 (145)

Parameter	Attribute	Fitted exponential model (minimised the SSE)
Total at start	382	-
Total at end (6 years)	275	-
Dropouts	28.0%	28.1%
Actual withdrawal rate		5.5%

6 Cost effectiveness

Unlike any other medical technology in England and Wales, an acceptable cost-effectiveness threshold has been established for disease modifying treatments for multiple sclerosis of £36 000 per quality adjusted life year (QALY) gained.

The incremental cost effectiveness ratio (ICER) of natalizumab compared with any comparator in the rapidly evolving severe subgroup is below this acceptable threshold for all evaluated decision problems. For natalizumab compared with interferon beta the ICER is £27 000 per QALY gained. Compared with glatiramer acetate and best supportive care the ICER is £27 400 and £34 900 respectively, in the same subgroup.

By comparison, using conservative values for key uncertain parameters, when natalizumab is compared with interferon beta in the sub optimally treated subgroup the ICER is £44 100 per QALY gained. When natalizumab is compared with glatiramer acetate and best supportive care in the sub optimally treated subgroup, the ICER is £45 000 and £57 000 respectively.

Given the threshold of £36 000 per QALY gained, the probabilistic sensitivity analysis resulted in a 70% probability of natalizumab being cost-effective in people with rapidly evolving severe multiple sclerosis compared with interferon beta. The result for the comparison with glatiramer acetate in the same subgroup was found to be 65%. If an alternative (societal) perspective is chosen, these values increase to 84% and 86% respectively.

The key determinants of the cost-effectiveness of natalizumab are the baseline characteristics of the model population, the natural history of the specific RES and SOT subgroups, the efficacies of natalizumab, interferon beta and glatiramer acetate, costs associated with managing MS, the health economic perspective adopted, and the time horizon over which incremental costs and health outcomes are evaluated. Safety and tolerability, discount rate and utility parameters have a marginal effect on the ICER. There is a higher degree of certainty in the rapidly evolving severe subgroup economic evaluation than in the evaluation of the sub optimally treated subgroup.

Despite every effort to source appropriate data for all components of the model, sufficient uncertainty exists in some of the input data for the sub optimally treated subgroup evaluation that the cost-effectiveness could be considered artificially pessimistic.

The absence of natural history data in the sub optimally treated subgroup and the decision to use data from the intention-to-treat placebo arm of the phase III natalizumab registration study (AFFIRM) (rather than data from the rapidly evolving severe subgroup) could be considered overly conservative.

The absence of specific efficacy data in the sub optimally treated subgroup and the assumption used to apply a relative risk of disability progression and relapse frequency from a broad relapsing remitting multiple sclerosis population from the intention-to-treat analysis in AFFIRM (rather than data from the rapidly evolving severe subgroup) could also be considered overly

conservative.

Using the less conservative, but arguably more realistic assumption that the sub optimally treated subgroup is equivalent to the rapidly evolving severe subgroup in all aspects except for a previous decision to treat with a comparator disease modifying treatment, then the cost-effectiveness of natalizumab in the sub optimally treated subgroup would become very similar to that of the rapidly evolving severe subgroup (at £27.0K, £27.4K and £34.9K per QALY compared with interferon beta and glatiramer acetate and best supportive care respectively).

A new Markov model (based on the ScHARR model previously commissioned by NICE) was developed for the submission since there are no relevant published, economic evaluations in the literature.

This highly active relapsing remitting multiple sclerosis specific model adopted the reference case approach specified by NICE.

Natural history data was sourced from the well-recognised London Ontario dataset, combined with a new multi state model based on the placebo arm of the AFFIRM study.

Clinical effects were based on meta-analyses of relevant available data for both natalizumab and the comparators.

The utility of treatment was taken from the largest survey of utility and resources ever conducted in multiple sclerosis in the UK (UK multiple sclerosis Survey 2005), supplemented by analyses of data from AFFIRM and previously published sources.

The UK multiple sclerosis Survey 2005 provided resource consumption data and unit costs were sourced from recognised UK sources

All of the nine published flaws of previous models submitted to NICE have been addressed within this model.

Recognised experts in the economics of multiple sclerosis have critically appraised the methods and assumptions used in the model and confirmed that: it has high external validity compared with the previous model commissioned by NICE. In addition, the Scottish Medicines Consortium critical appraisal of the model concluded that, 'good internal and external validation information was provided'

Model validation showed that the model was able to reproduce very similar ICERs to the previous NICE model for interferon beta and glatiramer acetate compared with best supportive care. The ICERs we generate for interferon beta and glatiramer acetate respectively of £57.4k and £107.2k per QALY compare well with the reported ICERS of £42-72k and £98k per QALY respectively.

6.1 Published cost-effectiveness evaluations

An acceptable cost-effectiveness threshold has been established for disease modifying treatments for relapsing remitting multiple sclerosis (RRMS) of £36 000 per quality adjusted life year (QALY) gained, which is unlike any other medical technology in England and Wales. (51)

This context is important for the evaluation of natalizumab in the treatment of highly active relapsing remitting multiple sclerosis (HARRMS).

6.1.1 Identification of studies

In order to identify and review any published material relating to economic evaluation of natalizumab as a treatment for HARRMS we undertook a systematic review. Specifically, the Medline, Medline in Process, EMBASE and NHS EED databases were searched for relevant material. The search included studies indexed up to the end of the second week of September 2006 and included all years covered by each database but was limited to articles published in the English language. The details of this systematic review, including the search strategies and inclusion criteria for articles are given in Appendix H.

Only four articles were identified by the search. The reviewer could identify no additional articles that met the inclusion criteria for this review.

Whilst there were no cost-effectiveness models directly relating to the decision problem, a previous NICE appraisal did consider the use of disease modifying therapies (DMTs) in the management of multiple sclerosis under the multiple technology assessment (MTA) process. During this appraisal, a number of models from the sponsors of IFN-beta and GA were considered. Karl Claxton raised 9 critical points in a presentation to the HTA group with regards to these models. (157) These have been summarised in Table 60

Table 60 Main failures identified in previous MS models (147;157)

1.	Failure to model the natural history of the disease as the comparator to treatment
2.	Failure to incorporate mortality in long-term treatment model
3.	Failure to model transition to SPMS from RRMS
4.	Failure to model the impact of treatment-related adverse events on cost-effectiveness
5.	Failure to incorporate treatment drop-outs into the model
6.	Linear extrapolation of short-term data
7.	Inappropriate time horizons
8.	Implausible assumptions regarding the impact of relapse on health-related quality of life
9.	Inadequate analysis of uncertainty around model parameter values

The model subsequently developed by the health technology assessment (HTA) group (denoted the ScHARR model (17;147) in this document), based on the work of Prosser 2000 (158), sought to address all of the above problems and formed the basis of the cost-effectiveness assessment of the DMTs used in the NICE 2001 appraisal. The model used in this evaluation is based on the ScHARR model, and much of the structuring of the natural history of the disease is similar. A comparison between this model and the ScHARR model is described in section 6.2.12.3 below.

6.1.2 Description of identified studies

No studies were identified.

6.2 De novo economic evaluation(s)

Table 61 The NICE reference case approach and the approach used in this assessment

Element	NICE reference case approach	Approach in this assessment
Defining the decision problem	The scope developed by the Institute	As reference case approach
Comparator	Alternative therapies routinely used in the NHS	As reference case approach
Perspective on costs	NHS and PSS	As reference case approach
Perspective on outcomes	Based on a systematic review	As reference case approach
Type of economic evaluation	Cost-effectiveness analysis	As reference case approach
Measure of health benefits	Quality-adjusted life years	As reference case approach
Description of health states for calculation of QALYs	Health states described using a standardised and validated generic instrument	As reference case approach, using EDSS
Method of preference elicitation for health state validation	Choice-based method, for example, time trade-off, standard gamble (not rating scale)	Preferences elicited from large sample of people with MS using the Multi Attribute Utility Scale (MAUS) EQ-5D
Source of preference data	Representative sample of the public	EQ-5D analysed using UK social tariff
Discount rate	An annual discount rate of 3.5% on both costs and health effects	As reference case approach
Equity position	An additional QALY has the same weight regardless of the other characteristics of the individuals receiving the health benefit	As reference case approach

6.2.1 Technology

Natalizumab is licensed for use in HARRMS, of which there are two subgroups as described in the summary of product characteristics (SPC). (1) In this economic evaluation we consider treatment of these two subgroups: those patients who are defined as sub optimally treated (SOT) patients; and those patients who are defined as having rapidly evolving severe (RES) disease, as defined in the decision problem in section 2.3 beginning on page 19 (repeated below). Treatment regimes for both groups are the same. No concomitant treatments are assumed in the model. Dose is as prescribed in the product licence as one 300mg IV infusion over 1 hour every 4 weeks at a neurology clinic. An observation period of 1 hour following the infusion is included in the evaluation.

The following definitions are used throughout:

- RRMS: Relapsing remitting multiple sclerosis, RRMS. Patients that experience acute exacerbations of symptoms followed by complete or incomplete recovery and periods of stable disease in between.
- HARRMS: Highly active relapsing remitting multiple sclerosis, HARRMS. For the purpose of this dossier, HARRMS is to be considered a subgroup of RRMS and comprises the two licensed indications for natalizumab defined below (RES and SOT).
- RES: Rapidly evolving severe relapsing remitting multiple sclerosis ('rapidly evolving severe', RES). Patients defined by 2 or more disabling relapses in one year, and with 1 or more Gadolinium-enhancing lesions on brain Magnetic Resonance Image (MRI) or a significant increase in T2 lesion load as compared to a previous MRI.

- SOT: High disease activity despite treatment with a interferon beta ('sub optimal therapy', SOT). Patients should have had at least 1 relapse in the previous year while on therapy, and have at least 9 T2-hyperintense lesions on brain MRI or at least 1 Gadolinium-enhancing lesion.

The RES and SOT subgroups are subgroups of RRMS that exhibit high disease activity, of a severity that is greater than the typical person with RRMS. Please refer to sections 2.3 and 5.8.1 for further explanation of this observation.

Treatment within both the SOT and RES subgroups is assumed to continue until either patients are diagnosed as having progressed to secondary progressive MS (SPMS) or have progressed to EDSS 7 or greater (i.e. the same stopping criteria as the current ABN/NCC-CC guidelines). (46;50) An EDSS score of 7 means that the patient is no longer ambulatory (Appendix J). There is an annual all-cause withdrawal rate of 6.4%, which is equivalent to that observed during the AFFIRM study (derived in section 5.8.9.1).

Treatment may be suspended for one dose, while the patient undergoes further tests, if the patient is suspected to have developed PML.

6.2.2 Patients

6.2.2.1 What group(s) of patients is/are included in the economic evaluation? Do they reflect the licensed indication? If not, how and why are there differences? What are the implications of this for the relevance of the evidence base to the specification of the decision problem?

Patients in the economic evaluation have been chosen to reflect the licensed indication, with initial conditions for the population taken to reflect the baseline characteristics of the AFFIRM study. The initial distribution of patients across EDSS states is taken to be the same as the baseline ITT population in the AFFIRM study for the placebo arm. The initial mean age of the cohort is assumed to be 36 years and the median time since diagnosis is assumed to be 5 years; these are both in line with the AFFIRM study. (4) The ratio of males to females is 3.1:1 (UK MS Survey 2005). Given these patient characteristics, we expect the evaluation to directly address the decision problem and licensed indication. These characteristics provide a valid basis for evaluating the effects of natalizumab in the licensed populations.

6.2.2.2 Was the analysis carried out for any subgroups of patients? If so, how were these subgroups identified, what clinical information is there to support the biological plausibility of this approach, and how was the statistical analysis undertaken?

No additional subgroup analysis has been undertaken in this submission over and above the highly active RES and SOT subgroups for which natalizumab is indicated. These two subgroups are already subgroups of a RRMS population and, for the RES subgroup, a subgroup of the AFFIRM study.

RES Subgroup: The RES licensed indication for natalizumab is based upon a subgroup of patients from the AFFIRM study. Genesis of this subgroup is described

in section 2.3.1, and the baseline characteristics of this subgroup, compared with the ITT population from the AFFIRM study, are described in section 5.4.2.

Statistical analysis of the endpoints 'annualised relapse rate' and 'sustained disability progression' for RES subgroup used the same methodology as that of the ITT population. The effect of natalizumab on disability progression and relapse rate was found to be superior in the RES subgroup compared with the ITT population.

The annualised relapse rate was calculated as the total number of relapses experienced in the group divided by the total number of days in the study for the group, and the ratio multiplied by 365. The number of days that a subject participated in the study was calculated using the date of first dose and the date of the last visit for those subjects who were dosed. Analysis of annualised relapse rate was evaluated using Poisson regression (log-likelihood ratio test assuming the number of relapses followed a Poisson distribution). The number of relapses was analysed as the response variable.

Sustained disability progression at 120 weeks was evaluated using a Cox proportional hazards model. Sustained progression of disability was determined to be:

- a change of at least a 1.0 point increase on the EDSS from baseline EDSS ≥1.0 that was sustained for 24 weeks
- or at least a 1.5 point increase on the EDSS from baseline EDSS=0 that was sustained for 24 weeks.

The start date for time to progression or censoring is defined as the day that a subject first started study drug treatment (i.e. day of first dose).

SOT Subgroup: The SOT licensed indication for natalizumab is based upon data from the SENTINEL study. (2;3) SENTINEL demonstrated that the addition of natalizumab to current IFN-beta therapy significantly reduced relapse frequency and risk of disability progression compared with IFN-beta therapy alone, in patients that were continuing to have relapses despite already being treated with IFN-beta (i.e. sub optimal therapy patients). Genesis of this subgroup is described in section 2.3.2. Since the SOT subgroup was justified based on a differential effect observed within the SENINEL study, no direct baseline data or efficacy data for the SOT subgroup is available.

We make a conservative assumption that the same efficacy and baseline characteristics seen in the ITT population from AFFIRM are applicable to the SOT subgroup. However, it is questionable whether that assumption is valid, as it is highly plausible that SOT patients merely represent the RES subgroup at a later point in time, after they have experienced suboptimal treatment with IFN-beta or GA.

The possibility that RES patients are less likely to respond adequately to IFN-beta is credible given that IFN-beta does not seem to have a specific mechanism of action in MS. If this is the case then it is arguably more appropriate to use the RES efficacy values adjusted for the effects of age (assuming that the SOT patients are likely to be slightly older than the RES patients). Analysis using RES disability progression rates and efficacy values adjusted for the effect of age are reported as a sensitivity analysis in Table 86 on page 156.

6.2.2.3 Were any obvious subgroups not considered? If so, which ones, and why were they not considered?

No additional subgroups over and above the RES and SOT subgroups of RRMS patients that formed the license for natalizumab were considered in this submission.

A number of subgroup analyses were pre-specified and undertaken for the AFFIRM study and these have been described previously in Section 2.3. None of these were specifically considered in this submission since they all represent subgroups of the original ITT population from AFFIRM. This means that an analysis of any one of them would result in a population that is broader in scope than the RES subgroup. However, a composite of the pre-specified subgroups '≥2 relapses in prior year', '≥1 gadolinium enhancing lesion on brain MRI' or '≥9 T2 weighted lesions on brain MRI' forms the basis of the RES subgroup.

6.2.2.4 At what points do patients 'enter' and 'exit' the evaluation? Do these points differ between treatment regimens? If so, how and why?

Patients enter the evaluation at an average of 5 years after diagnosis to reflect the experience of the AFFIRM study. Within the base case analysis, patients may exit the evaluation at death or at the end of the time horizon. Mortality rates of patients with MS are closely related to disease severity (see section 5.8.8). (156)

DMTs act to slow disability progression, which means that patients on treatment are less likely to experience the higher mortality rates associated with more severe disease.

6.2.3 Comparator technology

Active comparators used are those defined in the decision problem and are clearly described in sections 3.1 and 4.1.2.1. These are IFN-beta and GA. In this submission we use a published meta-analysis of available IFN-beta data to define a single 'class effect' of IFN-beta treatment. (73) The estimate of effect for GA is also based on a published meta-analysis of available data. (70)

Best supportive care is based on the resource requirements of patients identified in the UK MS Survey 2005. (143) We describe in section 3.1 that best supportive care may not be an appropriate comparator.

The comparator DMTs are currently available under the terms of a risk sharing scheme described in section 4.6 starting on page 47.

6.2.4 Study perspective

Costs and outcomes were assessed using the NICE reference case perspective. These include direct NHS and personal social service costs only.

Direct benefits in the reference case are those accrued to the patient through the effect of treatment on slowing disability progression and reducing the frequency of relapses. We also present a sensitivity analysis of indirect costs (i.e. pension costs, out-of-pocket costs, employment costs).

2006 is used as the formal price year for the health economic analysis.

6.2.5 Time horizon

The time horizon used in the base case of the analysis was 20 years. This time horizon was chosen to reflect the chronic nature of the disease and is in line with models for RRMS commissioned by NICE. (147) However a longer time horizon will arguably better reflect the life-long nature of the disease and is considered in the sensitivity analysis.

The duration of follow-up within the AFFIRM study was 2 years. However, the appropriate time horizon for the economic evaluation of MS therapies is uncertain. For shorter time horizons, less extrapolation from the study data is required, yet this approach ignores possible benefits in terms of the postponed progression to more advanced stages of MS. For longer time horizons, the extrapolation results in more favourable assumptions concerning the benefits attributable to the disease-modifying therapies, yet the extrapolation itself is subject to a greater degree of uncertainty. (159)

Section 5.4.1 presents data on an open label extension study of natalizumab monotherapy, which shows a comparable effect on relapse at 3 years.

6.2.6 Framework of model-based evaluations

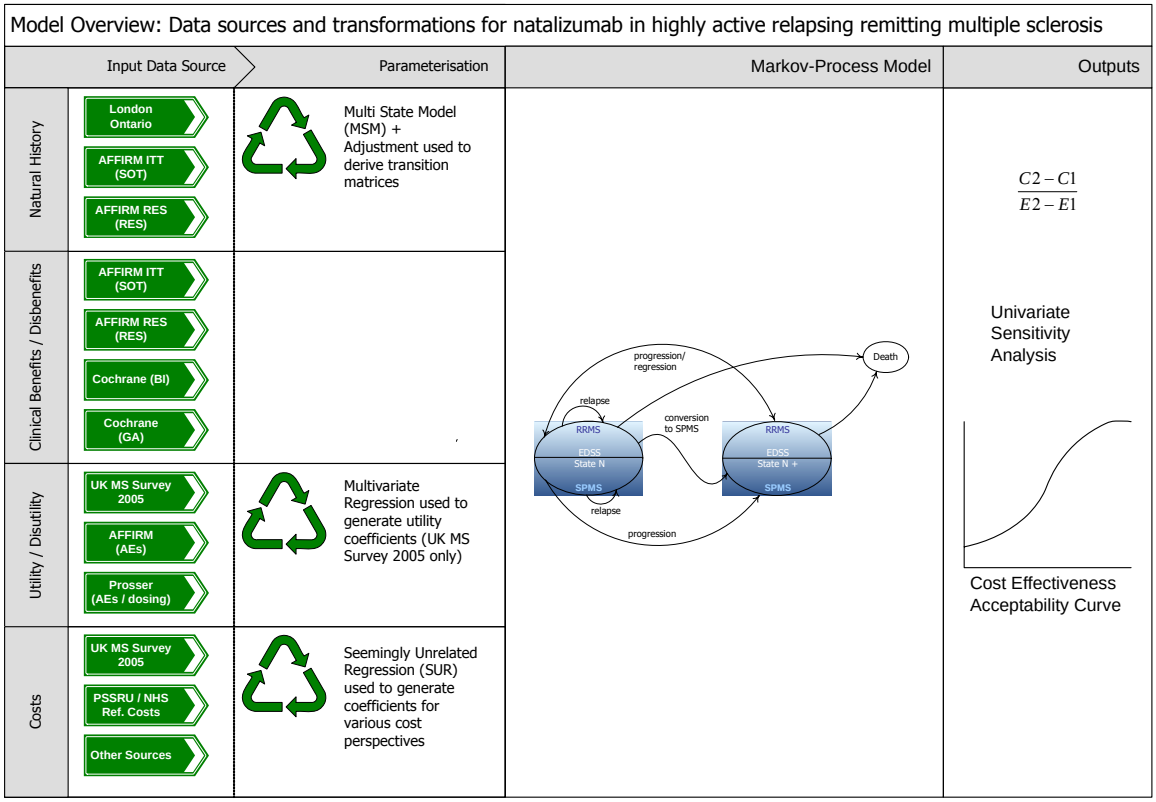
6.2.6.1 Description of the model type

The framework for the analysis is a model written in Excel for RRMS patients based on the natural history of the disease. The number of costs and QALYs gained per patient are dependent on the time in each EDSS state, the incidence of MS relapse and adverse events, and the amount of disease-modifying treatment received. The model structure has been developed based on the previous ScHARR model.

The model takes the form of a Markov-process cohort model. Disability progression is modelled according to Kurtzke's EDSS, an ordinal scale ranging from EDSS 0 (normal neurologic examination) to EDSS 10 (death due to MS). (116) The EDSS is reproduced in Appendix J. As with the Prosser model, EDSS scores are banded together and used as Markov states. (160)

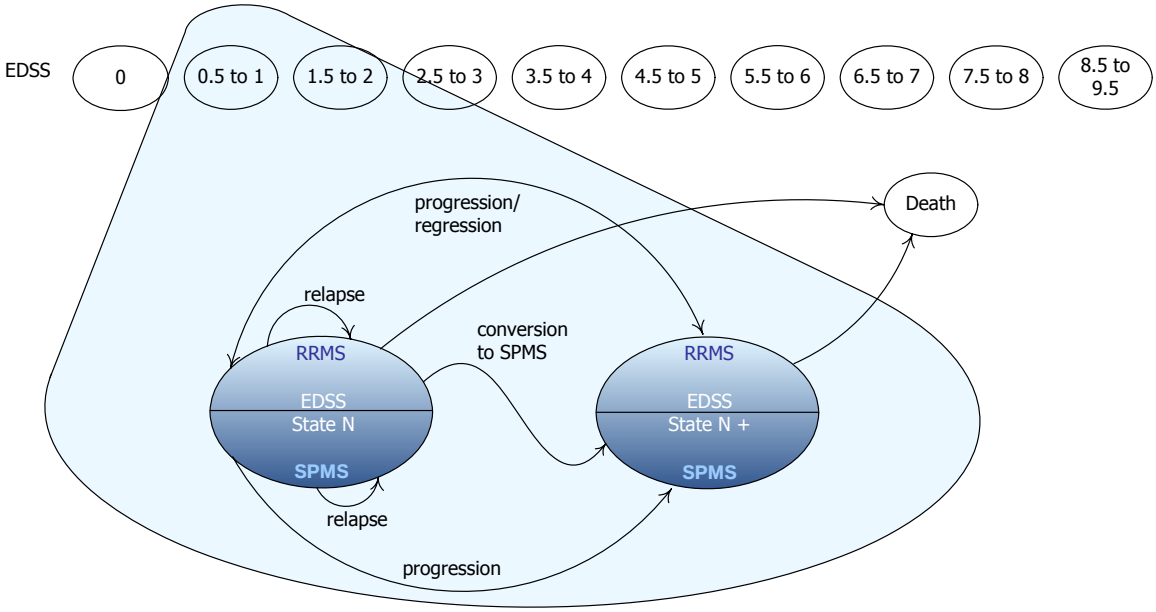
Figure 13 presents a simple overview of the main data inputs, data transformations and outputs from the model. Figure 14 provides a schematic of the Markov-process model we use to perform the analysis.

Figure 13 Overview of model data inputs, parameterisation and outputs



IFN-beta = interferon beta. GA = glatiramer acetate. NAT = natalizumab. RES = Rapidly Evolving Severe subgroup. SOT = Sub Optimal Therapy subgroup. Cochrane (GA) review by Munari et al (70). Cochrane (IFN-beta) review by Rice et al (73). For details on London Ontario, Prosser 2003. UK MS Survey 2005, see Section 5.8.

Figure 14: Conceptual framework of Markov-process model



6.2.6.2 The Natural History Model

The natural history model comprises of 21 health states, which represent patients with RRMS in EDSS 0-9, SPMS in EDSS 0-9 and death. The model uses a cycle duration of one year. During any cycle, patients with RRMS have a probability of either transiting to a higher or lower EDSS state, remaining in their current state, progressing to a higher SPMS EDSS state, or dying. For further details regarding the transition of patients to higher or lower states, please refer to the MSM in section 5.8.3. Patients with SPMS may progress to a higher EDSS state, remain in their current EDSS state, or die. Patients in any EDSS state may experience one or more relapses during any cycle. Relapse rates are assumed to be dependent on the EDSS state and the type of disease (RRMS or SPMS).

The parameterisation of natural history is centred on three types of events: (i) disability progression rates; (ii) MS relapse rates; and (iii) mortality rates.

(i) Disability progression rates

Three sets of transition probabilities are used in the model: RRMS to RRMS; RRMS to SPMS; and SPMS to SPMS. The London Ontario dataset, described in section 5.8.1.1, was used for many of the transition probabilities in this model. However, since it is not representative of HARRMS, we also used data from the placebo arm of the AFFIRM study to estimate transition probabilities in a HARRMS population.

The transition probabilities between one RRMS state and another is given in Table 62 for the RES subgroup and

Table 63 for the SOT subgroup. Both of these transition matrices were derived from the London Ontario data and data from the AFFIRM study and are discussed in detail in section 5.8.3.

Table 62 academic / commercial in confidence information removed

Table 63 academic / commercial in confidence information removed

Transition probabilities describing the probability of progressing from RRMS to SPMS health states are detailed in Table 64. These probabilities are applied to the RRMS population in order to estimate the proportion of patients who are expected to progress to a greater SPMS EDSS state during the given cycle (e.g. from EDSS 5 to EDSS 6). The RRMS to SPMS transition probabilities are estimated from the London Ontario dataset. Note that in the model the values in Table 62 and

Table 63 are adjusted to account for this transition to SPMS so that the total probability of transition to either a SPMS or RRMS EDSS states remains 1.

Table 64 academic / commercial in confidence information removed

Transition probabilities between different EDSS states for SPMS patients are given in Table 65; these probabilities were also derived from the London Ontario dataset.

Table 65 academic / commercial in confidence information removed

(ii) MS relapse rates

Relapse rates were derived from data from Patzold and Pocklington 1982, data from the AFFIRM study, and data from the UK MS Study 2005. (140) For the model we required relapse rates by EDSS state for SPMS and for the SOT and RES subgroups. The relapse rates by EDSS state and disease type are repeated in Table 66, with a description of their derivation in section 5.8.5.

Table 66 Number of relapses per patient for SOT and RES subgroups for RRMS and SPMS patients by EDSS state, Patzold and Pocklington 1982, UK MS Survey 2005, AFFIRM

	SOT Subgroup		RES Subgroup	
EDSS score	RRMS	SPMS	RRMS	SPMS
0	0.709	na	1.407	na
1	0.729	na	1.448	na
2	0.676	0.465	1.343	0.923
3	0.720	0.875	1.430	1.738
4	0.705	0.545	1.400	1.083
5	0.591	0.524	1.173	1.041
6	0.490	0.453	0.972	0.900
7	0.508	0.340	1.009	0.676
8	0.508	0.340	1.009	0.676
9	0.508	0.340	1.009	0.676

(iii) Mortality rates

Age- and sex-specific mortality rates are based on the latest interim life tables from England and Wales produced by the Government Actuary's Department. [5] Adjustments to the standard mortality rate were made on the basis of details from Pokorski 1997, which is detailed in section 5.8.8. (156) The multiplier on the standard mortality rate is repeated in Table 67.

[5]Available online at http://www.gad.gov.uk/Life_Tables/Interim_life_tables.htm.

Table 67 Multiplier to standard mortality rate, Pokorski 1997 (156)

Description	EDSS Range	Multiplier on Standard Mortality Rate
Mild	0-3	1.60
Moderate	4-6	1.84
Severe	7-9	4.44

Effect of DMT on natural history

In the model we assume that patients are treated as per the natalizumab product licence.

- Patients that stay on treatment do so until the end of the time horizon.
- Patients may not switch between therapies though may withdraw from treatment due to reasons stated below.
- Alternative treatments recommended for SPMS patients are not considered in this evaluation.
- Switching therapies or alternative uses of therapies are not modelled, as they are not relevant to the decision problem.

The modelled beneficial effect of the DMTs is to:

(i) delay disability progression

(ii) reduce the frequency of relapses

(iii) Patients may withdraw from each of the DMTs at different rates because of differences in adverse events, efficacy etc.

(iv) Each of the DMTs is associated with adverse events, which result in additional costs (and disutility for the patient, which is described later).

(i) Impact of DMT on progression

Two measures of relative risks are employed in this submission, the hazard ratio and the risk ratio. The hazard ratio is a comparison of the average level of hazard in one treatment arm compared to another, typically calculated after applying the Cox proportional hazards model. The measure is often used in clinical trials, where individual level data is available and the proportionality assumption underlying the Cox model can be assessed. The other measure, the risk ratio is a comparison of risk between two treatment arms (i.e. proportion of patients experiencing an event).

The risk ratio is used in systematic reviews where no patient level data is available and only aggregate measures can be calculated from results presented. The risk ratio does not take account of differences in the timing of events between arms or of differences in rates of censoring.

Lyman et al describe the hazard ratio as a more robust measure ofrelative risk as it is, 'particularly designed for comparing two survivalcurves by allowing for both censoring and time to an event'. (153) In the absence of censoring and with equality in the timing of events, the risk ratio and hazard ratio produce similar values.

For the natalizumab disability progression rate parameters we use the hazard ratio calculated from the Cox proportional hazard model as a measure of relative risk rather than the risk ratio, in order to capture as much information from the AFFIRM trial as possible. It was not possible to calculate the hazard ratio for progression rates for IFN-beta and GA, since only endpoint data was available. Instead, the risk ratio of disability progression has been calculated for IFN-beta and GA as part of the meta-analysis using data from the Cochrane reviews (section 5.6.1 on page 81).

Relative risks describing the difference in EDSS progression rates between the DMTs compared to placebo are provided in Table 68.

- These relative risks are applied to the transition probabilities between EDSS states for RRMS. The probability of:
  - transition to a lower EDSS state is unaffected by the relative risk (i.e. the baseline transition probability is applied to these transitions without any additional treatment effect).
  - transition to a higher EDSS is multiplied by the relative risk.
  - remaining in the same state is increased by the probability of those that do not progress as a result of the relative risk (i.e. the decrease in the probability of progression across higher EDSS states is added to the probability of remaining in the same state).

- A reduced relative risk for progression is also applied to transitions from a lower RRMS EDSS state to a higher SPMS state.
  - For RRMS to SPMS progression, a rate of 50% of the relative risk is used, thereby assuming that there is a constant risk of progression between these states across the year. This assumption provides a better fit between the model and the AFFIRM data than an alternative assumption that none of the patients are affected by treatment (see Table 82 on page 149).

- No effect is assumed in SPMS to SPMS transition and the costs and effects of SPMS treatments are not considered within our model.

Table 68 Relative risk for progression rates for DMTs compared to placebo

DMT	Sample size (DMT, Placebo)	Relative Risk	95% CI	Probability distribution used in model	Source
IFN-beta	466, 453	0.70 r	(0.55, 0.88)	lognormal	Meta-analysis (73)
GA	125, 126	0.88 r	(0.56, 1.38)	lognormal	Meta-analysis (67)
NAT (SOT)	627, 315	0.46 h	(0.33, 0.64)	lognormal	AFFIRM study
NAT (RES)	148, 61	0.36 h	(0.17, 0.76)	lognormal	AFFIRM study

IFN-beta = interferon beta, h = hazard ratio, GA = glatiramer acetate, NAT = natalizumab, r = relative risk ratio.

(ii) Impact of DMT on relapse rates

IFN-beta and GA

The relative risks of relapse for IFN-beta and GA from the relevant Cochrane reviews are in Table 69. Unfortunately the data in the form reported by Cochrane must be transformed before it can be used in the economic evaluation as it refers to the risk of one or more relapses rather than the actual number of relapses.

An estimate of the number of relapses (i.e. the relative relapse rate) can be derived from the relative risk of relapse using the formula below. (161)

Relative Rate = - LN(1 - Relative Risk x (1 – e^{p}))/p,

In the formula, *Relative Risk* is the relative risk of relapse from the relevant Cochrane reviews and *p* is the annualised relapse rate from the placebo group. The annualised relapse rates for the placebo group is taken from the AFFIRM study, as 0.733 (n = 169) for the SOT subgroup (using the ITT population as a proxy) and 1.455 (n = 44) for the RES subgroup. The relative relapse rates are shown in Table 69. The confidence intervals provided are used to sample values of the relative relapse rate for the probabilistic sensitivity analysis (PSA) using a lognormal distribution.

Table 69 Relapse rates per year for IFN-beta and GA in the SOT and RES subgroups, adapted from Munari et and Rice et al (70;73)

Relapse rates (n)	Sample size (DMT, Placebo)	Relative risk of relapse	Upper and lower 95% CI	Distribution	Source	Relative relapse rate
IFN-beta (SOT)	466, 453	0.81	(0.74, 0.89)	lognormal	Meta-analysis (73)	0.745 *
GA (SOT)	125, 126	0.84	(0.63, 1.12)	lognormal	Meta-analysis (67)	0.782 *
IFN-beta (RES)	466, 453	0.81	(0.74, 0.89)	lognormal	Meta-analysis (73)	0.667 **
GA (RES)	125, 126	0.84	(0.63, 1.12)	lognormal	Meta-analysis (67)	0.710 **

IFN-beta = interferon beta, GA = glatiramer acetate; * based on relapse rate of 0.733 in the ITT placebo group observed in AFFIRM study; ** based on relapse rate of 1.455 in RES subgroup observed in AFFIRM study;

Natalizumab

The relative relapse rates were available from the AFFIRM study and could be used directly in the economic evaluation. These are given for the SOT and RES subgroups in Table 69. Values for the PSA are sampled from a lognormal distribution using the confidence intervals in Table 70.

Table 70 Relative relapse rates for natalizumab compared to placebo, AFFIRM

Relapse rates (n)	Sample size (DMT, Placebo)	Relative rates of relapse	Upper and lower 95% CI	Distribution for DMT and placebo	Source
NAT (SOT)	627, 315	0.321	(0.26-0.40)	lognormal	AFFIRM study
NAT (RES)	148, 61	0.194	(0.12-0.30)	lognormal	AFFIRM study

NAT = natalizumab.

(iii) Withdrawal rates

We have assumed that in the first 10 years patients withdraw from natalizumab at the rate of 6.4% per year and from interferon beta and glatiramer acetate at a rate of 5.5% per year. These rates are based on observations from the AFFIRM study and a report from Herndon 2005 respectively, with the derivation of these rates provided in section 5.8.9.

In addition, patients are no longer recommended for treatment if they become SPMS or if they progress to the composite Markov state 'EDSS 6.5 or 7'. (50) In the evaluation these patients are also withdrawn from treatment.

(iv) Adverse events

Adverse events for natalizumab are based on a number of components. We model the costs and/or disutility associated with PML, anti-natalizumab anti-bodies (NAB), hypersensitivity reactions, anaphylactic and anaphylactoid reactions, and opportunistic infections. In addition, we model an on-treatment disutility for all DMTs (described later in Table 55 on page 107). Note that for the comparator DMTs, we assume that the total disutility associated with treatment is encompassed in the values in Table 55.

PML

Investigation of patients with suspected PML follows a stepwise approach. (5) In the first instance patients should receive an MRI scan. If the result of the MRI scan is equivocal or suggestive of PML then analysis of the patient's cerebrospinal fluid (CSF), collected by lumbar puncture (LP), should be performed to confirm or refute the diagnosis (CSF is tested for JC viral DNA by polymerase chain reaction). Patients undergoing investigation for possible PML are withdrawn from treatment whilst investigations are carried out and are expected to miss one month of treatment with natalizumab.

It is assumed that neurologists will wish to exclude a diagnosis of PML in all patients that suffer a severe relapse (defined as a relapse that is severe enough to require treatment with steroids). In the AFFIRM study 18% of natalizumab-treated patients had a relapse that required steroid treatment over the 2 year duration of the study. (113) It is therefore assumed that 9% of patients will require an MRI scan each year.

A proportion of those patients will require a CSF examination, which is derived from a safety study performed by Yousry et al (see section 5.7.2). (6) In this study, 33 out of 2917 (1.1%) patients that had an MRI scan were referred to an Adjudication Committee because the MRI scan indicated the possibility of PML (no cases of PML were subsequently found). Hence it is assumed that 1.1% of patients that have an MRI scan will subsequently require CSF testing. The PML surveillance pathway for the base case and the pessimistic scenario is given in Appendix K.

Two scenarios are modelled in the evaluation. These are described in Table 71 and refer to rates per year.

Table 71 Parameters used in scenarios to model the impact of PML

Parameter	Base case	Pessimistic scenario *
Severe relapse requiring MRI test	9.0%	14.0%
MRI clear rate	98.9%	98.9%
% of patients having MRI requiring LP and JC Virus test	1.1%	1.1%
Risk of PML per patient per year on natalizumab monotherapy	0.00000	0.00073 *

* This risk is equivalent the risk when receiving 13 doses over one year to a risk of 1 in 1000 for patient receiving on average 17.9 doses (6) (i.e. risk per year = 1 / (1000 x 17.9) x 13)

The costs associated with MRI scans, LPs and JC viral DNA tests are presented in Table 72. Costs are saved through any patient not receiving treatment for 1 month; this comprises 1 treatment dose plus associated administration costs (see below). As in the AFFIRM study, no patients are assumed to have PML and so disutility is zero. (6)

Table 72 Costs associated with monitoring and surveillance for PML

Procedure	Cost	Source
MRI cost (brain)	£313.00	NHS reference Costs 2004/05 (Table 49)
JC virus PCR	£46.87	Health Protection Agency for England and Wales (Table 49)
Lumbar Puncture	£89.15	Parkin et al (Table 49)

NAB

The next component is the proportion expected to require testing for anti-natalizumab anti-bodies (NAB), which we set at 23%. This is the proportion of patients experiencing one or more relapses in the AFFIRM study and is considerably higher than the number of patients who tested positive for NABs within AFFIRM (29 from 627 patients). An estimated 20.1% of those tested will require a second test to confirm NABS; this percentage was chosen to reflect the rate of positive tests observed during the AFFIRM study (i.e. % having a second test = 29/627 x % of total tested).

The cost associated with testing for NABs is estimated to be £46.87 per test, the same cost as that assumed for a JC virus PCR (assumed value). The model assumes that all patients are tested once during the first year only, as the development of NABs is likely to occur early on in the treatment period.

Withdrawals due to the development of NABs are already included in the overall dropout rate within the AFFIRM study.

Disutility and other costs associated with the symptoms of NABs are not explicitly included in the model as they are implicitly included in the costs and disutility associated with adverse events.

Table 73 Costs associated with serious adverse events (SAEs)

Resource	Cost per patient	Source
Hypersensitivity + Urticaria		
Steroids for one week at £51.90 per month	£11.94	BNF, Table 49
Antihistamines for one week (Piriton 4mg four per day at £0.19 for 20)	£1.16	BNF, Table 49
Inpatient stay at a neurology clinic (required by assumed 25%)	£55.50	http://www.pssru.ac.uk/pdf/uc2004/ uc2004.pdf (Accessed February 2005) (Inflated to May 2006(141))
Total per patient*	£68.86	
Anaphylactic and anaphylactoid reactions		
Non Elective In Patient HRG Data: S26 - Shock and Anaphylaxis	£471.79	Table 49, http://www.dh.gov.uk/assetRoot/ 04/13/32/25/04133225.xls (Accessed July 2006)
Total per patient*	£471.79	
Opportunistic Infections		
Urinary tract infections (ciprofloxacin 750mg one per day at £3.00 for 10) +	£3.00	BNF, Table 49
Two GP consultations	£60.00	Table 49
Total per patient*	£63.00	
Nasopharyngitis		
Two GP consultations	£60.00	Table 49

* Note this is not total per patient across the cohort but just per patient with condition

Adverse events

Three SAEs for natalizumab are included in the model. These are hypersensitivity, urticaria and anaphylactoid/anaphylactic reaction. The resources and costs for the

treatment of these conditions have been modelled according to their incidence from the AFFIRM study, and an estimate for the cost per treated patient.

In addition, resource use associated with the two most common opportunistic infections described in the SPC, urinary tract infection and nasopharyngitis, have also been modelled. (1) Costs associated with these conditions are in Table 73 and estimated incidence per patient treated in Table 74. Incidence of AEs are based on observations from the AFFIRM study over a two-year period.

As a substantial proportion of 'hypersensitivity or urticaria' and 'anaphylactic or anaphylactoid reactions' occurred in the first year, we have assumed an equivalent rate for that year. For subsequent years the rate of adverse events observed during the second year of the AFFIRM study are used.

The assumption for UTI and nasopharyngitis differs in that a constant rate is assumed over time.

Table 74 Incidence per patient of most common adverse events

Condition	First Year	Subsequent Years	Source
Hypersensitivity or Urticaria	2.88%	0.32%	Derived from SPC (1)
Anaphylactic or anaphylactoid reactions	0.72%	0.08%	Derived from SPC (1)
UTI + UTI NOS	2.00%	2.00%	Polman 2006
Nasopharyngitis	1.00%	1.00%	Assumption (actual difference -1%, Polman 2006)

Utilities for these conditions were estimated in Table 75, using expert opinion. These estimates are conservative as the disutilities are relatively high. We assume that patients with these AEs are included in the withdrawal rates within the AFFIRM study.

Table 75 Estimated decrease in utility per AE

Condition	Decrease in utility across year	Duration of condition	Assumed annual QALY loss per patient experiencing AE	Source
Urticaria or Hypersensitivity	0.25	1 weeks	0.005	Expert opinion
Anaphylactic and anaphylactoid reactions	1.00	1 weeks	0.019	Expert opinion
Urinary tract infection	0.1	2 weeks	0.004	Expert opinion
Nasopharyngitis	0.1	2 weeks	0.004	Expert opinion

Costs

Two categories of cost component are included in the model:

(i) treatment costs

(ii) the costs of managing the disease according to the degree of underlying EDSS progression

We consider each of these cost components separately below.

(i) Treatment costs

The total cost of treatment with natalizumab comprises 3 components: the price of the drug; the cost of managing adverse events and the cost of administration.

Treatment costs for natalizumab are based on the price for a 300 mg vial administered every four weeks. Each vial costs £1130.00. (1)

The costs of managing adverse events for natalizumab described above are added to the price of the product.

The administration cost in the first year is expected to be the same as the cost in subsequent years. The cost of an infusion of natalizumab is assumed to be equivalent to half the cost of an attendance at a neurology clinic. Given that each visit will last for approximately 2 hours we have conservatively assumed that the cost will be £81.38 per infusion. This is based on the 2004 estimate of the cost of a day admission to neurology clinic of £151.06 and inflated for two years at a rate of 3.8% per year. (141) We assume that the cost for an infusion of natalizumab is ½ this cost.

The total costs for patients treated with either IFN-beta or GA are calculated using the coefficients in Table 8 and values from the natural history and relapse rates. For patients on IFN-beta the additional cost is £8652, and £236 more for those in EDSS 3-6. For patients on GA the additional cost is £6202, and £587 less for those in states 3-6. These values were derived from the MS UK Survey 2005, with the prices based on the formulary prices from the risk-sharing scheme. These also included additional costs due to administration, diagnostics, and costs due to adverse events, which were also collected within the survey.

The costs that are used in the base case are those defined as NHS & PSS in Table 8. These costs are varied during the PSA using a multinomial distribution based on the covariance matrix derived from fitting the regression model.

(ii) EDSS state costs

Health state costs are defined as those associated with being in a particular EDSS state with a particular disease type. These are presented in 5.8.5 and were derived from a seemingly unrelated regression model fitted to data from the UK MS Survey 2005. (143) Further details on the derivation of these cost categories are in section 5.8.6.

Uncertainty surrounding the costs of treatment and the costs of managing the disease according to the degree of progression for IFN-beta and GA are varied by sampling from a multinomial distribution generated from the covariance matrix derived from the regression. (143)

Health-related quality of life

EDSS-specific utilities were derived from EQ-5D data collected from the UK MS Survey 2005 and described in section 5.8.7.1. Uncertainty surrounding EDSS scores was handled using a multinomial distribution generated from the covariance matrix derived from regression.

Disutility for relapse rates by EDSS state are in Table 53 with derivation in 5.8.7.1 and disutility due to treatment is given in Table 55 and described in section 5.8.7.2.

Additional disutility due to rare SAEs and opportunistic infections associated with natalizumab are provided in Table 75.

Additional parameters

The initial conditions for the model with respect to characteristics of the cohort are given in Table 76. Similarly, the initial distribution of patients in the model is based on the baseline characteristics of the placebo arm of the ITT population in the AFFIRM study, shown in Table 77. The initial distribution of patients is varied in the PSA using a Dirichlet distribution.

Table 76 Input values for base case, AFFIRM study, (4) UK MS Survey 2005

Parameter	Attribute	Notes
Age of cohort	36	Polman et al 2006 (4)
Years since diagnosis	5	Polman et al 2006 (4)
Value of female to male ratio	3.1:1	From UK MS Survey 2005
Number of patients assumed in model cohort	1000	-
Initial EDSS distribution	Baseline placebo	AFFIRM study

Table 77 Values used as initial distribution of EDSS scores across cohort, data on file AFFIRM study

	EDSS DSS?	% of patients in EDSS state	Sample size	Probability distribution used in mode
RRMS	0	6%	18	Dirichlet
	1	11%	35	Dirichlet
	2	37%	118	Dirichlet
	3	23%	74	Dirichlet
	4	16%	49	Dirichlet
	5	6%	19	Dirichlet
	6	1%	2	Dirichlet
SPMS	2	0%	0	Dirichlet
	3	0%	0	Dirichlet
	4	0%	0	Dirichlet
	5	0%	0	Dirichlet
	6	0%	0	Dirichlet
	7	0%	0	Dirichlet

In line with recommendations from NICE via the UK Treasury, costs and health outcomes are discounted at a rate of 3.5%. (161)

The duration of the average relapse is assumed to be 46 days; this duration was taken directly from the ScHARR model. The disutility of relapse is applied over this duration.

We use the most robust definition of disability progression sustained for 24 weeks since it is widely recognised as a more robust measure of efficacy than progression sustained for 12 weeks. Rio 2002 (115) concluded that progression sustained for six months (24 weeks) was, 'the best criterion for reducing noise in this group of patients', and, 'had the best correlations with outcome disability measures at 4 years'. The 24-week definition is also used in the SPC, which forms the license for natalizumab. (1) The superior robustness of the 24 week definition is also evidenced within the AFFIRM study by a more significant p value than the 12 week analysis.

Derivation of results

The total QALYs gained within the cohort was estimated by:

- calculating the number of patients both on and off treatment in a cohort in each EDSS state
- then multiplying this by the utility of being in that EDSS state
- then adjusting for time since diagnosis.

This total QALY gain was then adjusted by substracting QALYs lost due to the incidence of relapses and adverse events.

The total cost for the cohort was derived by calculating the number of patients both on and off treatment in each EDSS state. The cost coefficients in Table 8 were then used to derive the basic state costs. The relapse rates are used to estimate the costs of relapse of the cohort. Finally, administration costs and costs associated with the management of adverse events are added to estimate the total costs for each treatment strategy.

The estimated total costs and QALYs gained are then used to calculate the incremental cost-effectiveness ratios (ICERs) for each relevant health economic comparison. The univariate sensitivity analysis and the PSA are both performed using a visual basic macro built into the Excel worksheet.

6.2.6.3 Why was this particular type of model used?

The Markov model used to evaluate the cost-effectiveness of natalizumab uses health states described by EDSS. (116) This type of model is widely accepted to be appropriate for modelling long-term chronic diseases whereby:

- the risk of events is ongoing
- where events may occur more than once
- and where the timing of events is important (162;163)

It is of note that previous validated models of MS have employed similar approaches within a Markov framework. (17;147;160)

6.2.6.4 What was the justification for the chosen structure? How was the course of the disease/condition represented? Please state why any possible other structures were rejected.

The Markov methodology was used because evidence of disability progression is most commonly based on changes in EDSS score. (33;34;41) Quality of life, costs and treatment decisions are also commonly based on EDSS score. (1;14;143)

EDSS scores are used to define the state of disability associated with MS and this is reflected by the structure of the model. The same EDSS-based approach to modelling the natural history of MS was adopted within the previous models commissioned by NICE. (147)

The course of the disease is represented by patients being in a given health state for a year with a probability of transitioning to a different health state the following year. The costs of managing the disease and the impact upon patients' HRQoL are

highly dependent on their level of disability and impairment (UK MS Survey 2005).

The probability of experiencing relapse is dependent on the EDSS state in which the patient currently resides; EDSS-specific relapse rates are shown in Table 66. This same structure is appropriate for the RES and SOT subgroups.

It is possible to use a number of other approaches, such as a discrete event simulation, a pure decision-tree approach or a hybrid of these approaches. However, given the understanding of the natural history of the disease and the structure of the data available, it is reasonable to suggest that the state transition approach is the most appropriate methodological framework for this particular health economic evaluation.

6.2.6.5 What were the sources of information used to develop and inform the structure of the model?

The EDSS was used to inform the structure of the model. It is a highly validated instrument used to measure disability progression, which has been employed within natural history studies and randomised controlled trials of DMTs. (41;58;59;66;164)

6.2.6.6 Does the model structure reflect all essential features of the condition that are relevant to the decision problem? If not, why not?

The model encapsulates all the essential features of the decision problem. These are disability progression, probability of change from RRMS to SPMS, mortality and relapses. Other features, such as lesion load and other clinical aspects of the disease are not relevant to the decision problem as costs and quality of life are expressed in terms of EDSS score, frequency of relapse and mortality.

Also, the effect of DMTs on cognitive function (for example, difficulties with memory and general alertness) which has an impact on quality of life according to patient representatives (165), has not been explicitly included. This is implicitly included in the estimated quality of life by EDSS state.

6.2.6.7 For discrete time models, what was the model's cycle length, and why was this length chosen? Does this length reflect a minimum time over which the pathology or symptoms of a disease could differ? If not, why not?

A one-year cycle length was used within the model. This cycle length was considered suitable on three grounds:

- Firstly the long-term and chronic nature of the disease suggests that shorter cycle lengths are unlikely to increase the sensitivity of the model.
- Secondly, the clinical data used to populate the model was reported on an annual basis. (34)
- Furthermore, a one-year time cycle has been frequently used in previous models for RRMS (17;147).

6.2.6.8 Was a half-cycle correction used in the model? If not, why not?

Yes, estimates of the number of patients in each EDSS state during each Markov

cycle are made after applying a half-cycle correction.

6.2.6.9 Are costs and clinical outcomes extrapolated beyond the study follow-up period(s)? If so, what are the assumptions that underpin this extrapolation and how are they justified? In particular, what assumption was used about the longer-term difference in effectiveness between the technology and its comparator?

Both the model used in this evaluation and the ScHARR model use a time horizon of 20 years within the base case analysis. This was agreed to be appropriate by NICE and its stakeholders during the 2001 technology appraisal. (17;147)

The AFFIRM study followed patients for a duration of up to 2 years. The transition probabilities fitted from the placebo arm of the study and modelled costs were assumed to continue to apply over the full time horizon of the model to capture the full costs and health outcomes associated with natalizumab and the comparator DMTs. We assume that the EDSS progression free survival duration is exponentially distributed, but the relative hazards between treatment and no treatment are constant over time. This assumption is applied across both natalizumab and the comparator DMTs.

As is the case with all newly licensed products there is a lack of long-term data. In the absence of specific long-term data it is helpful to examine:

- other indicators to determine whether the product is likely to remain effective in the long term.
- the effect of natalizumab (compared with placebo) at different points in time during the available studies, to see if the efficacy changes over time.
- the available data for internal consistency; i.e. is the direction of change in the value of the endpoint the same for all relevant clinical and surrogate end points at all points in time?

These three considerations are discussed below:

Other indicators

As the natural history of MS is one of progressive disability, the relationship between baseline disability and the efficacy of natalizumab in preventing further disability progression is likely to be a good indicator of whether the benefits of natalizumab will be maintained in the long term. Baseline EDSS was pre-specified as a covariate in the statistical analysis plan of the AFFIRM study. (4) When the covariate analysis was performed there was no significant relationship ($p = 0.87$) between baseline EDSS and disability progression. (113) Only age at baseline had a significant effect on disability progression and was included in the final Cox proportional hazard model. (113)

In addition, natalizumab-treated patients had a highly significant reduction (compared with placebo) in the probability of reaching the pre-specified tertiary endpoints, EDSS ≥ 4 (hazard ratio = 0.33, $p < 0.001$) and EDSS ≥ 6 (hazard ratio = 0.30, $p = 0.002$). EDSS 4 signifies that the patient is experiencing significant limitation in walking ability and EDSS 6 means that the patient can only walk with assistance (e.g. with a walking stick).

These data therefore shows that natalizumab continues to reduce disability

progression across the whole range of relevant EDSS scores and this in turn supports the continued effectiveness of natalizumab over time. (113)

Change in efficacy over time in AFFIRM study

If the magnitude of effect of natalizumab (versus placebo) is considered over the first and second years of the study (Table 78) it can clearly be seen that the clinical and MRI indicators of disease activity are the same, or greater, in years 1-2 than in year 0-1.

This demonstrates that, within the AFFIRM study, there was no reduction in treatment effect with natalizumab over time.

Table 78 Variation in efficacy over time in the AFFIRM study

Outcome	Year 1	Year 1-2	Year 0-2
Reduction in annualised RR	66%	70%	68%
Hazard Ratio disability progression	0.61	na *	0.58
Reduction in Mean number Gd+ lesions	92%	92%	92%
Reduction in Mean number of new or enlarging T2 lesions	80%	86%	83%
Reduction in Mean number of new T1 lesions	74%	83%	76%

* Proportional hazards methodology does not allow for reliable estimation of 1-2 year hazard ratio.

Additional support for the continued efficacy of natalizumab over time comes from an open label extension study (data on file). Patients who participated in the phase III natalizumab program were eligible to enrol in an open-label extension study that evaluated the therapy's long-term effects. Approximately 1,900 patients and over 200 sites worldwide participated in the extension study. Approximately 250 of these patients remained on natalizumab monotherapy for nearly three years. The annualised relapse rate for these patients over the three-year period was 0.23, which is consistent with the 0.23 annualised relapse rate seen in the two-year AFFIRM study.

Internal Consistency – agreement over all endpoints at all time points

Table 78 shows that there is complete consistency across relevant clinical and surrogate endpoints over time. In fact the degree of efficacy for most endpoints increases over time.

Summary

In line with the assumptions of the ScHARR model, we assume no increase or reduction in the efficacy of any current DMT or natalizumab over time.

6.2.7 Clinical evidence

6.2.7.1 How was the baseline risk of disease progression estimated? Also state which treatment strategy represents the baseline.

The baseline risk of disability progression is based on combined data from the placebo arm of the AFFIRM study and data from the London Ontario dataset.

Annual transition probabilities for the SOT subgroup between EDSS states 0 to 7 and for the RES subgroup between EDSS states 0 to 6 were calculated by fitting the MSM to data from the AFFIRM study (section 5.8.3).

Before being used in the model to predict disability progression, the following additions are needed to the transition matrices from the AFFIRM study:

As these matrices represent transition between EDSS states 0 to 7 (and between states 0 to 6 for the RES subgroup), to model RRMS patients from 0 to 9, additional data from the London Ontario dataset was used for the missing states. In addition, we use transition probabilities taken from the London Ontario dataset to estimate transition between RRMS to SPMS and between SPMS states, since no other comparable data is available.

The London Ontario dataset was also explored in isolation in the model but provided an inferior fit (see 5.8.3).

These progression rates represent progression under best supportive care (without DMTs).

6.2.7.2 How were the relative risks of disease progression estimated?

The relative risks of disease progression for each treatment option are presented in Section 5.4.1. These relative risks are applied only to those transition probabilities that result in progression from one EDSS state to a greater (more disabling) EDSS state. See section 6.2.6.2 on page 122 for further discussion.

As the DMTs act to delay progression, those that do not progress as a result of the DMT are assumed to remain in their current EDSS state. This is a conservative assumption as some patients in the AFFIRM study were observed to have improved (i.e. moved to a less disabling EDSS state). In addition, a further conservative assumption is that probability of a patient progressing to SPMS at a greater EDSS state was unaffected by the DMT.

6.2.7.3 Were intermediate outcome measures linked to final outcomes (such as patient survival and quality-adjusted life years [QALYs])? If so, how was this relationship estimated, what sources of evidence were used, and what other evidence is there to support it?

Each EDSS state in the model was ascribed a health utility score in order to estimate the cumulative discounted number of QALYs gained for each treatment option. The valuation of each health state is presented in Table 51 on page 105. This was based on data collected during the UK MS Survey 2005 (Orme et al in press). It was based on the EQ-5D method of assessment, which has been used previously in cost effectiveness analyses in MS. (166;167)

The impact of adverse events is modelled as a reduction in utility; disutilities, based on each treatment option, are presented in Table 75 and Table 55. The values in Table 75 are assumed as no data on these disutilities could be found. However, these assumed disutilities use the most conservative assumption of the experts consulted. The utility values detailed in Table 55 are based on data from Prosser 2003 (144) and form the basis for treatment disutilities used in subsequent models. (147;160)

Disutility due to the incidence of relapse was also estimated by EDSS state, using relapse data from the AFFIRM study and disutilities from the UK MS Survey 2005 (Orme et al in press). The methods used to derive these disutilities are detailed in section 5.8.7.1. These disutilities due to relapse are applied for a duration of 46

days, as used in the ScHARR model.

The number of QALYs gained for the cohort during each cycle is calculated as a function of the:

- number of patients in each EDSS state
- treatment received by patients during the period
- number of relapses experienced
- incidence of adverse events

These are then summed over the time horizon for the model.

6.2.7.4 Were the health effects or adverse effects associated with the technology included in the economic evaluation? If not, would their inclusion increase or decrease the estimated cost effectiveness of this technology?

Health effects of natalizumab were incorporated within the model and are described throughout section 6.2. We make a conservative assumption that the same efficacy and baseline characteristics seen in the ITT population from AFFIRM are applicable to the SOT subgroup. It is questionable whether that assumption is valid. It is plausible that SOT patients merely represent the RES subgroup at a later point in time, after they have experienced suboptimal treatment with IFN-beta or GA.

The possibility that RES patients are less likely to respond adequately to IFN-beta is credible given that IFN-beta does not seem to have a specific mechanism of action in MS. If this is the case then it is arguably more appropriate to use the RES efficacy values adjusted for the effects of age (assuming that the SOT patients are likely to be slightly older than the RES patients). Analysis using RES disability progression rates and efficacy values adjusted for the effect of age are reported as a sensitivity analysis in Table 86 on page 156.

Adverse events of natalizumab were incorporated within the economic evaluation. As noted in section 6.2.7.3, there is no empirical evidence concerning the impact of these on a patient's HRQoL. The adverse event disutilities included in the model are likely to be over-estimated, thus representing a conservative assumption which is expected to decrease the cost-effectiveness of natalizumab.

During the AFFIRM study it was noted that the severity of relapse was less for patients on natalizumab than on placebo, with a greater proportion of patients in the placebo group requiring hospitalisation or steroids (see sections 5.4.2.5 and 5.4.3). Within this evaluation, we make the conservative assumption that the severity and cost of relapse is unaffected by the choice of DMT. If this were not the case, natalizumab would be expected to be more cost-effective.

A number of clinical advisors indicated that we might have underestimated the disutility of relapse because we do not explicitly include intangible measures such as a fear of relapse. The relapse reduction due to DMTs could reduce this fear, thereby resulting in a lasting and sustained improvement in HRQoL. However, due to uncertainty over what these values such utility gains might take, this phenomenon is not incorporated within the model. If this effect had been incorporated in the model, the cost-effectiveness of natalizumab would be expected to improve.

6.2.7.5 Was expert opinion used to estimate any clinical parameters? If so, how were the experts identified, to which variables did this apply, and what was the method of elicitation used?

Expert opinion from 4 consultant neurologists was used to estimate disutilities in Table 75. Pessimistic estimates were elicited; these parameters therefore represent a series of conservative assumptions.

We assume that patients who withdraw from treatment follow the disability progression trajectory of an untreated patient. This is supported by data from the AFFIRM study, which showed that patients that discontinued natalizumab did not rebound, but returned over several months to placebo levels of relapse activity. The same assumption was used in the ScHARR model.

We assume that patients in both subgroups may transition to less severe EDSS states as well as higher EDSS states. This assertion is supported by observations across EDSS states from the AFFIRM study, which are shown above in Table 38 and Table 39.

6.2.7.6 What remaining assumptions regarding clinical evidence were made? Why are they considered to be reasonable?

Patients in both subgroups may experience improvements in EDSS (see section 5.8.3). This is based on observations from the AFFIRM study to which the MSM model was fitted.

6.2.8 Measurement and valuation of health effects

6.2.8.1 Which health effects were measured and how was this undertaken?

Health effects by EDSS and disease type

Health effects for the baseline population were measured within the UK MS Survey 2005 (see section 5.8.4). Health effects of the DMTs result from changes to the disability progression and relapse rate, which lead to different numbers of patients in each of the EDSS states over time, different profiles of QALYs gained, and therefore different values for the health effects across the cohort.

Health effects for relapse by EDSS state

Orme at al (in press) do not consider the coefficient for recent relapse reliable enough for inclusion in a model. In order to provide a more reliable estimate, an analysis of patients within the AFFIRM study was undertaken to estimate the utility decrement associated with relapse. This analysis is presented in section 5.8.7 with the disutilities presented in Table 53 on page 106.

Health effects of adverse events

Prosser 2003, using the standard gamble technique in a community-based survey, measured the impact of adverse events for patients receiving IFN-beta and GA. (144) These values are shown in Table 55 on page 107. These data have since been published and used to parameterise economic evaluations by Prosser 2004 and the ScHARR model. (147;160) Further justification for this approach has been

provided in section 5.8.7.2 above.

Mortality rates

Mortality rates are required to estimate the numbers of people that will die over the course of the model. Background rates for all-cause mortality by age and gender from 2002-2004 were obtained from interim life tables for England and Wales. (168) Mortality is weighted by EDSS state. These weights are provided in Table 67, stratified by disease severity. (156)

Disutility of caregivers

An estimate of caregiver disutility, along with the associated derivation, is reported in section 5.8.7.3 on page 108. The estimate was based on a maximum disutility of 0.14, and was adjusted according to the expected intensity of care by EDSS score.

6.2.8.2 Which health effects were valued? If taken from the published literature, how and why were these values selected? What other values could have been used instead? If valued directly, how was this undertaken?

The health effects valued were:

(i) Utility associated with EDSS states

This was taken from the UK MS Survey 2005 (Orme et al in press. Section 5.8.7.1)

(ii) Disutility associated with relapse

Disutility due to relapse was taken from observations from the AFFIRM study and from the UK MS Survey 2005, as values for the treatment population by EDSS state were not available in the literature (section 5.8.7.1)

(iii) Disutility due to adverse effects of treatment

Values for the disutility of adverse events for natalizumab were conservative (Table 75 on page 127).

For IFN-beta and GA, estimates were taken from the literature (144) and were chosen as they were based on previous methodology used within the ScHARR model. These disutilities are applied each year to all patients on treatment, as evidence gathered suggests that adverse events observed during clinical studies persist over the long term. (145;148;150) We apply the same assumption to patients treated with natalizumab over the long term.

6.2.8.3 Were health effects measured and valued in a manner that was consistent with NICE's reference case? If not, which approach was used?

The large majority of health effects are measured using the EQ-5D, and the UK tariff was used to produce utility valuations for specific states of health for the model. These utilities are applied to the number of patients in each EDSS state, and adjusted according to the incidence of relapse and treatment-specific adverse events to produce robust and comprehensive estimates of the number of QALYs gained across the model cohort. The only assumptions made with respect to health effect were for disutilities associated with AEs for natalizumab, and the duration of

a relapse. These assumptions are necessary due to limitations in the current evidence base.

6.2.8.4 Were any health effects excluded from the analysis? If so, why were they excluded?

During the AFFIRM study it was noted that the severity of relapse was less for patients receiving natalizumab than for those receiving placebo, with a greater proportion of relapses in the placebo group requiring hospitalisation or steroid treatment. (169) This effect was excluded from the analysis due to insufficient data in order to parameterise consequences of the more severe relapses. However, it should be noted that this exclusion might also be considered to be a conservative assumption, as its inclusion would improve the cost-effectiveness of natalizumab.

6.2.8.5 If health effects were not expressed using QALYs, what health outcome measure was used and what was the justification for this approach?

This is not applicable, as all health effects were expressed in terms of QALYs.

6.2.9 Resource identification, measurement and valuation

6.2.9.1 What resources were included in the evaluation? (The list should be comprehensive and as disaggregated as possible.)

Resources used in the evaluation are reported in section 5.8.6 and are also included in the accompanying workbook ['UK MS Survey 2005.xls']. These were collected as part of the UK MS Survey 2005. (14;143)

State costs and cost of relapse

Basic costs in the model are defined by EDSS state and relapses. Costs for IFN-beta, GA and best supportive care are based on a seemingly unrelated regression (SUR) fitted to data described from the UK MS Survey 2005. (143) The attributes included in the cost model were age, gender, EDSS state, disease type, relapses, treatment and perspective (NHS & PSS, Government and Societal). These coefficients from the regression model were used to calculate the basic costs per patient for each treatment (including placebo) in terms of the different cost perspectives. These costs are shown in Table 8 on page 42.

The average NHS & PSS cost per relapse was estimated to be approximately £223.

For patients receiving IFN-beta, the additional cost is £8652; this cost estimate is £236 greater for patients in EDSS states 3-6. For patients receiving GA, the additional cost is £6202; this cost is £587 less for those patients in EDSS states 3-6. These costs are based on the DMT acquisition costs, which are currently being used in the Department of Health's risk-sharing scheme, (51) but also allow for additional costs derived from the regression for patients on treatment, and include the costs associated with adverse events and diagnostics. The lower cost for those patients in higher EDSS states reflects less intensive resource requirements, possibly due to lower diagnostic requirements.

Cost of natalizumab

Treatment costs are based on the price for a vial of natalizumab and frequency of administration. Each vial costs £1130.00 and is administered every 4 weeks. (104) We expect the administration cost in the first year to be the same as the cost in subsequent years, as no additional resources are likely to be required. We assume that the cost of an infusion of natalizumab is equivalent to half the cost of a neurology outpatient session; this is estimated to cost £81.38 per infusion.

In addition to these costs, the costs associated with adverse events, given in Table 73 and Table 74, are included in the treatment costs.

6.2.9.2 How were the resources measured?

Resource requirements for each person in the UK MS Survey 2005 were ascertained through a series of questions included in the survey questionnaire. The responses to these questions are used to estimate the resource requirements per patient. Section 5.8.4 provides further detail on these resource requirements.

6.2.9.3 Were the resources measured using the same source(s) of evidence as the baseline and relative risks of disease progression?

Resources are allocated by EDSS state with the same costs used across all comparator arms of the model; further details provided in section 5.8.

6.2.9.4 Were resources used to treat the disease/condition included for all relevant years (including those following the initial treatment period)?

The model accounts for all resources consumed over the time horizon of the model. Within the base case analysis, the time horizon is specified as 20 years.

6.2.9.5 What source(s) of information were used to value the resources?

The unit cost for the resources are given in section 5.8.6 and the data used to generate the costs for each perspective is provided in the accompanying worksheet [UK MS Survey 2005.xls]. These are based on a number of sources. Each unit cost estimate was inflated to reflect May 2006 prices.

6.2.9.6 What is the unit cost (excluding VAT) of the intervention(s) included in the analysis? Does this differ from the (anticipated) acquisition cost reported in section 1?

For natalizumab, the treatment costs are based on the price for a vial of natalizumab and frequency of administration. Each vial costs £1130 and is administered every 4 weeks. We expect the administration cost in the first year to be the same as the cost in subsequent years, as no additional resources are likely to be required. We assume that the cost of an infusion of natalizumab will be £81.38, equivalent to half the cost of an attendance at a neurology clinic. (141;170)

In addition to these costs, the costs associated with adverse events (Table 73, Table 74), PML (Table 72) and NAB testing are included.

For patients on IFN-beta the additional cost is £8652, and £236 more for those in EDSS 3-6. For patients on GA the additional cost is £6202, and £587 less for those in EDSS states 3-6. These are more than the current costs under the risk-sharing scheme. (51) However, the actual drug costs are based on these prices but include additional costs derived from the regression for patients on treatment, and include costs associated with adverse events and diagnostics. The lower price for those in higher EDSS states reflects less resource requirement, possibly due to lower diagnostic requirements.

6.2.9.7 Were the resources measured and valued in a manner consistent with the reference case? If not, how and why do the approaches differ?

The resource data used is the same across different comparator arms of the model.

6.2.9.8 Were resource values indexed to the current price year?

Yes, prices were inflated to May 2006.

6.2.9.9 Provide details of and a justification for any assumptions that were made in the estimation of resource measurement and valuation.

No values for the price for a NAB test for the UK were identified. We estimate the cost of a NAB test to be £46.87.

6.2.10 Time preferences

An annual discount rate of 3.5% was applied to both costs and health effects. (161)

6.2.11 Sensitivity analysis

6.2.11.1 Which variables were subject to sensitivity analysis? How were they varied and what was the rationale for this?

Extensive sensitivity analyses are presented (See Table 79). One-way and multi-way parametric sensitivity analyses are presented covering all areas of uncertainty within the health economic model, including:

- an exploration of the impact of assumptions concerning the baseline characteristics of the model cohort
- the natural history of MS
- the efficacy and tolerability of each of the DMTs,
- costs of care
- health utilities

An analysis of the impact of methodological uncertainty surrounding discount rates and the perspective for the model has also been undertaken. In addition, structural uncertainty analysis is presented, in terms of varying assumptions concerning the time horizon over which costs and outcomes are assessed. The rationale for each of these analyses, and the values used are provided in Table 79.

An additional sensitivity analysis that is not shown in Table 79 was conducted in the SOT subgroup. The rationale for this is as follows:

In the base case, we make a conservative assumption that the same efficacy and baseline characteristics seen in the ITT population from AFFIRM are applicable to the SOT subgroup. However, one can question whether this assumption is valid. We believe it is actually probable that SOT patients merely represent the RES subgroup at a later point in time, after they have tried and experience break-through disease activity on IFN-beta or GA.

The possibility that RES patients are more likely to fail to respond adequately to IFN-beta is plausible given that IFN-beta does not seem to have a specific mechanism of action in MS. Further evidence for this belief comes from a post hoc analysis of the SENTINEL study:

The comparator arm of SENTINEL study comprised patients on IFN-beta (AVONEX) monotherapy. Hence, disability progression in the patients from this arm that had one or more relapses over the duration of the study provides a good proxy for the likely disability progression of SOT patients, as SOT patients are, by definition, those that continue to experience relapses whilst on an IFN-beta. If the same baseline data that was used in the ITT transition matrix is used in the transition matrix derived from IFN-beta monotherapy patients in the SENTINEL study, the average progression over the two years is 0.31 EDSS points. This is higher than the progression of 0.27 EDSS points that was observed with the ITT placebo population from AFFIRM. However, one must also factor in that these patients from the SENTINEL study were on an active therapy hence masking the true progression for an equivalent untreated population.

Hence a more accurate estimate of cost effectiveness in the SOT subgroup is likely if one uses the RES subgroup values for disability progression and efficacy and then adjusts the ICER for the effects of age (assuming that SOT patients are likely to be slightly older that RES patients). The results of this sensitivity analysis are presented in section 6.3.3.1.

Table 79 Parameters included in the univariate sensitivity analysis

Scenario	Parameter / scenario	Rationale for sensitivity analysis 'To explore the effect of…'	Reference Value	New Value
	Baseline Characteristics			
1.1	Mean age at baseline = -10 years	Treating populations of different average ages.	36 years	26 years
1.2	Mean age at baseline = +10 years	"	36 years	46 years
1.3	Mean age at baseline = +20 years	"	36 years	56 years
2.1	EDSS at baseline = 0	Treating cohorts in different baseline disability states	AFFIRM	100%
2.2	EDSS at baseline = 1	"	AFFIRM	100%
2.3	EDSS at baseline = 2	"	AFFIRM	100%
2.4	EDSS at baseline = 3	"	AFFIRM	100%
2.5	EDSS at baseline = 4	"	AFFIRM	100%
2.6	EDSS at baseline = 5	"	AFFIRM	100%
	Safety & Tolerability			
3.1	Natalizumab withdrawal rate = +50%	Higher modelled rate of withdrawals	6.4% pa	9.6%
3.2	Natalizumab withdrawal rate = -50%	Lower modelled rate of withdrawals	6.4% pa	3.2%
3.3	IFN-beta/GA withdrawal rate = +50%	Higher modelled rate of withdrawals	5.5% pa	8.3%
3.4	IFN-beta/GA withdrawal rate = -50%	Lower modelled rate of withdrawals	5.5% pa	2.8%
3.5	PML effect = worst case scenario	PML related deaths in natalizumab monotherapy (death rate=0.67, disutility = 0.2)	6.5% MRI; 0.052% LP; PML rate = 0%	25% MRI 0.002% LP PML rate = 0.065%

Scenario	Parameter/scenario	Rationale for sensitivity analysis 'To explore the effect of…'	Reference Value	New Value
3.6	NABs = 100% people tested	Antibody testing in all treated patients	23% 1st test	100% 1st test
	Natural History			
4.1	Relapse rate	Treating a population with reduced baseline relapse rate	RRMS relapse rate x 1.99 for RES	Rel. x 1
4.2	Relapse duration +50%	Increased mean duration of relapse	46 days	69 days
4.3	Relapse duration –50%	Decreased mean duration of relapse	46 days	35 days
4.4	Progression data from AFFIRM	Removing observations from AFFIRM progression estimates when within 1 month of relapse	Table 62	MSM probabilities (see section 5.8.3)
4.5	Progression data from AFFIRM	Removing observations from AFFIRM progression estimates when within 3 months of relapse	Table 62	MSM probabilities (see section 5.8.3)
4.6	Progression data from AFFIRM	Removing observations from AFFIRM progression estimates when within 6 months of relapse	Table 62	MSM probabilities (see section 5.8.3)
4.7	Progression data from AFFIRM	All subgroup data used	Table 62	MSM probabilities (see section 5.8.3)
4.8	Progression data from London Ontario data *	Treating a RRMS population	Table 62	London Ontario data (see section 5.8.1.1)
4.9	No effect of treatment on transition from RRMS to SPMS	Decreasing effect to no effect	0.5	0
4.10	Full effect of treatment on transition from RRMS to SPMS	Increasing effect to RRMS equivalent effect	0.5	1
	Efficacy			
5.1	Disability progression 12 week definition **	An earlier, less robust definition of sustained progression	24 weeks	12 weeks
5.2a	NAT effectiveness (progression) lower SE (SOT)	Uncertainty in estimates of efficacy	0.46	0.54
5.2b	NAT effectiveness (progression) upper SE (SOT)	"	0.46	0.39
5.3a	NAT effectiveness (progression) lower SE (RES)		0.36	0.53
5.3b	NAT effectiveness (progression) upper SE (RES)		0.36	0.25
5.4a	NAT effectiveness (relapse) lower SE (SOT)	"	0.32	0.42
5.4b	NAT effectiveness (relapse) upper SE (SOT)	"	0.32	0.24
5.5a	NAT effectiveness (relapse) lower SE (RES)		0.19	0.24
5.5b	NAT effectiveness (relapse) upper SE (RES)		0.19	0.15
5.6a	IFN-beta effectiveness (progression) lower SE	"	0.70	0.79
5.6b	IFN-beta effectiveness (progression) upper SE	"	0.70	0.62
5.7a	GA effectiveness (progression) lower SE	"	0.88	1.0 (Actual lower se = 1.11)
5.7b	GA effectiveness (progression) upper SE	"	0.88	0.65
5.8a	IFN-beta effectiveness (relapse) lower SE	"	0.81	0.85
5.8b	IFN-beta effectiveness (relapse) upper SE	"	0.81	0.77
5.9a	GA effectiveness (relapse) lower SE	"	0.84	1.00
5.9b	GA effectiveness (relapse) upper SE	"	0.84	0.69
5.10	GA progression including Bornstien 1987	Impact of small sample outlier (109)	0.88	0.71
	Discounting			
6.1	Costs = 6%	Historical discount rate	3.5%	6%
6.2	Benefits = 1.5%	"	3.5%	1.5%
6.3	Costs = 6% and benefits = 1.5%	"	3.5%, 3.5%	6%, 1.5%
	Utility			
7.1a	Utility by EDSS – upper 95% CI values	Variation in utility rates	Table 51	Multinomial distribution
7.1b	Utility by EDSS – lower 95% CI values	Variation in utility rates	Table 51	Multinomial distribution
7.2	No variation in relapse effect by EDSS	A single utility value assumed regardless of EDSS state (Orme et al in press)	Table 53	-0.073 per relapse

Scenario	Parameter/scenario	Rationale for sensitivity analysis 'To explore the effect of…'	Reference Value	New Value
7.3a	Rate of disutility due to adverse events – upper 95% CI	Uncertainty in AE rates	Table 55	Beta distribution
7.3b	Rate of disutility due to adverse events – lower 95% CI	Uncertainty in AE rates	Table 55	Beta distribution
7.4	Literature derived relapse disutility	Alternative reference value for relapse disutility (12)	Table 55	-0.117
7.5	Disutility of AEs for natalizumab = half	Twice the disutility of AEs	Table 75	Twice values in Table 75
7.6	Disutility of AEs for natalizumab = double	Half the disutility of AEs	Table 75	Half values in Table 75
7.7	Disutility of caregivers = +50%	An increase in caregiver disutility	Table 56	Twice values in Table 56
7.8	Disutility of caregivers = + 0	A reduction in caregiver disutility	Table 56	0
	Costs			
8.1	Costs of resources and IFN-beta/GA – upper 95% CI	Assess variation due uncertainty in costs	Table 8	Multinomial distribution
8.1	Costs of resources and IFN-beta/GA – lower 95% CI	Assess variation due uncertainty in costs	Table 8	Multinomial distribution
	Perspective			
9.1	Societal perspective	Include all costs	NHS & PSS	Societal
9.2	Government costs perspective	Include direct government costs	NHS & PSS	Governmental
	Time horizon			
10.1	10 years	A range of time horizons	20 years	10 years
10.2	30 years	"	20 years	30 years
10.3	40 years	"	20 years	40 years
10.4	50 years	"	20 years	50 years

* Patients in EDSS 0 added to EDSS 1 as London Ontario dataset does not include progression to or from
EDSS 0, ** Only efficacy for natalizumab changed.

6.2.11.2 Was probabilistic sensitivity analysis (PSA) undertaken? If not, why not? If it was, the distributions and their sources should be clearly stated; including the derivation and value of 'priors'.

Comprehensive PSA was undertaken varying costs, utility, efficacy, the rate of adverse events for treatments, initial EDSS distribution of patients and disability progression rates for the natural history.

- Uncertainty surrounding cost parameters were sampled from a multinomial distribution; this was based on the covariance matrix generated from the seemingly unrelated regression (see section 5.8.6), based on the UK MS Survey 2005.
- Uncertainty surrounding health utilities were sampled from a multinomial distribution based the covariance matrix from the regression used to derive the utilities (see section 5.8.7.1), based on the UK MS Survey 2005.
- Probability distributions used to describe uncertainty surrounding relapse rates and progression hazards are presented in 5.8.5. Lognormal distributions were used to describe the uncertainty surrounding the relative estimates of efficacy.
- Probability distributions used to describe the uncertainty surrounding the rate of adverse event are presented in Table 55.

- Values for the initial distribution of patients was varied using a Dirichlet distribution. This was implemented by importing the simtools.xla macro. [6] Sample sizes for the distribution were taken as the sample sizes of the placebo arm of the ITT population in the AFFIRM study.
- The disability progression rates between RRMS states comprise two parts: The first part was generated using the MSM; and the second part was generated using the London Ontario dataset. Again, uncertainties surrounding these progression rates were modelled using Dirichlet distributions. Sample sizes for the MSM are reported in Table 38 for the SOT population and Table 39 for the RES population. Sample sizes by EDSS state for the RRMS population from the London Ontario dataset are unavailable. They may be estimated from the London Ontario dataset in a similar way to the sample sizes used for the SPMS patients below. However, the RRMS probabilities from the London Ontario dataset have not been varied during the PSA for the following reasons: The first is that the sample sizes from the London Ontario dataset are relatively large compared to the sample sizes from the AFFIRM study. This would reduce the variation across all the transition probabilities leading to a less conservative modelling of the variation; the second reason is that the actual number of patients in the higher EDSS states is relatively small compared to the majority of the population that is modelled by the MSM. Therefore using the RRMS data from the London Ontario dataset would be inappropriate due to the magnitude of the sample sizes and undue emphasis this would place on the PSA.
- We also model uncertainty in the transition probabilities from RRMS to SPMS using a beta distribution for each transition probability. The sample size for this is based on the number of SPMS patients, which we estimate to be 9250 (see next bullet point).
- Finally, a Dirichlet distribution was also used to estimate uncertainty in disability progression between SPMS states. Sample sizes required by the Dirichlet distribution were estimated from the number of observations in the London Ontario dataset. This contains in excess of 25,000 observations across different types of MS. An estimated 37% of MS patients are SPMS (UK MS Survey 2005), which, if assumed to be the same in the London Ontario dataset, would result in an estimated 9250 observations from SPMS patients. We assume that the number of patients per state is constant resulting in an estimated 925 observations per state, which we use as the sample size for the Dirichlet distribution.

6.2.11.3 Has the uncertainty associated with structural uncertainty been investigated? To what extent could / does this type of uncertainty change the results?

The structure of the health economic model presented within this submission is closely based upon the earlier work of Prosser and the ScHARR model. (17;147)

In order to test the structural uncertainty of the model, we refer back to the critique of MS models made during the previous MTA submissions to NICE modelling MS. (147;157) These criticisms are in Table 60 and our response in Table 80.

[6] Simtools.xla is distributed freely by the University of Chicago

Table 80 Response to critique of MS models made by HTA group during the previous MTA submission on MS to NICE (147;157)

Failure of previous models	Addressed in this model?
1. Failure to model the natural history of the disease as the comparator to treatment *Natural history has been model using data from non-treatment RCT or observational studies, with impact of DMT modelled as the impact on the natural history*	✓
2. Failure to incorporate mortality in long-term treatment model *Mortality included based both on age and disability severity*	✓
3. Failure to model transition to SPMS from RRMS *Model includes transition from RRMS to SPMS*	✓
4. Failure to model the impact of treatment-related adverse events on cost-effectiveness *Disutility and costs due to adverse events for all DMTs included*	✓
5. Failure to incorporate treatment drop-outs into the model *Treatment dropouts included in the model whereby they have the same progression and relapse rates as those not on DMTs*	✓
6. Linear extrapolation of short-term data *We assume that efficacy and progression rates are non-linear since the probability of transition between health states follows an exponential distribution. This is the same assumption as the ScHARR model.*	✓
7. Inappropriate time horizons *The same time horizon is used as the ScHARR model that was accepted by NICE*	✓
8. Implausible assumptions regarding the impact of relapse on health-related quality of life *Disutility of relapse rates are by EDSS state and based on UK utility measures and severity measurements collected during a clinical study*	✓
9. Inadequate analysis of uncertainty around model parameter values *Extensive univariate sensitivity is undertaken (Table 81) with adverse event rates, initial EDSS distribution, efficacy, costs and utility varied during the PSA*	✓

This model addresses all of the flaws identified in previous models submitted to NICE.

6.2.12 Statistical analysis

6.2.12.1 How were rates or probabilities based on intervals transformed into (transition) probabilities?

The derivation of the transition probabilities was estimated using the MSM method and based on data from the AFFIRM study. This is described in detail in section 5.8.3.

6.2.12.2 Is there evidence that (transition) probabilities should vary over time for the condition or disease? If so, has this been included in the evaluation? If there is evidence that this is the case, but it has not been included, provide an explanation of why it has been excluded.

No evidence was found to suggest that transition rates might vary over time. This is consistent with the assumption used in the ScHARR model.

6.2.12.3 Validity

We have structured this section in terms of Eddy's orders of validation: (171)

1. Does the model make sense to people that know about the disease?
2. Is the model internally consistent?
3. Does the model predict data used to inform the model?
4. Can the model predict the findings of other studies?

1. Does the model make sense to people who know about the disease?

We sought independent peer review on a number of aspects of the model from three experts. It was acknowledged that the model made sense.

A recognised expert in MS modelling undertook a detailed peer review of the methods used within the health economic model. The expert co-developed the ScHARR model and was the lead author for the report to NICE on the previous submission to assess the cost-effectiveness of IFN-beta and GA in the management of RRMS. His comments and suggestions have been incorporated in the submission. Paul's prior experience in the economics of MS is extensive:

1. Natural history and epidemiology review and modelling for the NCCHTA (2001)
2. Assessment of IFN-beta/GA for NICE (2001)
3. MS Risk-Sharing Scheme evaluation (2001-2006)
4. Value of Information analysis for MS therapies (2004)
5. AHRQ evaluation of IFN-beta/GA for Medicare (2006)

The originator of the R code for MSM and a recognised expert in the field reviewed the MSM modelling. He also generated the confidence intervals for the MSM outputs given in the document. The originator is a Research Associate in Statistics in the Department of Epidemiology and Public Health at Imperial College London with eight years experience in generating multi-state models. The originator wrote the MSM package for R.

A recognised expert in biostatistics performed the seemingly unrelated progression. The expert is a Research Associate at the MRC Biostatistics Unit, Cambridge. He is also an Honorary Fellow of ScHARR, University of Sheffield, an Honorary Fellow of the Faculty of Medical and Human Science, University of Manchester, and a member of the MRC Health Services and Public Health Research Board College of Experts.

The model has also undergone critical appraisal by the SMC, and concluded that, 'good internal and external validation information was provided'.

2. Is the model internally consistent?

In order to assess whether the model implementation was correct and structurally robust, a number of tests were performed. These tests are listed in Table 81, with the expected and observed effects, and any action taken.

Table 81 Test conducted on model as part of the model verification and internal validation

Index	Test	Expected effect	Observed Effect	Action Taken
1	Set initial number of cases to 0	Costs and QALY equal 0 across treatments	As expected	None required
2	Set initial cohort as only SPMS patients	No RRMS patients	As expected	None required
3	Set all efficacies and withdrawal rates the same and SAE disutility and mortality to 0.	Same number of QALYS for natalizumab and IFN-beta	As expected	None required
4	As 3 with all efficacies = 0	All incremental QALYs = 0	As expected	None required

Index	Test	Expected effect	Observed Effect	Action Taken
5	Set hazard ratios for progression to 0 + withdrawal = 0	No progression for RRMS patients on treatment	As expected	None required
6	Set efficacies the same for both ITT and RES	IFN-beta vs. Placebo ICER is the same for ITT or RES natalizumab efficacies	As expected	None required
7	Set withdrawals the same and efficacies the same disutilities due to AEs to 0	Same number of QALYs for IFN-beta and natalizumab on treatment	As expected	None required
8	Set withdrawals to 100%	No patients on treatment after first year	As expected	None required
9	Set withdrawals to 0	No patients off treatment in RRMS EDSS <7	Patients don't withdraw from treatment however are present in dropout worksheet for SOT subgroup due to EDSS improvement in treatment failures. Using alternative transition probabilities that censor improvement in EDSS (i.e. London Ontario dataset) produces expected result.	Define assumption: We assume treatment failures that subsequently improve do not resume treatment.
10	Set mortality to 0 and PML mortality to 0	No deaths	As expected	None required
11	Set death rate to 100% in first year	Whole cohort dead by end of first year	As expected	None required
12	Set mortality rate multiplier due to severity to 0	No deaths for any standard mortality rate	As expected	None required
13	Set number of relapses to 0	QALY is the same as when length of relapse is zero	As expected	None required
14	Transition matrices for RRMS patients having only 1's in diagonal and mortality set to zero	No change in the number of patients per EDSS state for those not treated	As expected	None required
15	As 14 with withdrawal rates for IFN-beta and natalizumab the same	No. of patients in each EDSS state on natalizumab and IFN-beta the same at any time	As expected	None required
16	As 15 with withdrawal rates for IFN-beta and natalizumab as 0	Number of patients per EDSS state the same for each treatment arm	As expected	None required
17	As 16 but vary initial distribution of patients across EDSS states	Number of patients per EDSS state the same for each treatment arm	As expected	None required
18	Let transition to SPMS = 1	No RRMS patients after 1st year off treatment	RRMS patients do occur after first year, as there is no transition state for RRMS to SPMS in EDSS 0. Setting this to 1 has expected effect.	Define assumption: We assume that RRMS patient in EDSS 0 cannot become SPMS patient in EDSS 0
19	Let transition to SPMS = 0	No patients develop SPMS	As expected	None required
20	Check sum of rows in each transition matrix	All rows should sum to 1	As expected	None required
21	Set withdrawal due to PML to 100% (MRI tested 100%, 0% clear and 0%	No natalizumab patients are left on treatment after first year	As expected	None required

Index	Test	Expected effect	Observed Effect	Action Taken
	LP clear)			
22	Set PML mortality to 100% and other mortality to 0 and withdrawal due to PML at 100% and withdrawal due to other causes to 0	All natalizumab patients die from PML	As expected	None required
23	Check the placebo group sums to cohort size plus deaths each year	The sum of patients on placebo and dying should equal initial cohort size	As expected	None required
24	Check the IFN-beta treatment group sums to cohort size plus deaths each year for both on treatment and withdrawals	The sum of patients on IFN-beta and dying should equal initial cohort size	As expected	None required
25	Check the natalizumab treatment group sums to cohort size plus deaths each year for both on treatment and withdrawals, including PML	The sum of patients on natalizumab and dying should equal initial cohort size	As expected	None required
26	Set natalizumab acquisition and administration costs to 0 and hazard ratios for efficacy equal to 1 and adverse event costs and utilities to 0	No difference between placebo and natalizumab in terms of cost or effects	As expected	None required
27	Set discount rate for cost to 0%	Discounted costs equal undiscounted costs	As expected	None required
28	Set discount rate for health outcomes to 0%	Discounted benefits equal undiscounted costs	As expected	None required
29	Set discount rate for benefits to 0%, set utilities for all EDSS states to 1, other utilities = 0, mortality = 0	Incremental QALY = 0 and undiscounted QALY per patient per year = 1	As expected	None required
30	Set relapse cost to £0	Same cost as relapse rate set to 0	As expected	None required
31	Set DMT costs to £0 and IFN-beta efficacy to 1, AEs disutility = 0	No difference between no treatment and IFN-beta	As expected	None required
32	Set cost of managing SPMS to £0, transition to SPMS to 0 and efficacies = 0	IFN-beta and no treatment QALY the same	As expected	None required
33	As 32 with natalizumab hazard ratios set to 1 and AE disutilities at 0, AEs disutility = 0	Same QALYs across treatments	As expected	None required
34	Set disutility of relapse to 0	Same QALY gain as when relapse rate is set to 0	As expected	None required
35	All utilities = 0	QALY gain = 0	As expected	None required
36	Set all utilities for states to 1 and other utility vales to 0 and deaths to 0	No loss of utility for any patient	As expected	None required

The findings of the 36 tests described in Table 81 serve as a strong internal

validation of the model structure and its underlying mathematical logic.

3. Does the model predict that data used to inform the model?

As the model is composed of a variety of subcomponents, which are drawn together within a necessarily complex framework of analysis, it was acknowledged that errors could occur in the process of combining these subcomponents. In order to eliminate these errors the following steps were taken to verify the implementation of the component parts derived externally.

MSM method

The MSM is a central component of the economic evaluation and involves outputs from R being combined with outputs from the London Ontario dataset to model transition rates, and then adjusted to remove the transition to EDSS 10. Its implementation in the model was compared to the values for transition rates, which were generated independently and were found to be consistent with each other. External validation is described in section 6.2.12.1.

The use of the MSM in the model was internally validated in the following way:

First of all, the number of people in each EDSS state at two years was estimated by the model and compared to endpoint data from the AFFIRM study. This was done using the transition matrices generated using the MSM, or generated from the London Ontario dataset alone. As the London Ontario dataset contains no transition rates to or from EDSS 0, base line and endpoint data from AFFIRM for EDSS 0 was added to EDSS 1, and estimates of the number of patients in EDSS 0 using the MSM at two years were added to EDSS 1. We measure the goodness of fit of the alternative models (MSM transition matrices of London Ontario matrix) by calculating the root-mean-square (RMS) errors between the observed and predicted data.

For both the ITT population and the RES subgroup from AFFIRM, our MSM models fitted to the data minimised RMS errors by comparison with the London Ontario data (see column 2 in Table 82 below):

- We found that the RMS error for the ITT data and the MSM fitted to the ITT data was lowest at 2.6%. In contrast the RMS error for the ITT data and the transitions derived from the London Ontario data was 3.8%.
- For the RES subgroup, the RMS error for the RES MSM model and the RES subgroup data was also lower than the analysis using the London Ontario dataset (3.6% and 4.6% respectively).

These results indicate that the best predictor for the transition rates for the ITT population was the matrix derived from the MSM for the ITT population. Similarly, the best predictor for the transitions rates for the RES subgroup was the matrix derived from the MSM for the RES subgroup.

Table 82 RMS errors derived by comparing estimated EDSS distributions from the model with different transition probabilities to the ITT and RES subgroup endpoint data

Comparison with the ITT data	RMS error in predicting ITT endpoint on placebo arm of AFFIRM (%)	RMS error in predicting ITT endpoint on natalizumab arm of AFFIRM (%)
ITT Transition probabilities	2.6	3.0
London Ontario Transition probabilities	3.8	4.4
ITT inc. RRMS to SPMS efficacy *	NA	2.6

Comparison with the RES subgroup data	RMS error in predicting RES endpoint on placebo arm of AFFIRM (%)	RMS error in predicting RES endpoint on natalizumab arm of AFFIRM (%)
RES Transition probabilities	3.6	3.3
London Ontario Transition probabilities	4.6	5.7
RES inc. RRMS to SPMS efficacy *	NA	2.8

* Reference case values

Secondly, the model was used to predict the endpoint data from the natalizumab arm of the AFFIRM study (RMS errors reported in column 3 in Table 82). For the ITT population and the RES subgroups the transitions from RRMS to SPMS were adjusted to 50% of the hazard ratio (see '(i) Impact of DMT on progression' on page 122). This provided the best fit to the data for both analyses (Table 82), and is used in the base case cost-effectiveness analysis.

Costs

Table 8 displays the coefficients used to estimate the costs in the model. It should be noted that the coefficients for each EDSS state are not the cost of being in that state due to the decrease in costs provided by the covariate for age. Therefore, the total cost for a reference case of a 30-year-old woman, in EDSS 0, with RRMS, not relapsing, five years from diagnosis, is £7014. This is similar to the reference case from a cost analysis from the UK MS Survey 2005, (Tyas et al in press) which found that the cost for a similar reference case was £6,947.

Whilst both this cost model and the cost model from Tyas et al used data from the same survey, Tyas et al included a number of covariates in their model, such as educational status, not included here as they are not relevant to the decision problems concerning health care resource allocation.

Additional checks were made within the model to ensure that this reference case was implemented correctly, and additional cases (e.g. male in EDSS 6 at age 40 and male in EDSS 4 at age 50 on DMT with SPMS) were consistent with expectations, following the removal of rounding errors.

Utility

The utility model is described in section 5.8.7. These utility values were compared to those derived by Orme et al, in press, from the same UK MS Survey 2005. The values were similar, though not identical since Orme et al fitted additional coefficients for educational status, gender and an additional EDSS state (EDSS 6.5). Here we did not include gender as it is included elsewhere (the male: female ratio in the model is the same as for the UK MS Survey 2005). Educational status was also excluded, as it was not considered relevant to a treatment decision.

The analysis to estimate the disutility of relapse by EDSS state was compared to the regression coefficient for disutility by taking the average relapse disutility by state across EDSS 0 to EDSS 6 and comparing it to the regression value. The value from the regression was -0.073 per relapse and the average across the estimates by EDSS state was -0.075 per relapse.

4. Can the model predict the findings of other studies

The structure chosen has been used frequently in previous MS models and follows the structure used within the ScHARR model. (147) In order to validate the structure further, the economic model developed for this submission was reparameterised by changing key input values to reflect those of the ScHARR model. We compare the ICERs for both IFN-beta and GA compared with best

supportive care by altering the following: [7]

- unit costs and utilities from the ScHARR model were used
- the discount rate for cost was set to 6% per year
- the discount rate for benefits was set to 1.5% per year
- disability progression rates from the London Ontario dataset were applied to describe progression without disease-modifying therapy
- a fixed rate for disutility during a relapse of 0.25 per relapse
- for the first year only a disutility for 30% of patient on treatment is set to 0.05
- a withdrawal rate of 10% was applied in the first year and 3% was applied in subsequent years

Under this scenario, the marginal cost-effectiveness of IFN-beta versus best supportive care was estimated to be £57.4k per QALY gained, whilst the marginal cost-effectiveness for GA versus best supportive care was estimated to be £107.2k per QALY gained. These estimates compare well with the marginal cost-effectiveness estimates quoted by Tappenden 2001 of £42-72k per QALY for IFN-beta versus best supportive care and £98k per QALY for GA versus best supportive care.

[7] Note that the model was provided to ScHARR, who undertook this reparameterisation.

6.3 Results

6.3.1 Base-case analysis

6.3.1.1 What were the results of the base-case analysis?

The results of the base case analysis are presented in Table 83. The ICER for natalizumab compared with an active comparator in the RES subgroup is approximately £27K per QALY gained (approximately £35K compared with BSC). The equivalent result in the SOT subgroup is £44K - £45K for an active comparator and £57K for BSC.

Table 83 Results for base-case analysis over a 20-year time horizon

RES Subgroup					
Comparison	**Cost per patient (£K) (natalizumab)**	**QALYs per patient (natalizumab)**	**Cost per patient (£K) (comparator)**	**QALYs per patient (comparator)**	**Incremental cost per QALY gained (£K)**
NAT vs. IFN-beta	162.6	7.02	125.3	5.64	27.0
NAT vs. GA	162.6	7.02	115.2	5.29	27.4
NAT vs. BSC	162.6	7.02	92.9	5.02	34.9
SOT Subgroup					
Comparison	**Cost per patient (£K) (natalizumab)**	**QALYs per patient (natalizumab)**	**Cost per patient (£K) (comparator)**	**QALYs per patient (comparator)**	**Incremental cost per QALY gained (£K)**
NAT vs. IFN-beta	156.6	7.51	116.3	6.59	44.1
NAT vs. GA	156.6	7.51	103.3	6.32	45.0
NAT vs. BSC	156.6	7.51	76.4	6.10	57.0

IFN-beta = interferon beta, BSC = best supportive care, GA = glatiramer acetate, NAT = natalizumab

Health and PSS perspective, costs and benefits discounted at 3.5%, 20-year time horizon. These results are based on mean values.

The absolute gain in QALYs between natalizumab and the comparators is substantial (> 1 QALY for 5/6 decision problems). The QALY gains in the RES subgroup are 2.00, 1.73 and 1.38 for natalizumab compared with BSC, GA and IFN-beta respectively. The equivalent QALY gains in the SOT subgroup are 1.41, 1.19 and 0.92 for natalizumab compared with BSC, GA and IFN-beta respectively.

The clear effect of natalizumab on other NHS and PSS costs is shown in Table 84. Cost savings in other NHS and PSS budgets offsets a large proportion of the treatment cost of natalizumab.

Table 84: Disaggregated discounted costs per patient from the base case over a 20-year time horizon

	SOT Subgroup			RES Subgroup		
Comparison	**Treatment costs (£K)**	**Other NHS & PSS costs (£K)**	**Total costs (£K)**	**Treatment costs (£K)**	**Other NHS & PSS costs (£K)**	**Total costs (£K)**
NAT	99.3	57.3	156.6	98.6	64.0	162.6
IFN-beta	50.4	65.8	116.3	45.2	80.1	125.3
GA	31.0	72.3	103.3	27.1	88.1	115.2
BSC	0.0	76.4	76.4	0.0	92.9	92.9

IFN-beta = interferon beta, BSC = best supportive care, GA = glatiramer acetate, NAT = natalizumab

6.3.2 Subgroup analysis

6.3.2.1 What were the results of the subgroup analysis / analyses if conducted?

No additional subgroup analyses were conducted over and above the two licensed subgroups (RES and SOT).

6.3.3 Sensitivity analyses

Uncertainty is ubiquitous in all economic models. The impact of uncertainty on the estimates of incremental costs and QALYs has been assessed through a process of comprehensive sensitivity analysis.

One-/multi-way sensitivity analysis and probabilistic sensitivity analysis (PSA) have been undertaken for each of the 6 decision problems in order to elucidate the effect of key parameters on the ICER. The one-way and multi-way sensitivity analyses are presented in section 6.3.3.1 in Table 85. The PSAs are presented in section 6.3.3.2 as cost-effectiveness acceptability curves (CEAC) in Figure 16 to Figure 26. Scatter diagrams that plot the results of the PSA simulation on the cost-effectiveness plane are also shown.

6.3.3.1 What were the main findings of the univariate sensitivity analyses?

The results of the one-way and multi-way sensitivity analysis are reported in Table 85 as change in £'000 per QALY. The results for all 6 decision problems appear in 6 columns to the right of the table and are represented as the difference from the base case. In the discussion of the sensitivity analysis we present changes to the ICER in italics as *-£XX* for favourable changes and *+£XX* for unfavourable changes. Absolute results are presented in standard font. For example, the base case for natalizumab compared with IFN-beta in RES is £27 000; taking a societal perspective for the analysis would change the base case cost-effectiveness estimate by *-£18 800*, to £8200 per QALY.

The parameters that have the greatest impact upon the ICER are the baseline characteristics of the model population, the natural history, the efficacy of the disease-modifying therapies, cost, the health economic perspective chosen and time horizon over which costs and outcomes are evaluated. Safety and tolerability, discount rate and utility parameters have only a marginal effect on the ICER. There is a greater degree of overall certainty surrounding the costs and effects of natalizumab in the RES subgroup economic evaluation than in the evaluation of the SOT subgroup.

The sensitivity analysis of baseline characteristics indicates that natalizumab appears to be more cost-effective compared with all comparators in all decision problems in younger patients, although the effect of age on the ICER is marginal for patients up to 46 years old. The cost-effectiveness does not appear to be altered by the initial severity of disability of patients in the RES subgroup although the influence of disability is slightly more pronounced in the SOT subgroup.

Safety and tolerability parameters have little impact on the ICERs for all comparisons in all decision problems.

The uncertainty in the natural history of HARRMS (or RRMS) has to our knowledge never been explored in depth in previous economic models. Varying censoring assumptions in the MSM had a marginal effect on the ICER of between *-£1.6K* and *+1.9K* (see scenarios 4.4 to 4.7). Treating a broad RRMS population (which is outside the license for natalizumab), applying only disability progression rates from the London Ontario dataset, results in a large unfavourable impact on the cost-effectiveness, confirming that natalizumab is most cost-effective within its licensed indications (see scenario 4.8).

The uncertainty in the effect of natalizumab and the comparators on relapse rate has a marginal effect on the ICERs (see scenarios 5.4a to 5.5b and 5.8a to 5.9b), although the impact of uncertainty in disability progression is more pronounced.

Discounting both costs and benefits under previously specified rates (i.e. costs at 6% and benefits at 1.5%) has a large favourable effect on the ICER (e.g. scenario 6.3 demonstrates that the ICER would be less than £25K for all RES subgroup decision problems had the previous rates been used, and as low as £18.8K for the comparison with IFN-beta).

Varying the assumptions related to utilities and disutilities had little effect on any ICER, except for uncertainty regarding caregiver disutility, which changed the ICER by between *-£2.8K* and *+£6.5K* per QALY.

Uncertainties in cost estimates have an impact on the ICER of between *-£14.5K* and *+£13.9K* in the SOT subgroup decision problems. The effect is less pronounced in the RES subgroup decision problems (*-£9.4K* to *+£9.5K*).

The chosen perspective for the economic evaluation has a considerable impact on the ICER, with broader governmental and societal perspectives changing the relative cost-effectiveness of natalizumab by as much as *-£8.1K* and *-£23.5K* respectively.

The ICERs are also sensitive to the time horizon chosen, with large improvements in the relative cost-effectiveness noted for natalizumab compared with all comparators as the horizon is extended. If costs and benefits were extended to 30 years for example, the ICER for natalizumab in the RES subgroup would reduce to between £20.6K per QALY (compared with GA) and £26.2K per QALY (compared with BSC). If the time horizon was extended to 50 years, as recommended by Richards et al, (29) the ICERs would become as low as £19.0K per QALY for the comparison with GA for the RES subgroup and £29.4K for the same comparison in the SOT subgroup.

Table 85 Results of the univariate sensitivity analysis

Scenario		Parameter	RES BSC (£K)	RES IFN-beta (£K)	RES GA (£K)	SOT BSC (£K)	SOT IFN-beta (£K)	SOT GA (£K)
		Base case	**34.9**	**27.0**	**27.4**	**57.0**	**44.1**	**45.0**
Baseline Characteristics	1.1	Mean age at baseline = -10 years	-0.9	-0.6	-0.7	-1.0	-0.6	-0.8
	1.2	Mean age at baseline = +10 years	2.1	1.4	1.8	2.6	1.4	2.0
	1.3	Mean age at baseline = +20 years	7.5	4.8	6.1	9.3	4.9	7.1
	2.1	EDSS at baseline = 0	1.7	0.8	1.0	3.0	1.3	1.7
	2.2	EDSS at baseline = 1	1.5	0.8	1.0	2.6	1.2	1.6
	2.3	EDSS at baseline = 2	2.8	1.9	2.0	3.7	2.1	2.6
	2.4	EDSS at baseline = 3	-0.2	0.0	0.1	-1.2	-0.5	-0.5
	2.5	EDSS at baseline = 4	-4.9	-3.3	-3.6	-7.2	-4.1	-4.9
Safety & Tolerability	3.1	Natalizumab withdrawal rate = 50%	-0.8	-3.3	-2.4	-1.3	-5.9	-4.1
	3.2	Natalizumab withdrawal rate = -50%	0.9	2.9	2.3	1.6	5.0	3.9
	3.3	IFN-beta/GA withdrawal rate = +50%	0.0	1.4	0.9	0.0	3.0	1.8
	3.4	IFN-beta/GA withdrawal rate = -50%	0.0	-1.9	-1.1	0.0	-4.1	-2.2
	3.5	PML effect = worst case scenario	0.0	-0.1	-0.1	0.4	0.3	0.3
	3.6	NABs = 100% people tested	0.2	0.3	0.3	0.3	0.5	0.4
Natural History	4.1	Relapse rate	0.3	0.2	0.2	0.0	0.0	0.0
	4.2	Relapse duration +50%	-0.3	-0.2	-0.2	-0.3	-0.3	-0.2
	4.3	Relapse duration –50%	0.1	0.1	0.1	0.1	0.1	0.1
	4.4	Progression data from AFFIRM	1.1	0.7	0.8	1.5	0.8	1.1
	4.5	Progression data from AFFIRM	1.7	1.1	1.2	1.5	0.8	1.0
	4.6	Progression data from AFFIRM	1.9	1.2	1.4	1.0	0.6	0.7
	4.7	Progression data from AFFIRM	-1.6	-1.4	-1.3	1.5	0.4	1.0
	4.8	Progression data from London Ontario data *	34.6	16.6	24.3	28.3	12.1	19.6
	4.9	No effect of tx. on transition from RRMS to SPMS	4.2	0.9	1.9	13.3	3.9	7.7
	4.10	Full effect of tx. on transition from RRMS to SPMS	-3.4	-0.8	-1.6	-9.6	-3.6	-6.0
Efficacy	5.1	Disease progression 12 week definition **	8.1	9.9	7.4	17.8	25.2	17.4
	5.2a	NAT effectiveness (progression) lower SE (SOT)	-	-	-	10.8	14.0	10.3
	5.2b	NAT effectiveness (progression) upper SE (SOT)	-	-	-	-7.1	-7.6	-6.3
	5.3a	NAT effectiveness (progression) lower SE (RES)	14.2	19.2	13.4	-	-	-
	5.3b	NAT effectiveness (progression) upper SE (RES)	-5.7	-5.6	-4.8	-	-	-
	5.4a	NAT effectiveness (relapse) lower SE (SOT)	-	-	-	0.2	0.2	0.2
	5.4b	NAT effectiveness (relapse) upper SE (SOT)	-	-	-	-0.2	-0.2	-0.1
	5.5a	NAT effectiveness (relapse) lower SE (RES)	0.1	0.1	0.1	-	-	-
	5.5b	NAT effectiveness (relapse) upper SE (RES)	-0.1	-0.1	-0.1	-	-	-
	5.6a	IFN-beta effectiveness (progression) lower SE	-	-5.1	-	-	-9.5	-
	5.6b	IFN-beta effectiveness (progression) upper SE	-	6.9	-	-	14.6	-
	5.7a	GA effectiveness (progression) lower SE	-	-	-5.5	-	-	-10.0
	5.7b	GA effectiveness (progression) upper SE	-	-	23.0	-	-	53.8
	5.8a	IFN-beta effectiveness (relapse) lower SE	-	-0.1	-	-	-0.1	-
	5.8b	IFN-beta effectiveness (relapse) upper SE	-	0.1	-	-	0.1	-
	5.9a	GA effectiveness (relapse) lower SE	-	-	-0.2	-	-	-0.3
	5.9b	GA effectiveness (relapse) upper SE	-	-	0.2	-	-	0.2
	5.10	GA progression including Bornstien 1987	-	-	14.1	-	-	30.3
Disc	6.1	Costs = 6%	-3.7	-3.4	-3.1	-7.1	-6.2	-5.9
	6.2	Benefits = 1.5%	-7.5	-5.5	-5.9	-12.6	-8.7	-9.8
	6.3	Costs = 6% and benefits = 1.5%	-10.4	-8.2	-8.3	-18.1	-13.6	-14.4
Utility	7.1a	Utility by EDSS – Upper 95% limit	8.6	4.8	6.1	15.6	9.2	13.6
	7.1b	Utility by EDSS – Lower 95% limit	-5.6	-4.0	-3.9	-9.0	-6.1	-7.3
	7.2	No variation in relapse effect by EDSS	-0.3	-0.2	-0.2	-0.3	-0.1	-0.2
	7.3a	Disutility of adverse events – Upper 95% limit	0.3	2.4	0.2	0.3	6.9	0.9
	7.3b	Disutility of adverse events – Lower 95% limit	-0.7	-3.3	-1.2	-1.6	-6.9	-3.6
	7.4	Literature derived relapse disutility	-0.8	-0.6	-0.5	-0.8	-0.6	-0.6
	7.5	Disutility of AEs for natalizumab = half	0.0	0.0	0.0	0.0	0.0	0.0
	7.6	Disutility of AEs for natalizumab = double	0.0	0.0	0.0	0.0	0.1	0.0
	7.7	Disutility of caregivers = +50%	-1.8	-1.1	-1.4	-2.8	-1.5	-2.1
	7.8	Disutility of caregivers = + 0	4.2	2.6	3.2	6.5	3.3	4.8
Cost	8.1a	Costs of resources and IFN-beta/GA – Upper 95% limit	2.6	9.6	9.5	2.7	12.7	13.9
	8.1b	Costs of resources and IFN-beta/GA – Lower 95% limit	-2.4	-8.3	-9.4	-3.4	-12.0	-14.5
Prsp	9.1	Societal perspective	-20.3	-18.8	-21.0	-22.7	-19.2	-23.5
	9.2	Government costs perspective	-7.8	-6.5	-7.6	-8.1	-5.9	-7.8
Time	10.1	10 years	41.5	21.3	30.6	67.3	26.5	46.7
	10.2	30 years	-8.7	-5.9	-6.8	-15.7	-9.3	-12.0
	10.3	40 years	-10.6	-7.4	-8.3	-19.8	-12.1	-15.1
	10.4	50 years	-10.8	-7.5	-8.4	-20.4	-12.6	-15.6

* Patients in EDSS 0 added to EDSS 1 as London Ontario dataset does not include progression to or

from EDSS 0, ** Only efficacy for natalizumab changed - = no sensitivity analysis possible, AE = adverse event, IFN-beta = interferon beta, BSC = best supportive care, GA = glatiramer acetate, NAT = natalizumab, NAB = Neutralising Antibody, PML = Progressive Multifocal Leukoencephalopathy, RES = rapidly evolving severe RRMS, RRMS = relapsing remitting multiple sclerosis, SOT = sub optimal treatment RRMS.

We also present two scenarios that do not appear in Table 85 to further investigate the uncertainty in the SOT subgroup.

Firstly, we explore the uncertainty in the rate of disability progression in the SOT subgroup by applying a more rapid rate of disability progression, which is in line with the estimated natural history of the RES subgroup. If this assumption is correct, it would be plausible that the underlying effect of natalizumab on disability progression would be in line with the efficacy observed in the RES subgroup.

Secondly, we explore alternative efficacy assumptions for IFN-beta and GA in the SOT subgroup, since there is very limited evidence for the effect of either comparator in this subgroup.

Uncertainly in progression rate and natalizumab efficacy in the SOT Subgroup

In section 6.2.11.1 we suggested that it is plausible that the SOT subgroup merely represent the RES subgroup at a later point in time, after they have experienced suboptimal treatment with IFN-beta or GA. Table 86 presents the effect of altering the efficacy and disability progression rates to those of the RES subgroup and assuming that the population is five years older (at 41 years). Altering individual assumptions results in a more favourable ICER. Recalculation of the ICER applying the RES disability progression rates and efficacy to the SOT population gives cost effectiveness values of £27.0k, £27.4k, and £34.9k per QALY for comparison with IFN-beta, GA and BSC respectively.

Table 86 Exploration of the uncertainty or progression and efficacy rates in the SOT subgroup

	RES subgroup efficacy		RES subgroup progression rates		RES subgroup efficacy + progression rates	
	ICER (£k)	Change from base case (£k)	ICER (£k)	Change from base case (£k)	ICER (£k)	Change from base case (£k)
IFN-beta	33.9	-10.7	36.8	-7.8	27.5	-17.1
GA	36.7	-9.0	35.1	-10.6	28.0	-17.7

IFN-beta = Interferon beta, GA = glatiramer acetate; base-case refers to base-case with initial average age of cohort is greater by 5 years (i.e. base case for IFN-beta = £44.6K; for GA = £45.7k)

Effect of alternative efficacy assumptions for comparators

The effect of increased relative risks for disability progression for IFN-beta and GA in this subgroup is explored in Table 87. A reduced efficacy assumption was not reported in the base case for the SOT subgroup, but is plausible based on the findings from the QUASIMS study. (75) Reducing the effect on disability progression of each active comparator changes the ICER by up to *-£21.0K*.

Table 87 Impact of reduction in efficacy of IFN-beta and GA on the ICER

	Relative risk of progression	ICER £k	Change from base case (£k)
IFN-beta	0.7 *	44.0	-
	0.8	33.7	-10.3
	0.9	27.4	-16.7
	1.0	23.0	-21.0
GA	0.88 *	45.0	-
	0.9	43.0	-2.0
	1.0	35.0	-10.8

* base case. IFN-beta = interferon beta, GA = glatiramer acetate.

6.3.3.2 What were the main findings of the PSA?

The results from the PSA analysis are presented in this sub-section. The results shown are the cost-effectiveness (CE) planes and cost-effectiveness acceptability curves (CEAC) for the 6 decision problems.

- RES subgroup comparisons
  - Natalizumab vs. IFN-beta (page 159)
  - Natalizumab vs. GA (page 160)
  - Natalizumab vs. BSC (page 161)
- SOT subgroup comparisons
  - Natalizumab vs. IFN-beta (page 162)
  - Natalizumab vs. GA (page 163)
  - Natalizumab vs. BSC (page 164)

Table 88 contains summary of the results from the CEACs generated, giving the probability of cost-effectiveness at different willingness-to-pay thresholds for the decision problems using a NHS & PSS perspective. Unlike any other medical technology in England and Wales, an acceptable cost-effectiveness threshold has been established for disease modifying treatments (DMT) for multiple sclerosis (MS) of £36 000 per quality adjusted life year (QALY) gained. (51) Table 88 includes an estimate of the probability of cost-effectiveness at this threshold and also at thresholds of £30 000 and £40 000.

Table 88: Probability of acceptability at different threshold values for the six baseline scenarios (NHS & PSS perspective)

Comparison		Willingness to pay threshold		
		£30,000	**£36,000**	**£40,000**
RES subgroup	BSC	25%	52%	65%
	IFN-beta	57%	70%	75%
	GA	52%	65%	72%
SOT subgroup	BSC	0%	1%	3%
	IFN-beta	17%	32%	41%
	GA	14%	28%	38%

IFN-beta = interferon beta, BSC = best supportive care, GA = glatiramer acetate, RES = rapidly evolving severe subgroup, SOT = sub optimally treated subgroup

We also present summaries of the probability of acceptability using societal and governmental perspectives in Table 89 and Table 90. No CEACs or CE planes are shown for these perspectives.

Table 89: Probability of acceptability at different threshold values for the six baseline scenarios (societal perspective)

Comparison		Willingness to pay threshold		
		£30,000	£36,000	£40,000
RES subgroup	BSC	84%	88%	90%
	IFN-beta	81%	84%	85%
	GA	82%	86%	87%
SOT subgroup	BSC	34%	56%	70%
	IFN-beta	62%	69%	75%
	GA	60%	66%	70%

IFN-beta = interferon beta, BSC = best supportive care, GA = glatiramer acetate, RES = rapidly evolving severe subgroup, SOT = sub optimally treated subgroup

There is greater than an 80% probability of natalizumab being cost-effective in all RES subgroup decision problems, if society is willing to pay £30 000 per QALY gained, generated by the PSA from a societal perspective.

Results for the SOT subgroup societal perspective analysis also indicate a considerably greater probability of of natalizumab being cost-effective compared with a health and PSS perspective, if society is willing to pay £30 000 per QALY gained.

Table 90: Probability of acceptability at different threshold values for the six baseline scenarios (governmental perspective)

Comparison		Willingness to pay threshold		
		£30,000	£36,000	£40,000
RES subgroup	BSC	58%	75%	82%
	IFN-beta	69%	76%	80%
	GA	69%	77%	80%
SOT subgroup	BSC	0%	7%	19%
	IFN-beta	31%	47%	55%
	GA	32%	46%	52%

IFN-beta = interferon beta, BSC = best supportive care, GA = glatiramer acetate, RES = rapidly evolving severe subgroup, SOT = sub optimally treated subgroup

The PSA results from a governmental perspective follow a similar trend. A probability in excess of 58% of natalizumab being cost-effective is noted in all RES subgroup decision problems if society is willing to pay £30 000 per QALY gained.

Figure 15 C-E plane for natalizumab vs. IFN-beta for RES subgroup

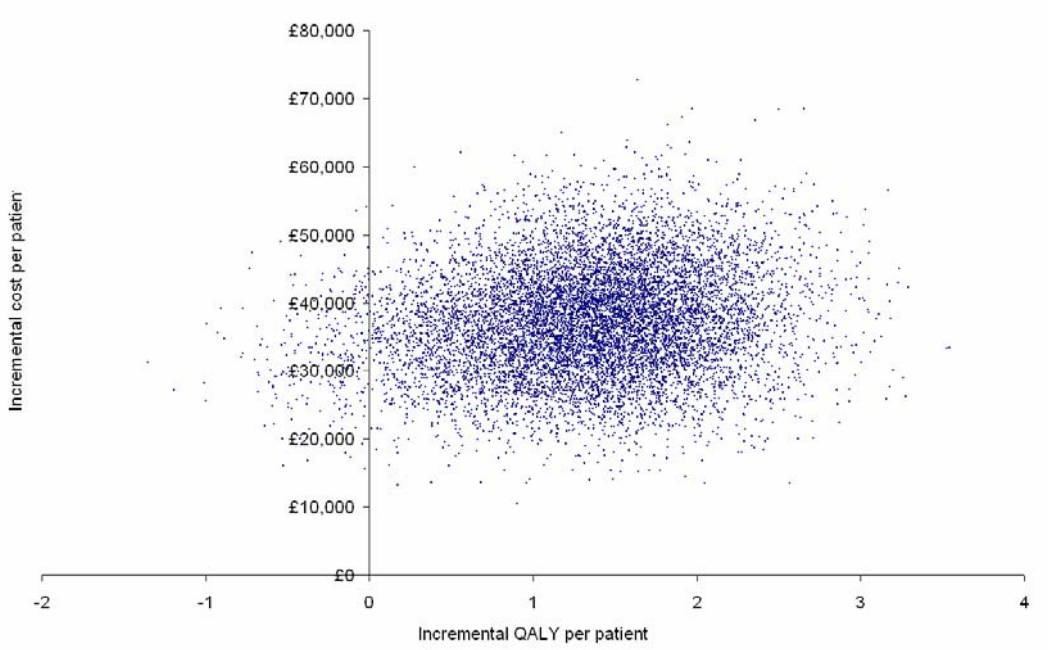


Figure 16 CEAC for natalizumab vs. IFN-beta for RES subgroup

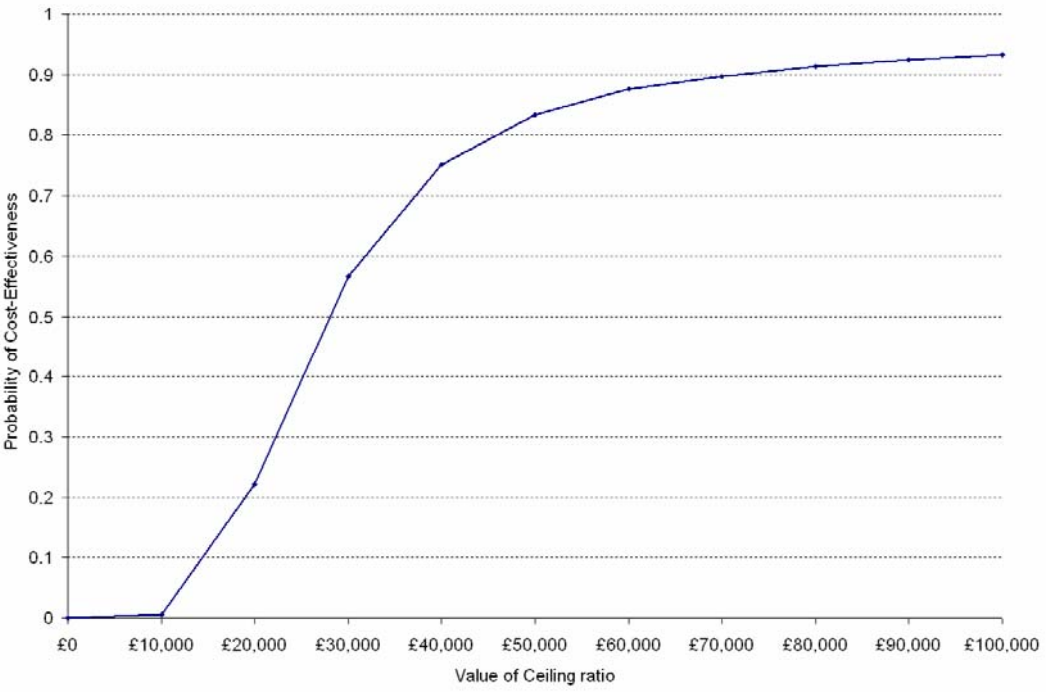


Figure 17 C-E plane for natalizumab vs. GA for RES subgroup

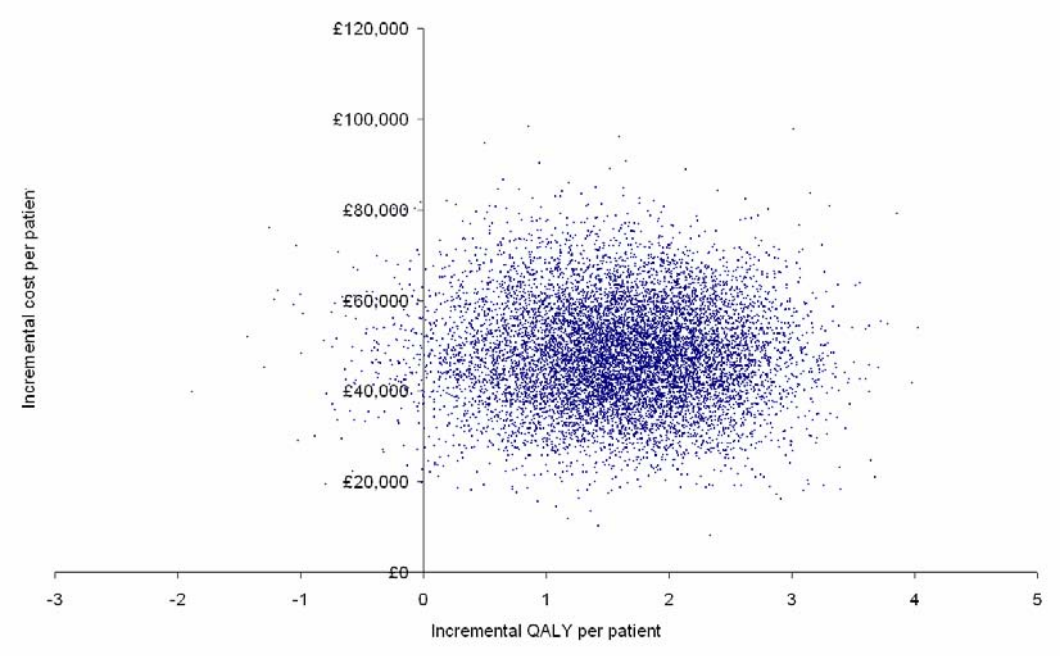


Figure 18 CEAC for natalizumab vs. GA for RES subgroup

Figure 19 C-E plane for natalizumab vs. BSC for RES subgroup

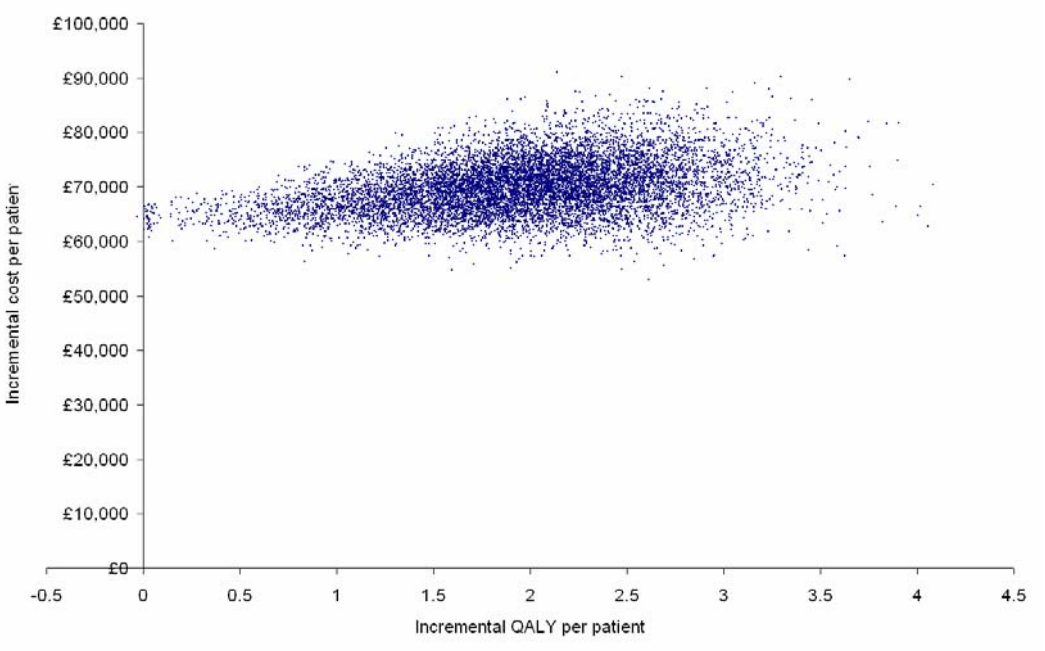


Figure 20 CEAC for natalizumab vs. BSC for RES subgroup

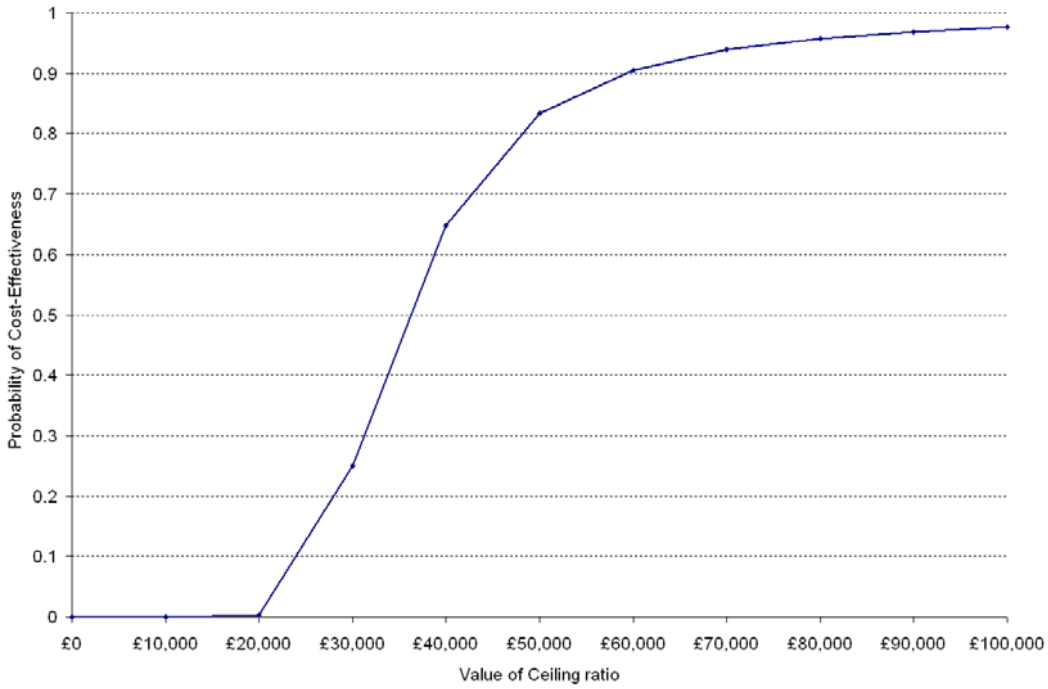


Figure 21 C-E plane for natalizumab vs. IFN-beta for SOT subgroup

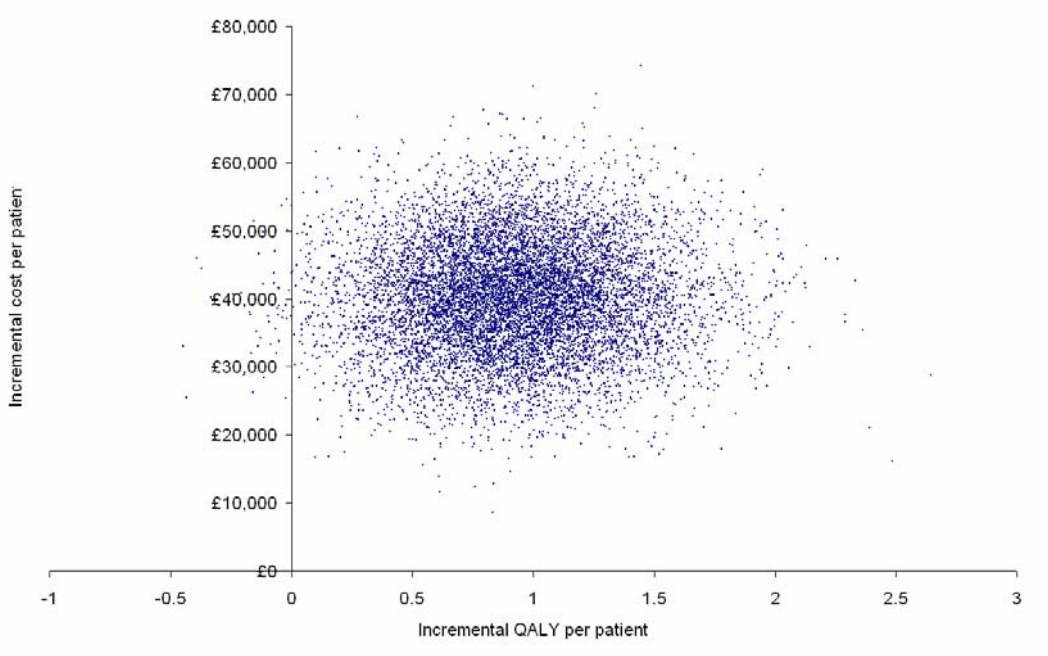


Figure 22 CEAC for natalizumab vs. IFN-beta for SOT subgroup

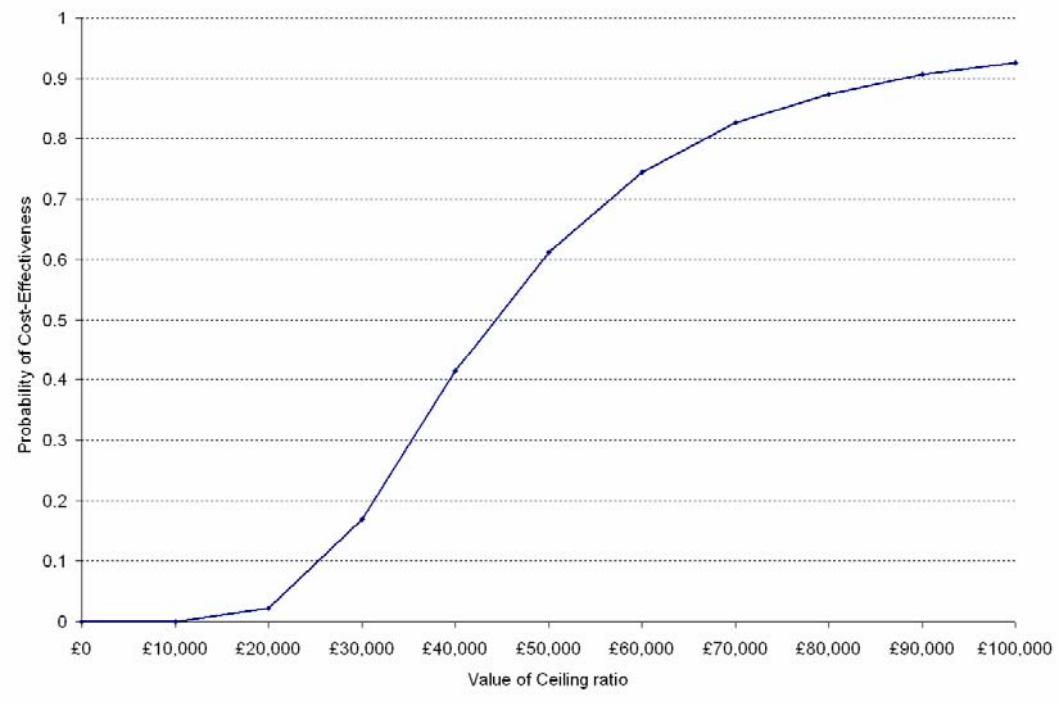


Figure 23 C-E plane for natalizumab vs. GA for SOT subgroup

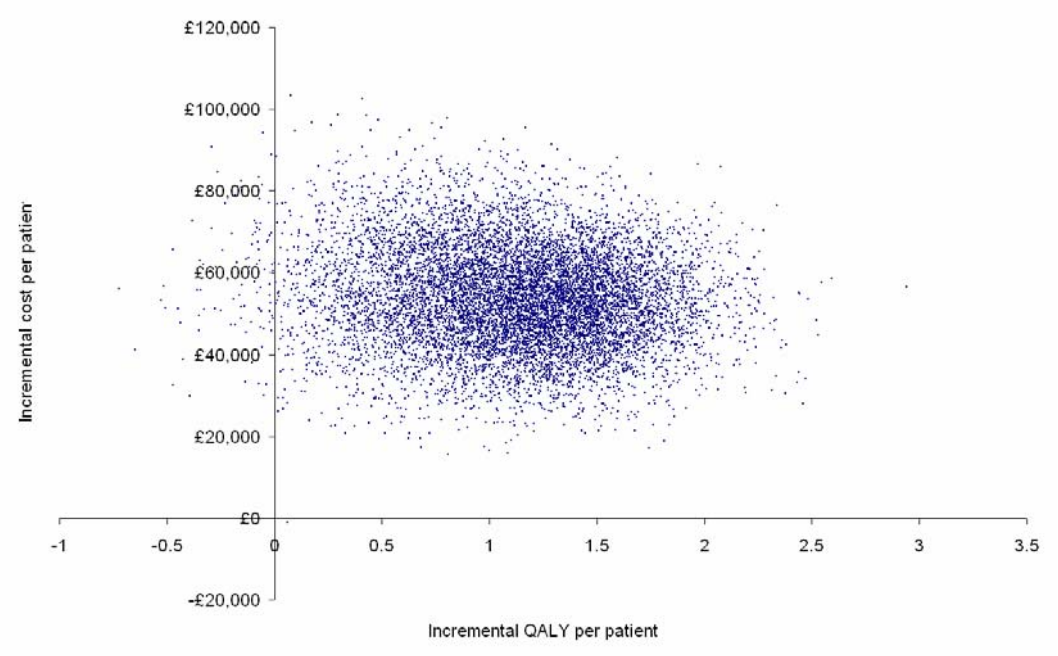


Figure 24 CEAC for natalizumab vs. GA for SOT subgroup

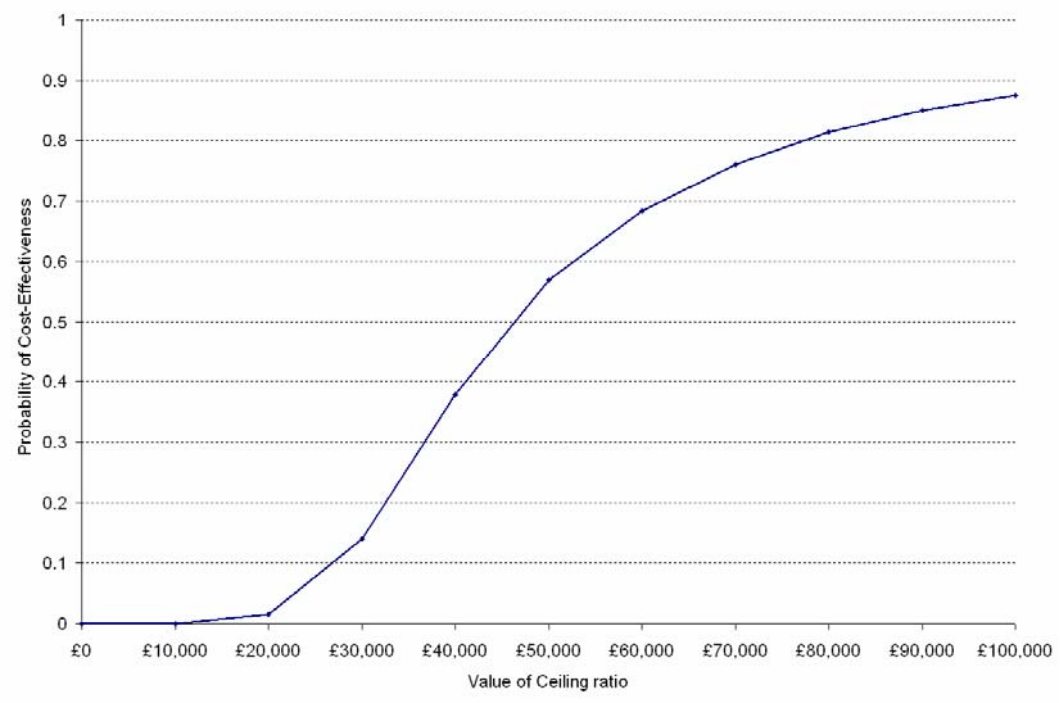


Figure 25 C-E plane for natalizumab vs. BSC for SOT subgroup

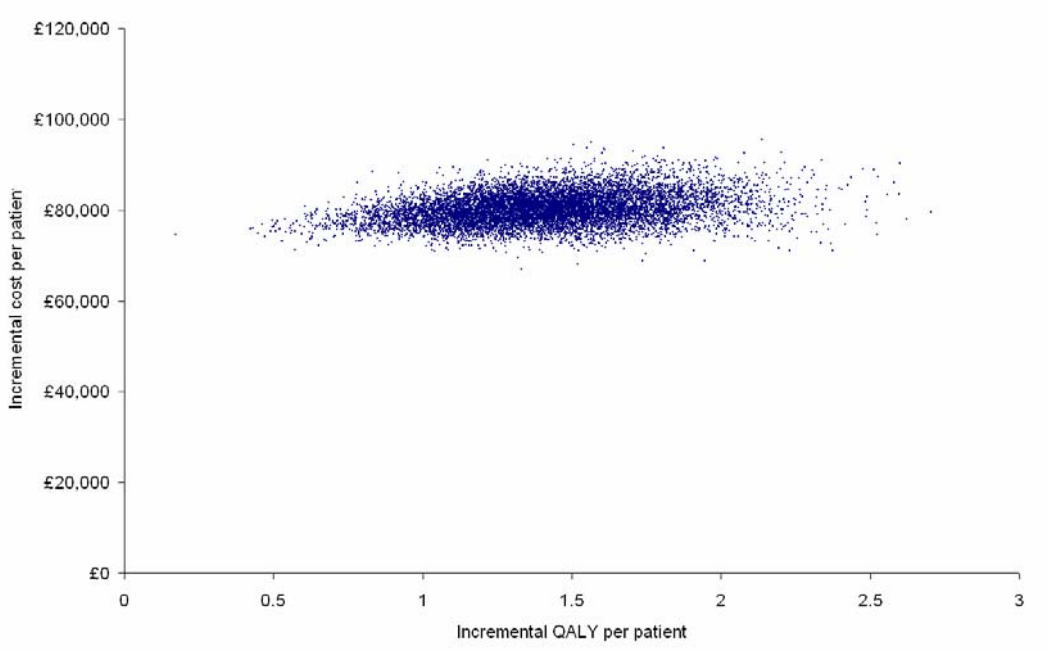
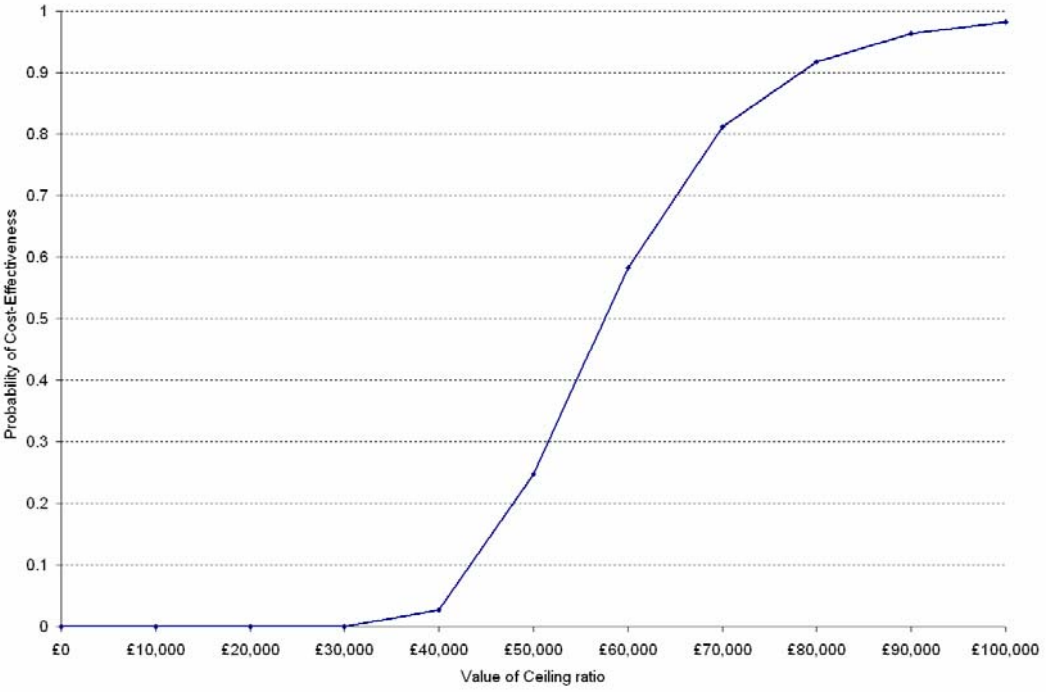


Figure 26 CEAC for natalizumab vs. BSC for SOT subgroup



6.3.4 Interpretation of economic evidence

6.3.4.1 Are the results from this economic evaluation consistent with the published economic literature? If not, why do the results from this evaluation differ, and why should the results in the submission be given more credence than those in the published literature?

To our knowledge, no previous economic evaluations within the HARRMS population have been published, which makes it impossible to directly compare the results of this evaluation with an alternative analysis. However, we concluded in the sub-section entitled, '4. Can the model predict the findings of other studies', on page 150 that a re-parameterised model was able to generate similar results to the ScHARR model previously commissioned by NICE:

> The ICERs we generate for IFN-beta of £57.4k per QALY and for GA of £107.2k per QALY compare well with the values quoted by Tappenden 2001 of £42-72k per QALY for IFN-beta and £98k per QALY for GA (vs. best supportive care).

This finding gives additional credence to the results for the HARRMS evaluations presented in this submission.

6.3.4.2 Is the economic evaluation relevant to all groups of patients who could potentially use the technology?

The evaluation is relevant to the licensed RES and SOT subgroups. The baseline characteristics of the subgroups matches the baseline characteristics of the AFFIRM study. Resource and utility data were sourced from people with MS in the UK.

6.3.4.3 What are the main strengths and weaknesses of the evaluation? How might these affect the interpretation of the results?

Strengths: The main strength of the economic evaluation is that it has addressed all the flaws identified in previous models submitted to NICE (see section 6.2.11.3). Additional strengths of the model that should increase the confidence in the results are:

- Rich resource and utility data was collected from the largest resource and utility survey of people with MS in the UK (UK MS Survey 2005)
- Specific data from the AFFIRM study is relevant to the RES subgroup
- Internal and external validity was established with the assistance of recognised experts in the field and acknowledged by the SMC to be high
- A new MSM demonstrated that data from the AFFIRM study was superior to the London Ontario dataset at predicting the distribution of patients at endpoint
- A novel SUR approach to the cost analysis enabled investigation into different cost perspectives and interaction between coefficients
- The variation in relapse disutility by EDSS score was explored

The model has addressed all the flaws identified in previous models submitted to NICE (see 6.2.11.3).

Weaknesses: We note that there are some weaknesses in the data used to parameterise the model. These are described in section 6.3.4.4 below.

6.3.4.4 What further analyses could be undertaken to enhance the robustness/completeness of the results?

We describe additional analyses that enhance the model under four sub-sections below. All additional analyses rely on the collection of additional input data, not substantive changes to the model.

Natural history

There is a paucity of longitudinal natural history data in a HARRMS population despite clear evidence that disability progresses more rapidly in people with highly active disease (see section 5.8.1). The MSM analysis conducted in this submission has provided valuable insight into the more rapid rate of disability progression in people with highly active disease. A re-analysis of point estimates and associated uncertainty of existing natural history datasets may provide further confirmation of the findings of our analysis.

We present a hypothesis in this submission that the SOT subgroup may be the same as the RES subgroup at a later point in time, after treatment with IFN-beta or GA has become sub optimal. Assessment of whether the SOT subgroup is similar to RES subgroup would provide justification for a more favourable ICER in SOT comparisons.

The model used MS-specific mortality data to adjust the SMR, however, this data was sourced from a general MS population and not a highly active population. An understanding of the SMR in a RES/SOT subgroup would further improve the certainty in the ICER.

Clinical benefits/disbenefits

The available efficacy data for IFN-beta and GA was representative of a RRMS population, not a HARRMS population. The effect of IFN-beta and GA in a HARRMS population is not known, although the results from the QUASIMS study shows that there is no benefit to be realised from switching from one IFN-beta to another. (75) A RCT of IFN-beta and GA in people with HARRMS is necessary to confirm the effect in this population.

A head to head study between natalizumab and the comparators would be the best source of data on the relative effects of the treatments. This study would confirm the validity of our assumptions concerning the relative effect sizes between treatments.

Long-term efficacy data from the existing risk sharing scheme or an alternative source would enhance the evidence of a long-term treatment effect of DMTs.

Utility/disutility

EQ-5D measurement in a treated population would provide superior evidence on the effect of treatment on the utility of someone with HARRMS. Currently we assess utility gain in a treated cohort indirectly through changes in disability progression and relapse rate. Measuring the utility in this population directly would capture the

full impact of treatment.

Adverse event disutility estimates could be improved by conducting a short-term study. These would enhance the estimates we make in this model, although they are not likely to have a tangible effect on the ICERs reported and these parameters are not a key source of uncertainty surrounding the incremental costs and health outcomes of natalizumab.

Carer disutility was based on an estimate taken from a study of Alzheimer's disease. A study that elucidated this estimate would further enhance the model.

The duration and utility profile of a relapse are not fully described in the literature and a study into these variables would enhance the model. These data would allow for improved estimates in the disutility associated with a relapse.

Costs

A governmental perspective will have more resonance with taxpayers than the perspective of the NHS and PSS, as it includes all relevant costs to the taxpayer. Few taxpayers distinguish between inter-governmental budgets when they pay tax, which means that the choice of a NHS and PSS underestimates cost to the taxpayer and the cost-effectiveness of treatment with natalizumab.

A cost study into administration and monitoring of natalizumab would further improve our understanding of the direct costs of natalizumab. This could be combined with an assessment of alternative clinic structures and updated treatment algorithms.

7 Assessment of factors relevant to the NHS and other parties

Natalizumab uptake at forecast levels represents a modest budget impact in England and Wales (maximum forecast total incremental discounted cost in year 5 of £15.5 million).

Rapidly evolving severe:

The budget impact in the rapidly evolving severe subgroup is forecast to be £0.8 million in year 1, rising to £4.4 million in year 5.

Sub optimally treated:

The budget impact in the sub optimally treated subgroup is forecast to be £0.3 million in year 1, rising to £11.1 million in year 5.

Large cost offsets of approximately half the acquisition cost of natalizumab may be realised due to a reduction in use in interferon beta and glatiramer acetate.

The budget impact model does not include costs associated with disability progression and is likely overestimate the incremental cost of natalizumab introduction.

The forecast is based on Biogen Idec estimates of market penetration.

7.1 What is the estimated annual budget impact for the NHS in England and Wales?

The net resource implications for England and Wales in each of the first five years following the introduction of natalizumab was derived using estimates for the total direct costs of natalizumab treatment. These were calculated on the assumption that the rapidly evolving severe (RES) multiple sclerosis (MS) patient subgroup and the sub optimally treated (SOT) subgroup received one of the following:

- estimated market rates of interferon beta (IFN-beta) and glatiramer acetate (GA)
- best supportive care (BSC)

The total annual costs for years 1 to 5 are shown in Table 91. Note that cost offsets associated with delays in disability progression are not included in these estimations so the incremental budget impact presented is likely to be an overestimate.

The discounted *incremental* cost associated with the introduction of natalizumab (Table 96) based on assumptions described in section 7.2 is:

- For RES subgroup: £0.77 million in year 1 rising to £4.43 million in year 5
- For SOT subgroup: £0.32 million in year 1 rising to £11.05 million in year 5

Table 91: Summary of the incremental resource implications based on the introduction of natalizumab from year 1 to year 5 for RES and SOT subgroups

Patient subgroup	Treatment	Total cost per year (million £s)				
		Year 1	Year 2	Year 3	Year 4	Year 5
RES MS	Incremental cost of natalizumab plus administration and AE costs compared with current DMTs *	0.77	1.85	2.68	3.61	4.43
	Incremental price of natalizumab compared with current DMTs *	0.72	1.75	2.53	3.41	4.18
SOT MS	Incremental cost of natalizumab plus administration and AE costs compared with current DMTs *	0.32	1.50	3.71	6.93	11.05
	Incremental price of natalizumab compared with current DMTs *	0.30	1.41	3.50	6.54	10.43

* Weighted average DMT cost based on estimated market shares. Costs discounted at 3.5%. AE = adverse event, BSC = best supportive care, DMT = disease modifying treatment, MS = multiple sclerosis, RES = rapidly evolving severe, SOT = sub optimally treated

The discounted *absolute* cost of natalizumab is reported in Table 92 below. The total cost of natalizumab plus associated administration and adverse event (AE) costs is estimated to be:

- For RES subgroup: 1.64 million in year 1 rising to £9.43 million in year 5
- For SOT subgroup: £0.68 million in year 1 rising to £23.53 million in year 5

Table 92: Summary of the absolute resource implications based on the introduction of natalizumab from year 1 to year 5 for RES and SOT subgroups

Patient subgroup	Treatment	Total cost per year (million £s)				
		Year 1	Year 2	Year 3	Year 4	Year 5
RES MS	Absolute cost of natalizumab plus administration and AE costs	1.64	3.94	5.70	7.70	9.43
	Absolute cost of natalizumab	1.53	3.68	5.32	7.18	8.79
SOT MS	Absolute cost of natalizumab plus administration and AE costs	0.68	3.19	7.90	14.77	23.53
	Absolute cost of natalizumab	0.63	2.98	7.37	13.78	21.95

Costs discounted at 3.5%. AE = adverse event, MS = multiple sclerosis, RES = rapidly evolving severe, SOT = sub optimally treated

Direct drug cost offsets realised by natalizumab uptake are reported in Table 93. Approximately half the cost of natalizumab is offset through a reduction in the use of IFN-beta and GA.

Table 93: Summary of the cost savings from patients no longer receiving IFN-beta and GA based on the introduction of natalizumab

Patient subgroup	Treatment	Total cost per year (million £s)				
		Year 1	Year 2	Year 3	Year 4	Year 5
RES MS	Costs of current DMTs offset by using natalizumab	0.87	2.09	3.02	4.08	5.00
SOT MS	Costs of current DMTs offset by using natalizumab	0.36	1.69	4.19	7.83	12.48

Costs discounted at 3.5%. AE = adverse event, MS = multiple sclerosis, RES = rapidly evolving severe, SOT = sub optimally treated

7.2 What number of patients were assumed to be eligible? How was this figure derived?

The sections below describe the underlying assumptions and their application in derivation of the estimates of total eligible population for natalizumab (see Table 94).

The eligible patient population comprises RES and SOT patients. Derivation of the number of patients in each of these groups is described in Table 94 and separately below.

The RES and SOT patients are a subgroup of the RRMS patients eligible for treatment with the existing disease modifying treatments (DMTs). Health Service Circular 2002/04 estimated that the prevalence of patients eligible for treatment with an existing DMT under the criteria set out by the Association of British Neurologists (ABN) is between 7500 and 9000. (50;51) We have used the upper limit of 9000 in our calculations. This figure comprises RRMS patients and relapsing SPMS patients. However, SPMS patients are not eligible for natalizumab treatment within the terms of the product license.

Data from the Risk Sharing Scheme for IFN-beta and GA shows that approximately 14% of patients initiated on a DMT have SPMS. (172) Hence, the total number of RRMS patients receiving a DMT is calculated as 86% of 9000, which equates to 7740 patients.

The derivation of the estimated number RES and SOT patients eligible for natalizumab treatment is shown below.

RES Patients: Data from the AFFIRM study show that 22.2% of RRMS patients eligible for treatment with a current DMT are likely fall within the definition of RES. The total estimated number of RES patients (prevalent RES patients) is therefore 1719 (0.222 × 7740).

SOT Patients: Data from a meta analysis of IFN-beta products was used to derive an estimate of the proportion of prevalent DMT patients that relapse each year. (73) This estimate is 27.53%. The number of new (incident) SOT patients eligible for natalizumab therapy each year is therefore calculated as 2131 patients by multiplying the proportion of RRMS patients that relapse whilst on DMTs each year by the total number of RRMS patients receiving a DMT (27.53% × 7740 = 2131).

The calculation of SOT patients eligible to receive natalizumab each year is complex because, unless SOT market penetration is 100%, there will be a backlog of untreated incident patients from prior years. Hence the total number of SOT patients potentially eligible for natalizumab treatment (prevalent SOT patients) in any year is the sum of the eligible 'backlog' patients and the incident SOT patients arising in that year.

However, these 'backlog' patients only remain eligible for treatment if they have experienced a relapse in the prior year.

Data from patients treated with IFN-beta monotherapy in the SENTINEL trial showed that 51% of patients remained relapse free at the one year primary analysis point. (3) Hence it is assumed that 51% of 'backlog' patients are no longer eligible for treatment in any given year.

Table 94 Estimates of MS patients in England and Wales in year 2006

Ref.	Parameter	Estimate	Source
	Total HARRMS population		
a	Number of MS patients eligible for treatment with DMT under ABN guidelines	9000	HSC 2002/004 (upper estimate) (51)
b	Proportion of these with SPMS	14%	Palace et al (172)
c	Total number of SPMS patients eligible for DMT	1260	Calculated from estimate of proportion of patients in this state applied to estimate of total number of patients (a × b)
d	Total number of RRMS patients eligible for DMT	7740	Calculated from estimate of proportion of patients in this state applied to estimate of total number of patients eligible for treatment with a DMT (a - c)
e	Market share of IFN-beta	89%	(data on file)
f	Market share of GA	11%	(data on file)
	RES subgroup		
g	% of prevalent RRMS (eligible for treatment with a DMT) that is RES	22.2%	AFFIRM Study (data on file)
h	Total number of prevalent cases of RES	1719	Calculated from estimate of proportion of RRMS cases that are RES and total number of RRMS in England and Wales eligible for treatment with a DMT (d × g)
	SOT subgroup		
i	% prevalent RRMS experiencing 1 or more relapses per year on treatment with a DMT	27.53%	Meta-analysis of included IFN-beta studies by Rice et al. Derived from 2-year data, annualised. (73)
j	Total number of incident cases of SOT per year.	2131	Derived from (d × i)
K	% of prevalent SOT patients that are no longer eligible for natalizumab treatment in any year	51%	Proportion of interferon beta monotherapy patients that experienced zero relapses in year 1 of the SENTINEL trial (3)
l	% SOT patients discontinuing natalizumab treatment in any year	6.4%	AFFIRM trial (section '(iii) Withdrawal rates' on page 124)

DMT = disease modifying treatment, GA = glatiramer acetate, HARRMS = highly active relapsing remitting multiple sclerosis, IFN-beta = interferon beta, RES = rapidly evolving severe, SOT = sub optimally treated

Table 95: Estimates of eligible RES and SOT patients from year 1 to year 5

Year	Year 1	Year 2	Year 3	Year 4	Year 5
Prevalent RES cases	1719	1719	1719	1719	1719
Prevalent SOT cases	2131	3134	3544	3569	3619
Total eligible patients	3850	4853	5263	5288	5338

RES = rapidly evolving severe, SOT = sub optimally treated

7.2.1 Estimates of natalizumab use

In the calculations presented we assume a steady rate of uptake of natalizumab over a year but we present full-year equivalents (FYE). E.g. if 100 new patients start treatment during the year, the FYE equates to 100/2 = 50 (i.e. equivalent to 50 patients treated for a full year).

RES patients: The total number of RES patients on natalizumab in any year is the number of prevalent RES patients (1719) multiplied by the market penetration for that year.

The prevalent RES patients are derived from a prevalent RRMS population (Table 94). This latter population is derived from the estimate cited in the risk sharing scheme for current DMTs and is in equilibrium, therefore inclusion of a discontinuation rate for natalizumab therapy is not relevant to the RES calculation.

SOT patients: The total number of SOT patients starting natalizumab in any year (incident natalizumab treated SOT patients) is the total number of eligible, prevalent SOT patients multiplied by the market penetration for that year. Derivation of the total number of eligible, prevalent SOT patients is shown in section 7.1.

As the above calculates incident rather than prevalent natalizumab treated SOT patients, the cumulative total of the incident cases provides the figure for the prevalent natalizumab treated SOT patients. The cumulative total natalizumab treated SOT patients in any year is derived as follows:

Cumulative total SOT	=	cumulative total of natalizumab treated patients from the prior year	+	FYE treated with natalizumab in the current year	-	the number of patients that discontinue treatment in the prior year

The proportion of natalizumab treated patients that discontinue treatment in any year is derived from the proportion of natalizumab treated patients that discontinued treatment in the AFFIRM study and estimated as 6.4% (section 5.8.9.1).

Table 96: Estimated natalizumab use from year 1 to year 5 in full-year equivalents

	Year				
	Year 1	**Year 2**	**Year 3**	**Year 4**	**Year 5**
RES patients					
Assumed market uptake	12%	18%	27%	36%	44%
Prevalent RES patients eligible for natalizumab treatment	1719	1719	1719	1719	1719
Total RES patients likely to be prescribed natalizumab (rounded up) *	207	310	465	619	757
Cumulative total FYE in RES patients	104	259	388	542	688
SOT patients					
Assumed market uptake	4%	8%	12%	17%	22%
Incident SOT patients	2131	2131	2131	2131	2131
Untreated incident SOT patients from prior year(s) that remain eligible ('backlog')	0	1003	1413	1528	1488
Total SOT patients eligible for natalizumab treatment	2131	3134	3544	3659	3619
SOT patients likely to be prescribed natalizumab	86	251	426	623	797
Number of patients that discontinue natalizumab treatment in the prior year (6.4%)	na	-6	-17	-28	-40
Total treated SOT patients minus discontinuations in prior year	86	246	410	596	758
Cumulative total FYE in SOT patients	43	209	537	1040	1717
Total RES + SOT patients					
Cumulative total FYE in RES + SOT patients	147	468	925	1582	2405

Note that numbers may not sum due to rounding. FYE = full-year equivalent, RES = rapidly evolving severe, SOT = sub optimally treated

We predict that a total of 104 RES FYE of natalizumab + 43 SOT FYE (total 147 FYE) will be prescribed natalizumab in year 1, increasing in year 5 to 688 RES FYE + 1717 SOT FYE (total 2405 FYE) (Table 96).

7.3 What assumption(s) were made about current treatment options and uptake of technologies?

The estimate for the number of people likely to be prescribed natalizumab was based on:

- an assumed uptake applied to a prevalent population for RES patients
- and the cumulative total of an assumed uptake applied to an incident plus a residual ('backlog') population for SOT patients

These derivations are described in section 7.2.

The assumed uptake is based upon Biogen Idec's projections for penetration of the RES and SOT market segments.

7.4 What assumption(s) were made about market share (where relevant)?

The market penetration (assumed uptake) is based upon Biogen Idec's projections for penetration of the RES and SOT market segments.

7.5 What unit costs were assumed? How were these calculated?

The costs considered in calculating the total direct cost of natalizumab treatment were the costs of treatment, administration and the management of adverse events. The total annual cost for each patient treated with natalizumab was estimated to be £15 802 (Table 97). These costs are those derived in the pharmacoeconomic evaluation described previously (see section 6 and Table 97).

Table 97: Direct per patient annual costs associated with natalizumab for year 1

Item	Absolute cost of Natalizumab (£)	Incremental cost vs IFN-beta (£)	Incremental cost vs GA (£)	Incremental cost vs weighted average DMT (£) **
Cost of treatment	14 740 *	6765	8917	7002
Cost of administration & adverse events	1062	385	683	418
Total cost	15 802	7150	9600	7420

* The annual cost of natalizumab includes adjustment to account for leap years. Without this adjustment, the annual cost per patient would be £14 690. ** Weighted average DMT cost is derived in the equation below:

$$\text{Weighted average annual incremental cost of natalizumab} = \left[\text{Incremental cost over IFN-Beta} \times \text{Market Share of IFN-Beta}\right] + \left[\text{Incremental cost over GA} \times \text{Market Share of GA}\right]$$

7.6 In addition to drug costs, consider other significant costs associated with treatment. What is the recommended treatment regime for example, what is the typical number of visits, and does treatment involve daycase or outpatient attendance? Is there a difference between recommended and observed doses? Are there likely to be any adverse events or a

need for other treatments in combination with the technology?

The unit costs given under the NHS perspective in section 7.5 include costs associated with drugs and administration. The derivation of these values, together with values assumed for the other perspectives, has been described in more detail in section 6.

7.7 Were there any estimates of resource savings? If so, what were they?

The direct costs associated with the treatment of MS increase as the severity of the disease increases. The beneficial effect of natalizumab in preventing disease relapse and reducing the risk of disability progression will therefore result in some direct cost savings in the treatment of MS. For simplicity and because the model is sensitive to changes in market penetration estimates, we have not included these resource savings in the budget impact model. Therefore it is likely that the incremental budget impact presented is an overestimate.

7.8 Are there any other opportunities for resource savings or redirection of resources that it has not been possible to quantify?

Compliance with natalizumab is likely to be better since it is administered in a clinical setting. This is likely to have the following benefits:

- The true efficacy of natalizumab will be realised as it can be assured that the patient is receiving the drug. This cannot be said for the comparator treatments, which are self-administered in the home.
- Wastage of drug (through patients filling prescriptions and then not using all of the drug before the next prescription) will be eliminated.

It was not possible to quantify these savings.

Appendix A Summary of Product Characteristics

1. NAME OF THE MEDICINAL PRODUCT

TYSABRI 300 mg concentrate for solution for infusion.

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Concentrate: Each ml of concentrate contains 20 mg of natalizumab.

Natalizumab is a recombinant humanised anti-α4-integrin antibody produced in a murine cell line by recombinant DNA technology.

When diluted (see section 6.6), the solution for infusion contains approximately 2.6 mg/ml of natalizumab.

For a full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Concentrate for solution for infusion.

Colourless, clear to slightly opalescent solution.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

TYSABRI is indicated as single disease modifying therapy in highly active relapsing remitting multiple sclerosis for the following patient groups:

- Patients with high disease activity despite treatment with a beta-interferon (see 5.1);

or

- Patients with rapidly evolving severe relapsing remitting multiple sclerosis (see 5.1).

4.2 Posology and method of administration

TYSABRI therapy is to be initiated and supervised by specialised physicians experienced in the diagnosis and treatment of neurological conditions, in centres with timely access to MRI.

Patients treated with TYSABRI must be given the special alert card.

Resources for the management of hypersensitivity reactions and access to MRI should be available.

After dilution (see section 6.6), the infusion is to be administered over approximately 1 hour and patients are to be observed during the infusion and for 1 hour after the completion of the infusion for signs and symptoms of hypersensitivity reactions.

TYSABRI must not be administered as a bolus injection.

Patients can switch directly from beta interferon or glatiramer acetate to natalizumab providing there are no signs of relevant treatment-related abnormalities e.g. neutropenia. If there are signs of treatment-related abnormalities these must return to normal before treatment with natalizumab is started.

Some patients may have been exposed to immunosuppressive medications (e.g. mitoxantrone, cyclophosphamide, azathioprine). These drugs have the potential to cause prolonged immunosuppression, even after dosing is discontinued. Therefore the physician must confirm that such patients are not immunocompromised before starting treatment with TYSABRI.

Continued therapy must be carefully reconsidered in patients who show no evidence of therapeutic benefit beyond 6 months.

Data on the safety and efficacy of natalizumab beyond 2 years are not available. Continued therapy beyond this time should be considered only following a reassessment of the potential for benefit and risk.

Adults

TYSABRI 300 mg is administered by intravenous infusion once every 4 weeks.

Elderly

TYSABRI is not recommended for use in patients aged over 65 due to a lack of data in this population.

Children and adolescents

TYSABRI is contraindicated in children and adolescents (see section 4.3).

Renal and hepatic impairment

Studies have not been conducted to examine the effects of renal or hepatic impairment.

The mechanism for elimination and results from population pharmacokinetics suggest that dose adjustment would not be necessary in patients with renal or hepatic impairment.

Readministration

The efficacy and safety of re-administration have not been established.

4.3 Contraindications

Hypersensitivity to natalizumab or to any of the excipients.

Progressive Multifocal Leukoencephalopathy (PML).

Patients with increased risk for opportunistic infections, including immunocompromised patients (including those currently receiving immunosuppressive therapies or those immunocompromised by prior therapies, e.g. mitoxantrone or cyclophosphamide, see also sections 4.4 and 4.8).

Combination with beta-interferons or glatiramer acetate.

Known active malignancies, except for patients with cutaneous basal cell carcinoma.

Children and adolescents.

4.4 Special warnings and precautions for use

Progressive Multifocal Leukoencephalopathy (PML)

Use of TYSABRI has been associated with an increased risk of PML.

Before initiation of treatment with Tysabri, a recent (usually within 3 months) Magnetic Resonance Image should be available. Patients must be monitored at regular intervals for any new or worsening neurological symptoms or signs that may be suggestive of PML. If new neurological symptoms occur, further dosing is to be suspended until PML has been excluded. The clinician should evaluate the patient to determine if the symptoms are indicative of neurological dysfunction, and if so, whether these symptoms are typical of MS or possibly suggestive of PML. If they are suggestive of PML, or if any doubt exists, further evaluation, including MRI scan (compared with pre-treatment MRI), CSF testing for JC Viral DNA and repeat neurological assessments, should be considered. Once the clinician has excluded PML, dosing of natalizumab may resume.

The physician should be particularly alert to symptoms suggestive of PML that the patient may not notice (e.g. cognitive or psychiatric symptoms). Patients should also be advised to inform their partner or caregivers about their treatment, since they may notice symptoms that the patient is not aware of.

If a patient develops PML the dosing of TYSABRI must be permanently discontinued.

Following reconstitution of the immune system in immunocompromised patients with PML, stabilisation or improved outcome has been seen. It remains unknown if early detection of PML and suspension of TYSABRI therapy may lead to similar stabilisation or improved outcome.

Other Opportunistic Infections

Other opportunistic infections have been reported with use of TYSABRI, primarily in patients with Crohn's disease who were immunocompromised or where significant co-morbidity existed, however increased risk of other opportunistic infections with use of TYSABRI in patients without these co-morbidities cannot currently be excluded. Opportunistic infections were also detected in MS patients treated with TYSABRI as a monotherapy (see section 4.8).

Prescribers should be aware of the possibility that other opportunistic infections may occur during TYSABRI therapy and should include them in the differential diagnosis of infections that occur in TYSABRI-treated patients. If an opportunistic infection is suspected, dosing with TYSABRI is to be suspended until such infections can be excluded through further evaluations.

If a patient receiving TYSABRI develops an opportunistic infection, dosing of TYSABRI must be permanently discontinued.

Educational guidance

Physicians must discuss the benefits and risks of TYSABRI therapy with the patient and provide them with a Patient Alert Card. Patients should be instructed that if they develop any infection then they should inform their physician that they are being treated with Tysabri.

Hypersensitivity

Hypersensitivity reactions have been associated with TYSABRI, including serious systemic reactions (see section 4.8). These reactions usually occurred during the infusion or up to 1 hour after completion of the infusion. The risk for hypersensitivity was greatest with early infusions, but the risk of hypersensitivity reactions should be considered for every infusion administered.

Patients are to be observed during the infusion and for 1 hour after the completion of the infusion (see section 4.8). Resources for the management of hypersensitivity reactions should be available.

Discontinue administration of TYSABRI and initiate appropriate therapy at the first symptoms or signs of hypersensitivity.

Patients who have experienced a hypersensitivity reaction must be permanently discontinued from treatment with TYSABRI.

Concurrent or prior treatment with immunosuppressants

The safety and efficacy of TYSABRI in combination with other immunosuppressive and antineoplastic therapies have not been fully established. Concurrent use of these agents with TYSABRI may increase the risk of infections, including opportunistic infections, and is contraindicated (see 4.3).

Patients with a treatment history of immunosuppressant medications, including cyclophosphamide and mitoxantrone, may experience prolonged immunosuppression and therefore may be at increased risk for PML. Care should be taken with patients who have previously received immunosuppressants to allow sufficient time for immune function recovery to occur. Physicians must evaluate each individual case to determine whether there is evidence of an immunocompromised state prior to commencing treatment with TYSABRI (see section 4.3).

In Phase 3 MS clinical trials, concomitant treatment of relapses with a short course of corticosteroids was not associated with an increased rate of infection. Short courses of corticosteroids can be used in combination with TYSABRI.

Immunogenicity

Disease exacerbations or infusion related events may indicate the development of antibodies against natalizumab. In case these events occur the presence of antibodies should be evaluated and if these remain positive in a confirmatory test after 6 weeks, treatment should be discontinued as persistent antibodies are associated with a substantial decrease in the effectiveness of TYSABRI and an increased incidence of hypersensitivity reactions (See section 4.8).

Stopping TYSABRI therapy

If a decision is made to stop treatment with natalizumab, the physician needs to be aware that natalizumab remains in the blood, and has pharmacodynamic effects (e.g. increased lymphocyte counts) for approximately 12 weeks following the last dose. Starting other therapies during this interval will result in a concomitant exposure to natalizumab. For drugs such as interferon and glatiramer acetate, concomitant exposure of this duration was not associated with safety risks in clinical trials. No data are available in MS patients regarding concomitant exposure with immunosuppressant medication. Use of these medicines soon after the discontinuation of natalizumab may lead to an additive immunosuppressive effect. This should be carefully considered on a case-by-case basis, and a wash-out period of natalizumab might be appropriate. Short courses of steroids used to treat relapses were not associated with increased infections in clinical trials.

4.5 Interaction with other medicinal products and other forms of interaction

See section 4.3.

4.6 Pregnancy and lactation

There are no adequate data from the use of natalizumab in pregnant women. Studies in animals have shown reproductive toxicity (see section 5.3). The potential risk for humans is unknown. Natalizumab should not be used during pregnancy unless clearly necessary. If a woman becomes pregnant while taking TYSABRI, discontinuation of TYSABRI should be considered.

It is not known whether TYSABRI is excreted in human milk, but it has been observed in animal studies (see section 5.3). Patients receiving TYSABRI should not breastfeed their infants.

4.7 Effects on ability to drive and use machines

No studies on the effects on the ability to drive and use machines have been performed. Based on the pharmacological mechanism of action of natalizumab, the use of TYSABRI is not expected to affect patient's ability to drive and use machines.

4.8 Undesirable effects

In placebo-controlled trials in 1,617 MS patients treated with natalizumab for up to 2 years (placebo: 1,135), adverse events leading to discontinuation of therapy occurred in 5.8% of patients treated with natalizumab (placebo: 4.8%). Over the 2-year duration of the studies, 43.5% of patients treated with natalizumab reported adverse drug reactions (placebo: 39.6%)[8]. Adverse drug reactions reported with natalizumab with an incidence of 0.5% greater than reported with placebo are shown below. The reactions are reported as MedDRA preferred terms under the MedDRA primary system organ class. Frequencies were defined as follows:

Common (> 1/100, < 1/10), uncommon (> 1/1,000, < 1/100).

Within each frequency grouping, undesirable effects are presented in order of decreasing seriousness.

Infections and infestations

Common	Urinary tract infection
	Nasopharyngitis

Immune system disorders

Common	Urticaria
Uncommon	Hypersensitivity

Nervous system disorders

Common	Headache
	Dizziness

Gastrointestinal disorders

Common	Vomiting
	Nausea

Musculoskeletal and connective tissue disorders

Common	Arthralgia

General disorders and administration site conditions

Common	Rigors
	Pyrexia
	Fatigue

Infusion reactions

In 2-year controlled clinical trials in MS patients, an infusion-related event was defined as an adverse event occurring during the infusion or within 1 hour of the completion of the infusion. These occurred in 23.1% of MS patients treated with natalizumab (placebo: 18.7%). Events reported more commonly with natalizumab than with placebo included dizziness, nausea, urticaria and rigors. See section 4.4.

Hypersensitivity reactions

In 2-year controlled clinical trials in MS patients, hypersensitivity reactions occurred in up to 4% of patients. Anaphylactic/anaphylactoid reactions occurred in less than 1% of patients receiving TYSABRI. Hypersensitivity reactions usually occurred during the infusion or within the 1-hour period after the completion of the infusion. See section 4.4.

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[8] An adverse event judged related to therapy by the investigating physician.

Immunogenicity

In 10% of patients antibodies against natalizumab were detected in 2-year controlled clinical trials in MS patients. Persistent anti-natalizumab antibodies (one positive test reproducible on retesting at least 6 weeks later) developed in approximately 6% of patients. Antibodies were detected on only one occasion in an additional 4% of patients. Persistent antibodies were associated with a substantial decrease in the effectiveness of TYSABRI and an increased incidence of hypersensitivity reactions. Additional infusion-related reactions associated with persistent antibodies included rigors, nausea, vomiting and flushing. (see section 4.4).

If, after approximately 6 months of therapy, persistent antibodies are suspected, either due to reduced efficacy or due to occurrence of infusion-related events, they may be detected and confirmed with a subsequent test 6 weeks after the first positive test. Given that efficacy may be reduced or the incidence of hypersensitivity or infusion-related reactions may be increased in a patient with persistent antibodies, treatment should be discontinued in patients who develop persistent antibodies.

Infections, including PML and opportunistic infections

In 2-year controlled clinical trials in MS patients, the rate of infection was approximately 1.5 per patient-year in both natalizumab- and placebo-treated patients. The nature of the infections was generally similar in natalizumab- and placebo-treated patients. A case of *cryptosporidium* diarrhoea was reported in MS clinical trials. In other clinical trials, cases of additional opportunistic infections have been reported, some of which were fatal. Early post-marketing experience included one fatal case of herpes encephalitis. See section 4.4.

The majority of patients did not interrupt natalizumab therapy during infections and recovery occurred with appropriate treatment.

In clinical trials, cases of PML have been reported. PML usually leads to severe disability or death (see section 4.4). In pivotal clinical trials, two cases, including one fatality, occurred in MS patients who were being treated with concomitant interferon beta-1a therapy for more than 2 years. In another trial, one patient with Crohn's disease, who had a long history of treatment with immunosuppressants and associated lymphopenia also developed PML and died.

Although each case of PML occurred in patients either with concomitant use of immune modulating drugs or with evidence of immunosuppression, it remains possible that the risk of PML is associated with natalizumab alone.

Malignancies

No differences in incidence rates or the nature of malignancies between natalizumab- and placebo-treated patients were observed over 2 years of treatment. However, observation over longer treatment periods is required before any effect of natalizumab on malignancies can be excluded. See section 4.3.

Effects on laboratory tests

TYSABRI treatment was associated with increases in circulating lymphocytes, monocytes, eosinophils, basophils and nucleated red blood cells. Elevations in neutrophils were not seen. Increases from baseline for lymphocytes, monocytes, eosinophils and basophils ranged from 35% to 140% for individual cell types but mean cell counts remained within normal ranges. During treatment with TYSABRI, small reductions in haemoglobin (mean decrease 0.6 g/dl), haematocrit (mean decrease 2%) and red blood cell counts (mean decrease 0.1 x 10^6/l) were seen. All changes in haematological variables returned to pre-treatment values, usually within 16 weeks of last dose of TYSABRI and the changes were not associated with clinical symptoms.

4.9 Overdose

No case of overdose has been reported.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Selective Immunosuppressive Agent, ATC code: L04AA23.

Pharmacodynamic properties

Natalizumab is a selective adhesion-molecule inhibitor and binds to the α4-subunit of human integrins, which is highly expressed on the surface of all leukocytes, with the exception of neutrophils. Specifically, natalizumab binds to the α4β1 integrin, blocking the interaction with its cognate receptor, vascular cell adhesion molecule-1 (VCAM-1), and ligands osteopontin, and an alternatively spliced domain of fibronectin, connecting segment-1 (CS-1). Natalizumab blocks the interaction of α4β7 integrin with the mucosal addressin cell adhesion molecule-1 (MadCAM-1). Disruption of these molecular interactions prevents transmigration of mononuclear leukocytes across the endothelium into inflamed parenchymal tissue. A further mechanism of action of natalizumab may be to suppress ongoing inflammatory reactions in diseased tissues by inhibiting the interaction of α4-expressing leukocytes with their ligands in the extracellular matrix and on parenchymal cells. As such, natalizumab may act to suppress inflammatory activity present at the disease site, and inhibit further recruitment of immune cells into inflamed tissues.

In MS, lesions are believed to occur when activated T-lymphocytes cross the blood-brain barrier (BBB). Leukocyte migration across the BBB involves interaction between adhesion molecules on inflammatory cells and endothelial cells of the vessel wall. The interaction between α4β1 and its targets is an important component of pathological inflammation in the brain and disruption of these interactions leads to reduced inflammation. Under normal conditions, VCAM-1 is not expressed in the brain parenchyma. However, in the presence of pro-inflammatory cytokines, VCAM-1 is upregulated on endothelial cells and possibly on glial cells near the sites of inflammation. In the setting of central nervous system (CNS) inflammation in MS, it is the interaction of α4β1 with VCAM-1, CS-1 and osteopontin that mediates the firm adhesion and transmigration of leukocytes into the brain parenchyma and may perpetuate the inflammatory cascade in CNS tissue. Blockade of the molecular interactions of α4β1 with its targets reduces inflammatory activity present in the brain in MS and inhibits further recruitment of immune cells into inflamed tissue, thus reducing the formation or enlargement of MS lesions.

Clinical efficacy

TYSABRI is indicated as a single disease modifying therapy in relapsing remitting multiple sclerosis to prevent relapses and delay progression of disability. Due to safety concerns (see 4.4 and 4.8) treatment is restricted to the following patient groups:

- Patients who have failed to respond to a full and adequate course of a beta-interferon. Patients should have had at least 1 relapse in the previous year while on therapy, and have at least 9 T2-hyperintense lesions in cranial MRI or at least 1 Gadolinium-enhancing lesion.

or

- Patients with rapidly evolving severe relapsing remitting multiple sclerosis, defined by 2 or more disabling relapses in one year, and with 1 or more Gadolinium enhancing lesions on brain MRI or a significant increase in T2 lesion load as compared to a previous recent MRI.

Efficacy as monotherapy has been evaluated in one randomised, double-blind, placebo-controlled study lasting 2 years (AFFIRM study) in relapsing-remitting MS patients who had experienced at least 1 clinical relapse during the year prior to entry and had a Kurtzke Expanded Disability Status Scale (EDSS) score between 0 and 5. Median age was 37 years, with a median disease duration of 5 years. The patients were randomised with a 2:1 ratio to receive TYSABRI 300 mg (n = 627) or placebo (n = 315) every 4 weeks for up to 30 infusions. Neurological evaluations were performed every 12 weeks and at times of suspected relapse. MRI evaluations for T1-weighted gadolinium (Gd)-enhancing lesions and T2-hyperintense lesions were performed annually.

Study features and results are presented in the table below.

AFFIRM study: Main features and results		
Design	Monotherapy; randomised double-blind placebo-controlled parallel-group trial for 120 weeks	
Subjects	RRMS (McDonald criteria)	
Treatment	Placebo / Natalizumab 300 mg i.v. every 4 weeks	
One year endpoint	Relapse rate	
Two year endpoint	Progression on EDSS	
Secondary endpoints	Relapse rate derived variables / MRI-derived variables	
Subjects	Placebo	Natalizumab
Randomised	315	627
Completing 1 years	296	609
Completing 2 years	285	589
Age yrs, (range)	37 (19-50)	36 (18-50)
MS-history yrs (range)	6.0 (0-33)	5.0 (0-34)
Time since diagnosis, yrs (range)	2.0 (0-23)	2.0 (0-24)
Relapse in previous 12 months (range)	1.0 (0-5)	1.0 (0-12)
EDSS-baseline (range)	2 (0-6.0)	2 (0-6.0)
RESULTS		
Annual relapse rate		
After one year (primary endpoint)	0.805	0.261
After two years	0.733	0.235
One year	Rate ratio 0.33 $CI_{95\%}$ 0.26 ; 0.41	
Two years	Rate ratio 0.32 $CI_{95\%}$ 0.26 ; 0.40	
Relapse free		
After one year	53%	76%
After two years	41%	67%
Disability		
Proportion progressed[1](12-week confirmation; primary outcome)	29%	17%
Time to progression	1.78 years	1.90 years
	Hazard ratio 0.58, $CI_{95\%}$ 0.43; 0.73, p<0.001	
Proportion progressed[1](24-week confirmation)	23%	11%
Time to progression	1.65 years	1.96 years
	Hazard ratio 0.46, $CI_{95\%}$ 0.33; 0.64, p<0.001	
MRI (0-2 years)		
Median % change in T2-hyperintense lesion volume	+8.8%	-9.4% (p<0.001)
Mean number of new or newly-enlarging T2-hyperintense lesions	11.0	1.9 (p<0.001)
Mean number of T1-hypointense lesions	4.6	1.1 (p<0.001)
Mean number of Gd-enhancing lesions	1.2	0.1 (p<0.001)

[1] Progression of disability was defined as at least a 1.0 point increase on the EDSS from a baseline EDSS >=1.0 sustained for 12 or 24 weeks or at least a 1.5 point increase on the EDSS from a baseline EDSS =0 sustained for 12 or 24 weeks.

In the sub-group of patients indicated for treatment of rapidly evolving relapsing remitting MS (patients with 2 or more relapses and 1 or more Gd+ lesion), the annualised relapse rate was 0.282 in the Tysabri treated group (n = 148) and 1.455 in the placebo group (n = 61) (p <0.001). Hazard ratio for disability progression was 0.36 (95% CI: 0.17, 0.76) p = 0.008. These results were obtained from a *post hoc* analysis and should be interpreted cautiously. No information on the severity of the relapses before inclusion of patients in the study is available.

5.2 Pharmacokinetic properties

Following the repeat intravenous administration of a 300 mg dose of natalizumab to MS patients, the mean maximum observed serum concentration was 110 ± 52 µg/ml. Mean average steady-state trough natalizumab concentrations over the dosing period ranged from 23 µg/ml to 29 µg/ml. The predicted time to steady-state was approximately 36 weeks.

A population pharmacokinetics analysis was conducted on samples from over 1,100 MS patients receiving doses ranging from 3 to 6 mg/kg natalizumab. Of these, 581 patients received a fixed 300 mg dose as monotherapy. The mean ± SD steady-state clearance was 13.1 ± 5.0 ml/h, with a mean ± SD half-life of 16 ± 4 days. The analysis explored the effects of selected covariates including body weight, age, gender, hepatic and renal function, and presence of anti-natalizumab antibodies upon pharmacokinetics. Only body weight and the presence of anti-natalizumab antibodies were found to influence natalizumab disposition. Body weight was found to influence clearance in a less-than-proportional manner, such that a 43% change in body weight resulted in a 31% to 34% change in clearance. The change in clearance was not clinically significant. The presence of persistent anti-natalizumab antibodies increased natalizumab clearance approximately 3-fold, consistent with reduced serum natalizumab concentrations observed in persistently antibody-positive patients**,** (see section 4.8).

The pharmacokinetics of natalizumab in paediatric MS patients or in patients with renal or hepatic insufficiency has not been studied.

5.3 Preclinical safety data

Non-clinical data reveal no special hazard for humans based on conventional studies of safety pharmacology, repeated dose toxicity and genotoxicity.

Consistent with the pharmacological activity of natalizumab, altered trafficking of lymphocytes was seen as white blood cell increases as well as increased spleen weights in most *in vivo* studies. These changes were reversible and did not appear to have any adverse toxicological consequences.

In studies conducted in mice, growth and metastasis of melanoma and lymphoblastic leukaemia tumour cells was not increased by the administration of natalizumab.

No clastogenic or mutagenic effects of natalizumab were observed in the Ames or human chromosomal aberration assays. Natalizumab showed no effects on *in vitro* assays of α4-integrin-positive tumour line proliferation or cytotoxicity.

Reductions in female guinea pig fertility were observed in one study at doses in excess of the human dose; natalizumab did not affect male fertility.

The effect of natalizumab on reproduction was evaluated in 5 studies, 3 in guinea pigs and 2 in *cynomolgus* monkeys. These studies showed no evidence of teratogenic effects or effects on growth of offspring. In one study in guinea pigs, a small reduction in pup survival was noted. In a study in monkeys, the number of abortions was doubled in the natalizumab 30 mg/kg treatment groups versus matching control groups. This was the result of a high incidence of abortions in treated groups in the first cohort that was not observed in the second cohort. No effects on abortion rates were noted in any other study. A study in pregnant *cynomolgus* monkeys demonstrated natalizumab-related changes in the foetus that included mild anaemia, reduced platelet counts, increased spleen weights and reduced liver and thymus weights. These changes were associated with increased splenic extramedullary haematopoiesis, thymic atrophy and decreased hepatic haematopoiesis. Platelet counts were also reduced in offspring born to mothers treated with natalizumab until parturition, however there was no evidence of anaemia in these offspring. All changes were observed at doses in excess of the human dose and were reversed upon clearance of natalizumab.

In *cynomolgus* monkeys treated with natalizumab until parturition, low levels of natalizumab were detected in the breast milk of some animals, indicating the possibility for transfer of natalizumab into breast milk in humans (see section 4.6).

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Sodium phosphate, monobasic, monohydrate
Sodium phosphate, dibasic, heptahydrate
Sodium chloride
Polysorbate 80 (E433)
Water for Injections

6.2 Incompatibilities

TYSABRI must not be mixed with other medicinal products except those mentioned in section 6.6.

6.3 Shelf life

Concentrate

2 years.

Diluted solution

After dilution, immediate use is recommended. If not used immediately, the diluted solution must be stored at 2˚C - 8˚C and infused within 8 hours of dilution. In-use storage times and conditions prior to use are the responsibility of the user.

6.4 Special precautions for storage

Concentrate

Store in a refrigerator (2˚C - 8˚C).
Do not freeze.
Keep the vial in the outer carton in order to protect from light.

For storage conditions of the diluted medicinal product see section 6.3.

6.5 Nature and contents of container

15 ml TYSABRI in a vial (type I glass) with a stopper (bromobutyl rubber) and a seal (aluminium) with a flip-off cap. Pack size of one vial per carton.

6.6 Special precautions for disposal

Instructions for use:

1. Inspect the TYSABRI vial for particles prior to dilution and administration. If particles are observed and/or the liquid in the vial is not colourless, clear to slightly opalescent, the vial must not be used.

2. Use aseptic technique when preparing TYSABRI solution for intravenous (IV) infusion. Remove flip-off cap from the vial. Insert the syringe needle into the vial through the centre of the rubber stopper and remove 15 ml concentrate for solution for infusion. Add the 15 ml concentrate for solution for infusion to 100 ml sodium chloride 9 mg/ml (0.9%) solution for injection. Gently invert the solution to mix completely. Do not shake.

3. TYSABRI must not be mixed with other medicinal products or diluents.

4. Visually inspect the diluted product for particles or discolouration prior to administration. Do not use if it is discoloured or if foreign particles are seen.

5. The diluted product is to be used as soon as possible and within 8 hours of dilution. If the diluted product is stored at 2˚C - 8˚C (do not freeze), allow the solution to warm to room temperature prior to infusion.

6. The diluted solution is to be infused intravenously over 1 hour at a rate of approximately 2 ml/minute.

7. After the infusion is complete, flush the intravenous line with sodium chloride 9 mg/ml (0.9%) solution for injection.

8. Each vial is for single–use only.

9. Any unused product or waste material must be disposed of in accordance with local requirements.

7. MARKETING AUTHORISATION HOLDER

Elan Pharma International Ltd., Monksland, Athlone, County Westmeath, Ireland

8. MARKETING AUTHORISATION NUMBER(S)

EU/1/06/346/001

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

27 June 2006

10. DATE OF REVISION OF THE TEXT

27 June 2006

Detailed information on this product is available on the website of the European Medicines Agency (EMEA) http://www.emea.eu.int/

Appendix B Systematic review of interferon beta for RRMS

An Update to an Existing Systematic Review

Heron Evidence Development Ltd, Letchworth, Hertfordshire

Date of Most Recent Substantive Amendment: 09/11/06

Note: This systematic review updates an earlier review undertaken by The Cochrane Collaboration (73) and is based on the same search strategy and inclusion/exclusion criteria with some exceptions that are given herein.

B.1 Abstract

We reviewed and updated the Cochrane systematic review of Rice et al that assessed the effectiveness and safety of interferons in the treatment of multiple sclerosis (MS). (73) The original review included all recombinant interferons, whereas, we restricted this update to IFN-beta, which reflects the scope of this submission

There were no results in this update to warrant any changes made to the authors' original statements, except, that in this update we conclude that the statements made in this review are still applicable up to September 2006. This is because there was no new data available to further substantiate of refute the results of the Cochrane review.

B.2 Plain language summary

'Interferons can help to reduce disability and attacks for people with multiple sclerosis, but there is not enough evidence about their usefulness in the long term.' (73)

No new information in the form of randomised clinical studies has been published; hence, this statement is still applicable up to September 2006.

B.3 Background

This is an update of the systematic review by Rice et al and uses the same methodology described therein to assess the efficacy and safety of IFN-beta in the treatment of MS. (73) While we have summarised some of the data given in the review by Rice et al, the reader should refer to the published systematic review for more detail.

BIs have been shown to suppress both the clinical and MRI measures of disease activity in patients with RRMS. Specifically, the aim of the review of Rice et al was to assess the effects of recombinant interferons in adults with RRMS

B.4 Objectives

The objective of this review was to update the Cochrane review that assessed the effects of recombinant interferons in adults with RRMS. The primary questions addressed in this review were to determine whether IFN-beta was more effective than placebo in decreasing the number of patients who experience clinical relapses and experienced disability progression.

The secondary objectives were of this review were to examine the efficacy of IFN-beta in reducing the need for corticosteroid treatment and hospitalisation of RRMS patients and to assess the effect of IFN-beta on MRI. Additionally, the review

assessed the safety and tolerance of IFN-beta.

B.5 Differences between this update and the original systematic review

The differences between this update and the systematic review of Rice et al were:

- Only studies of IFN-beta were included. This was in contrast to the review of Rice et al, which included studies examining both alpha and interferon beta.
- The patient population included was 16-years of age and over compared to any age in the Rice et al review.
- Four researchers reviewed the data independently in the Rice et al review; in this update two independent reviewers were involved in the review.
- Unlike the authors of the Rice et al review, we did not contact specific companies to identify unpublished studies or researchers participating in the studies. However, we did consult four UK Neurologists, who had participated in studies in MS, for expert advice.
- We only included studies with the data on the outcome measures for (i) Disability progression: patients who progressed at 2-years and/or (ii) Patients with at least 1 exacerbation at 2 years and/or (iii) reported data on AEs.
- We only included studies of RRMS populations in the efficacy analyses, however studies of all types of MS were included in analyses of AEs.

B.6 Criteria for including studies

Only randomised, double blind, placebo-controlled studies of IFN-beta were included and non-controlled and non-randomised studies were excluded. Noteworthy is that this review focused on studies that examined RRMS patients. All studies that compared IFN-beta to placebo were included.

Studies were not excluded on the basis of dose, duration of treatment, route of administration or length of follow up. For studies in which treatment effects were reported for more than one dose, the authors restricted the analysis to the higher dose (which is the dose most frequently used in clinical practice).

There were a number of differences in the criteria used in our update of this review and these are outline in section B.5.

B.7 Search strategy and results

The search strategy used by Rice et al initially identified 208 articles. Specifically they identified 125 articles in MEDLINE, a further 23 in EMBASE, 46 by hand

searching and 14 in the Cochrane Controlled trials Register (CENTRAL). After inspecting the titles and abstracts of the articles retrieved from the searches, a total of 7 studies remained in the systematic review. These 7 studies were described in 33 different articles, which formed the basis of the Rice et al systematic review. The interventions compared in these studies were: IFNA-2a (2 studies), IFNB-1a (3 studies) and IFNB-1b (2 studies). The key characteristics of the IFN-beta studies and results of critical appraisal by Rice et al were adapted from this publication and are given in section B.11.

In our update, we searched MEDLINE, Medline in Process, CENTRAL and EMBASE (January 2001 to September 2006) using the OVID platform. In addition to these searches, we consulted four UK Neurologists who had participated in studies in MS for expert advice. The search strategies are given in section B.12.

We retrieved a total of 930 publications that comprised respectively from Embase, Medline and Medline in process and CENTRAL, 207, 582 and 141 publications. Each abstract and title from these articles was appraised by two independent reviewers to decide on their suitability for inclusion based on the criteria (see section B.6 & B.5). No publications met the inclusion criteria specified for this update. However, two publications were initially considered for inclusion, but were later excluded. The publication of Rudick et al. (reporting the SENTINEL natalizumab plus Interferon beta 1a trial) was excluded because there was not a placebo comparator for the IFN-beta treatment arm, and the article of Kappos et al did not contain relevant data for 2-year disability progression or patients with at least 1 exacerbation at 2 years. (3;173)

B.8 Data collection and analysis

In the review of Rice et al, 4 independent reviewers were responsible for assessing study quality and extraction of data. However, in this update, 2 reviewers independently assessed data. We did not consider studies of alpha interferon for the update, as they were not relevant to the decision problems.

B.9 Main results from Rice et al

Seven studies involving 1215 participants were included in the Rice et al review, but only 919 (76%) contributed to the results concerning exacerbations and progression of the disease at 2 years. Specifically, interferon significantly reduced the occurrence of exacerbations (Relative risk [RR] 0.80, 95% confidence interval [CI] 0.73 to 0.88, $p < 0.001$) and progression of the disease (RR 0.69, 95% CI 0.55 to 0.87, $p = 0.002$) 2 years after randomisation. However, if interferon-treated participants who dropped out were deemed to have progressed (worst case scenario) the significance of these effects was lost (RR 1.31, 95% CI 0.60 to 2.89, $p = 0.5$).

It was not possible for the authors to perform a quantitative analysis of the MRI results. Both clinical and laboratory side effects reported in the studies were more frequent in treated participants than in controls; there was no information after 2 years of follow-up. The impact of interferon treatment (and its side effects) on the quality of life of patients was not reported in any study included in this review.

B.10 Authors' conclusions

'The efficacy of interferon on exacerbations and disability 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 studies might have allowed for a more convincing conclusion.'

In this update, we conclude that the statements made in this review are still applicable to September 2006. This is because there was no new data available to further substantiate of refute the results of this review.

B.11 Characteristics of included studies (adapted from Rice et al)

B.11.1 Durelli 1994

This was a study of alpha interferon and is not relevant to the updated review.

B.11.2 IFNB MS Group 1993

Methods

- Randomised controlled trial.
- Central randomisation.
- Intention to treat mentioned.
- Double-blind; however, the occurrence of side effects, mainly injection site reactions, raises doubt as to real blindness of patients.
- Treatment 2 years.
- Follow-up 2 years.
- After 2nd year all patients still in study given choice of continuing treatment, extending the treatment period to 5 years for some patients. Therefore after 2nd year the study was not blind. For this reason this review considers only 2 years of follow-up.
- Withdrawal: steady worsening of EDSS (1 point) for 6 months; 3 courses of ACTH or steroid in 1-year period; non-compliance for 2 consecutive weeks; moderate or severe drug toxicity re-occurring on rechallenge.

Withdrawals and losses at 2 years = 68 patients:

- 1.6 MIU IFNB-1b = 20 patients (5 adverse events, 3 worsening, 2 prohibited drugs, 2 non-compliance or losses to follow up, 1 entry violation, 7 other reasons),
- 8.0 MIU IFNB-1b = 25 patients (10 adverse events, 9 worsening, 1 prohibited drugs, 2 non-compliance or losses to follow up, 1 entry violation, 2 other reasons),
- placebo = 23 patients (1 adverse events, 5 worsening, 9 prohibited drugs, 2 non-compliance or losses to follow up, 1 entry violation, 5 other reasons).

Participants

- 372 patients: 1.6 MIU IFNB-1b = 125, 8.0 MIU IFNB-1b = 124, placebo = 123.
- US and Canada 11 Centres.
- Sex: both.
- Age: 18-50 years.
- Included: clinically or laboratory-supported definite relapsing-remitting MS (105) of more than 1 year duration; at least 2 exacerbations in the 2 years before study entry; free of exacerbations for at least 1 month before entry; EDSS = 5.5 or less.
- Excluded: use of ACTH or prednisone in the month before entry; prior treatment with azathioprine or cyclophosphamide.

Baseline characteristics:

- 70% female
- mean age: IFNB 1.6 MIU 35.3 years, IFNB 8 MIU 35.2 years, placebo 36.0 years
- mean EDSS: IFNB 1.6 MIU 2.9, IFNB 8 MIU 3.0, placebo 2.8
- mean disease duration: IFNB 1.6 MIU 4.7 years, IFNB 8 MIU 4.7 years, placebo 3.9 years.

Interventions

- Rx 1: 1.6 MIU IFNB-1b (Betaseron or Betaferon)
- Rx 2: 8.0 MIU IFNB-1b
- Placebo: human albumin and dextrose
- IFNB or placebo self-administered subcutaneously every other day for 2 years
- Co-intervention: ACTH or prednisone for exacerbation

Outcomes

- Primary outcomes: annual exacerbation rate and proportion of exacerbation-free patients over the 2 years.
- Secondary clinical outcomes: number of patients who progressed at 2 years, median time to first exacerbation, exacerbation duration and severity, mean (and standard deviation) annual change in EDSS, median time to progression.
- Exacerbation defined as 'a new symptom or worsening of old symptom accompanied by new neurologic abnormality, lasting at least 24 hours in absence of fever and preceded by stability or improvement for at least 30 days' (174).
- Severity of exacerbation defined as change in the NRS (0 to 7 = mild; 8 to 14 = moderate; 14 = severe).
- Disability progression defined as, 'increase in EDSS of at least 1.0 point sustained over at least 3 months'.
- MRI: annual mean and median % change in total lesion area from baseline.
- Proportion of active scans/patient and annual rate of active lesions/patient in a subgroup (14%) who had scans every 6 weeks.
- Active scan and new or enlarging lesion: defined.

- Adverse events: criteria for monitoring and recording were not specified.
- Neutralizing antibodies: reported.

Notes

- Recruitment period: June 1988-May 1990.
- Sponsored by Triton Biosciences, Inc., Alameda, CA and Berlex Laboratories Inc.
- Withdrawals and losses to follow-up: conflicting figures in the articles and letters reporting study.
- Blindness: 80% patients in 8 MIU IFNB-1b arm, 51% in 1.6 MIU IFNB-1b arm and 30% placebo correctly guessed treatment.

Allocation concealment B - Unclear

B.11.3 Knobler 1993

Methods

- Randomised controlled trial, 30 initially randomised; one more patient randomised to substitute one withdrawn at 14th day.
- Allocation concealment: not reported.
- Intention to treat not mentioned.
- Double-blind; however, occurrence of side effects and crossing to different IFNB-1b dose after 6 months raise doubt as to true blindness of patients.
- After 24 weeks all patients initially randomised to IFNB-1b crossed to 8.0 MIU.
- Treatment 3 years.
- Follow-up 3 years
- After the 3rd year all patients still in the study given choice of continuing open label treatment, extending the treatment period to 6 years. Therefore after 3rd year the study was not randomised. Therefore this review considered 3 years of follow-up
- Withdrawals: steady worsening of EDSS (1 point) for 6 months; 3 courses of ACTH or steroid over 1- year; non-compliance 2 consecutive weeks; persistence or recurrence of moderate or severe drug toxicity after rechallenge with half dose.
- Withdrawals = 6 patients: 0.8 MIU IFNB-1b = 1 prohibited treatment, 4.0 MIU IFNB-1b = 2 (1 prohibited treatment, 1 non-compliance), 8.0MIUIFNB-1b = 1 prohibited treatment, 16.0 MIU IFNB-1b = 0, placebo= 1 prohibited treatment. Unknown treatment for 1 for accidental un-blinding. Losses to follow-up = 7 patients (all self-terminated):
- 0.8 MIU IFNB-1b = 1
- 4.0 MIU IFNB-1b = 1
- 8.0 MIU IFNB-1b = 1
- 16 MIU IFNB-1b = 2
- placebo = 2

Participants

- 31 patients: 6 patients to each IFNB-1b arm and 7 to placebo.
- US 3 Centres.
- Sex: both.
- Age: 18-50 years.
- Included: clinically definite relapsing-remitting MS (105) of at least 1 year duration and not more than 15 years; at least 2 exacerbations in the 2 years before study entry; in remission at entry.
- EDSS = 5.5 or less.
- Exclusion criteria: not reported.

Baseline characteristics:

- 48.4% female
- mean age: IFNB-1b 0.8 MIU 34.3 years; IFNB-1b 4.0 MIU 38.4 years; IFNB-1b 8.0 MIU 35.4 years; IFNB-1b 16.0 MIU 35.7 years; placebo 34.5 years
- mean EDSS: IFNB-1b 0.8 MIU 2.8; IFNB-1b 4.0 MIU 4.0; IFNB-1b 8.0 MIU 2.7; IFNB-1b 16.0 MIU 2.9; placebo 3.1
- mean disease duration: IFNB-1b 0.8 MIU 6.2 years; IFNB-1b 4.0 MIU 8.2 years; IFNB-1b 8.0 MIU 4.2
- years; IFNB-1b 16.0 MIU 7.3 years; placebo 7.0 years.

Interventions

- Rx 1: 0.8 MIU IFNB-1b (Betaseron or Betaferon)
- Rx 2: 4.0 MIU IFNB-1b
- Rx 3: 8.0 MIU IFNB-1b
- Rx 4: 16.0 MIU IFNB-1b
- Placebo: human albumin.
- IFNB or placebo self-administered subcutaneously 3 times weekly for 3 years.
- Co-intervention: intravenous ACTH, methylprednisolone, or oral prednisone for exacerbations.

Outcomes

- Primary outcomes: number of patients who continued to experience exacerbations during the first 24 weeks, annual exacerbation rate, median time to first exacerbation and proportion of exacerbation-free patients at 3 years.
- Exacerbation was defined as 'new symptom or worsening of an old symptom in absence of fever, associated with a new abnormality of at least 24 h. duration, which followed clinical stability or improvement of at least 30 days duration' (174).
- Adverse events: reported.
- Neutralizing antibodies: reported.

Notes

- Recruitment period: June-October 1986.
- Sponsored by Triton Biosciences, Inc., Alameda, CA and Berlex Laboratories Inc.
- Poor description of results.

Allocation concealment B - Unclear

B.11.4 Myhr 1999

This was a study of alpha interferon and is not relevant to the updated review.

B.11.5 MSCRG 1996

Methods

- Randomised controlled trial.
- Randomisation at statistical centre of Buffalo General Hospital, one of the participating centres (biased coin).
- Allocation concealment: schedule sent to each clinical centre, included patients were sequentially assigned the next ID number from the schedule.
- Intention to treat mentioned.
- Double-blind; however, occurrence of side effects, mainly injection site reactions, raises doubts as true blindness of patients.
- Treatment = 104 weeks.
- Follow-up = 2 years.
- Reasons for withdrawal: pregnancy, encephalopathy, increased levels of hepatic enzymes and creatinine, white blood count . 2300, platelet count . 80.000, heart failure, adverse events, non-compliance, protocol violation.
- Withdrawals = 23 patients: IFNB-1a = 14 (non-compliance), placebo = 9 (non-compliance).
- Losses to follow-up: 5 patients (reasons and treatment group not reported).
- 129 patients did not reach 2 years of follow-up because study ended prematurely.

Participants

- 301 patients: IFNB-1a = 158, placebo = 143.
- United States 4 Centres.
- Sex: both.
- Age: 18-55 years.
- Included: definite relapsing-remitting MS (105) of at least 1-year duration; at least 2 exacerbations in the 3 years before study entry (patients with disease duration less than 3 years must have had at least one exacerbation per years prior to entry); free of exacerbations for at least 2 months before entry; EDSS = 1-3.5.
- Exclusion: prior therapy with immunosuppressants or interferon; ACTH or corticosteroids in 2 months before entry; concurrent infection or other serious disease; chronic progressive MS; pregnant or lactating; unwilling to use contraception during study.

Baseline characteristics:

- 73.5% female

- mean age (range): IFNB-1a = 36.7 years (18 - 55), placebo = 36.9 years (16 - 54)
- mean EDSS (range): IFNB-1a = 2.4 (1.0 - 3.5), placebo = 2.3 (1.0 - 3.5)
- mean disease duration (range): IFNB-1a = 6.6 years (1.0 - 30.7), placebo = 6.4 years (1.0 - 31.0).

Interventions

- Rx: 6.0 MIU IFNB-1a (Avonex)
- Placebo: human albumin.
- IFNB-1a or placebo intramuscular given weekly for 104 weeks by study nurses or local health professionals under supervision of study personnel.
- Co-intervention: intramuscular ACTH or intravenous methylprednisolone followed by tapered oral prednisone for exacerbations.

Outcomes

- Primary outcome: mean time to disability progression (EDSS-measured).
- Other clinical outcomes: median time to first exacerbation, proportion of exacerbation-free patients at 2 years, number of relapses per patient at 1 and 2 years, annual exacerbation rate, mean (without standard deviation) change in EDSS.
- Sustained worsening in disability defined as 'deterioration from baseline 1.0 points on EDSS persisting at least 6 months'.
- Exacerbation defined as 'new symptom or worsening of an old symptom of at least 48 hours which followed clinical stability or improvement of at least 30 days duration' (65;175).
- MRI: number of patients who had active lesions at 1st and 2nd years. Mean (standard error) number and volume of active lesions per patient. Median % change of total lesion volume from baseline. New lesion: defined.
- Other clinical outcomes: time to first worsening in visual function and time to beginning of sustained visual function progression (EDSS-measured); time to beginning of sustained progression of disability in upper and lower extremity function (EDSS-measured)
- Other measures: neuropsychological (MSCRG battery), emotional status (defined), functional assessment (defined), quality of life (Sickness Impact Profile).
- Adverse events: criteria for monitoring and recording clearly described (according to Food and Drug Administration, HHS 21 CFR, Chapters 1,312.32, part c, 4/1/90).
- Neutralizing antibodies: reported.

Notes

- Recruitment period: November 1990 - early 1993
- Supported by National Institutes of Health, National Institute of Neurological Disorders and Stroke (NINDS) and Biogen, Inc, Cambridge, MA
- Withdrawals and losses to follow-up: poorly described.

Allocation concealment B - Unclear

B.11.6 OWIMS 1999

Methods

- Randomised controlled trial.
- Randomisation performed at Corporate Biometrics Department of Ares-Serono (computer-generated list).
- Allocation concealment: code sent to each centre in sealed envelopes.
- Intention to treat mentioned.
- Double-blind; however, occurrence of side effects, mainly injection site reactions, raises doubts as true blindness of patients.
- Treatment = 24 weeks.
- Follow-up = 48 weeks.
- Withdrawal criteria: not described.
- Withdrawals = 10 patients: 6.0 MIU = 2 (1 allergy to Gadolinium, 1 adverse events), 12.0 MIU = 8 (5 adverse events, 1 protocol deviation, 1 worsening, 1 pregnancy), placebo = 0.
- Losses to follow-up = 14 patients: 6.0 MIU = 6, 12.0 MIU = 5, placebo = 3.

Participants

- 293 patients: 6.0 MIU = 95, 12.0 MIU = 98, placebo = 100.
- Canada, Netherlands, Italy, Israel and France 11 Centres.
- Sex: both.
- Age: 18-50 years.
- Included: clinically or laboratory-supported definite relapsing-remitting MS (105) of at least 1 year duration; at least one exacerbation in the 2 years; free of exacerbations for at least 8 weeks before entry; EDSS= 0-5.0; at least 3 lesions consistent with MS were required on a screening magnetic resonance.
- Exclusion: prior interferon, cyclophosphamide, or lymphoid irradiation treatment; use of any immunosuppressive or experimental therapies in the preceding 12 months before entry; corticosteroids in 8 weeks before entry; pregnancy; lactation; other severe medical or psychiatric disease.

Baseline characteristics:

- 73% female
- mean age: IFNB-1a 6 MIU = 35.4 years; IFNB-1a 12 MIU = 35.5 years; placebo = 34.9 years
- mean EDSS: IFNB-1a 6 MIU = 2.7; IFNB-1a 12 MIU = 2.6; placebo = 2.6
- mean disease duration: IFNB-1a 6 MIU = 6.9 years; IFNB-1a 12 MIU = 6.7 years; placebo = 6.3 years.

Interventions

- Rx 1: 6.0 MIU IFNB-1a (Rebif)

- Rx 2: 12.0 MIU IFNB-1a
- Placebo: human albumin and mannitol.
- IFNA or placebo administered subcutaneously weekly for 24 weeks, by study treating physician.
- Co-intervention: methylprednisolone intravenous for 3 consecutive days for exacerbations.

Outcomes

- Primary MRI outcomes (at 24 weeks): mean active lesion rate/ patient/scan expressed as median for each group.
- Secondary MRI outcomes (at 48 weeks): median of active lesions and %change in total lesion area at monthly scans.
- Active lesion and change in total lesion area: defined.
- Clinical outcomes: number of exacerbations/patient, exacerbation severity (EDSS and NRS-measured), median time to first exacerbation, proportion of exacerbation-free patients, mean steroid treatments/patient and hospitalisations related to MS.
- Exacerbation defined as 'new symptom or worsening of old symptom in absence of fever, associated with new abnormality of at least 24 h. duration, which followed clinical stability or improvement of at least 30 days duration' (174).
- Adverse effects: reported.
- Neutralizing antibodies: reported.

Notes

- Recruited: March-November 1995
- Sponsored by Ares-Serono International SA, Geneva, Switzerland.

Allocation concealment A – Adequate

B.11.7 PRISMS 1998

Methods

- Randomised controlled trial.
- Randomisation at Corporate Biometrics Department of Ares-Serono (computer-generated list, stratified by centre, equal allocation of the treatment groups by a block size of 6).
- Intention to treat mentioned.
- Double-blind; however, occurrence of side effects, mainly injection site reactions, raises doubts as to true blindness of patients.
- Treatment period = 2 years.
- Follow-up = 2 years.
- Reason for withdrawal: WHO grade IV toxic effects; protocol violations; non-compliance.
- Withdrawals = 32 patients: 6.0 MIU = 12 (1 worsening, 1 death, 6 adverse events, 2 unknown, 2 pregnant), 12.0 MIU = 13 (9 adverse events, 3 pregnant, 1 protocol violation), placebo = 7 (3 worsening, 2 adverse events, 1 death, 1 pregnant).

- Losses to follow-up = 26 patients: 6.0 MIU= 10; 12.0 MIU = 6; placebo = 10.

Participants

- 560 patients: 6.0 MIU = 189, 12.0 MIU = 184, placebo = 187.
- Canada, Germany, Netherlands, Australia, Sweden, Finland, Belgium, United Kingdom and Switzerland 22 Centres.
- Sex: both.
- Included: clinically or laboratory-supported definite relapsing-remitting MS (105) of at least 1 year duration; at least 2 exacerbations in the 2 years before entry; EDSS = 0-5.0.
- Exclusion: prior interferon, lymphoid irradiation, cyclophosphamide, immunomodulatory or immunosuppressive treatment in the preceding 12 months.

Baseline characteristics:

- 69% female
- median age: IFNB-1a 6 MIU = 34.8 years, IFNB-1a 12 MIU = 35.6, placebo 34.6
- mean EDSS: IFNB-1a 6 MIU = 2.5, IFNB-1a 12 MIU = 2.5, placebo = 2.4
- median disease duration: IFNB-1a 6 MIU = 5.4 years, IFNB-1a 12 MIU = 6.4 years , placebo = 4.3 years.

Interventions

- Rx 1: 6.0 MIU IFNB-1a (Rebif)
- Rx 2: 12.0 MIU IFNB-1a
- Placebo: constituents not reported.
- IFNB or placebo administered subcutaneously 3 times weekly for two years, by treating study physician.
- Co-intervention: paracetamol for influenza-like side effects and intravenous methylprednisolone for 3 consecutive days for exacerbations.

Outcomes

- Primary outcomes: number of exacerbations/patient, exacerbation severity (NRS or the activities of daily living scale-measured).
- Other outcomes: number of patients who progressed at 2 years, median times to first and second exacerbation, proportion of exacerbation-free patients, first quartile time to progression, mean (and standard deviation) change of EDSS from baseline.
- Exacerbation defined according to Schumacher (174).
- Progression in disability defined as 'increase in EDSS of at least 1.0 point sustained over at least 3 months, ambulation index (175), arm-function index (175;176), need for steroid therapy and hospital admission'.
- Severity of exacerbations defined as 'change in NRS (0 to 7 = mild; 8 to 14 = moderate; 14 = severe) or the activities of daily living scale (mild: no effect; moderate: significant effect; severe: hospital admission)'.
- MRI: annual change of total lesion area.

- Total lesion area: not defined.
- Adverse events: reported.
- Neutralizing antibodies: reported.

Notes

- Recruited: May 1994-February 1995
- Supported by: Ares-Serono International SA, Geneva, Switzerland.

Allocation concealment A - Adequate

B.12 Search strategy

The search strategy for the review is reported in Appendix E.

B.13 References included in this review

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[letter]. 50[6], 1931-1932. 1998. Neurology.

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(14) Sibley W, Ebers GC, Panitch HS, Reder A. Interferon beta treatment of multiple sclerosis [letter]. 44[1], 188-190. 2006. Neurology.

Knobler, 1993

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The PRISMS, 1998

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(3) Randomised double-blind placebo-controlled study of interferon beta-1a in relapsing/remitting multiple sclerosis. PRISMS (Prevention of Relapses and Disability by Interferon beta-1a Subcutaneously in Multiple Sclerosis) Study Group: Lancet 1998; 352(9139):1498-1504.

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Appendix C Systematic review of glatiramer acetate for RRMS

An Update to an Existing Systematic Review

Heron Evidence Development Ltd, Letchworth, Hertfordshire

Date of Most Recent Substantive Amendment: 09/11/06

Note: This systematic review updates an earlier review undertaken by the Cochrane Collaboration by Munari et al, 2003 and is based on the same search strategy and inclusion/exclusion criteria with some exceptions that are given herein.

C.1 Abstract

We reviewed and updated a systematic review by Munari et al that assessed whether GA can prevent relapses or slow progression of multiple sclerosis (MS). (70) The original review included both patients with relapsing remitting (RR) and chronic progressive (CP) MS, whilst our updated restricted inclusion to those studies of patients with RRMS.

One new study, evaluating an oral formulation of GA, was identified in our update. Efficacy data presented in this publication were not suitable for inclusion the existing meta-analyses, however the results from the study further substantiated the conclusions of the Cochrane review. There were no results in this update to warrant any changes made to the authors' original statements in RRMS, except that in this update we conclude that the statements made in this review are still applicable up to September 2006.

C.2 Plain language summary

'Currently available data do not provide definite evidence that glatiramer acetate (Copaxone ®) can prevent relapses or slow progression of the disease, and more research is needed'. (70)

The conclusions from this study are applicable to September 2006. One further large clinical study, with 1912 RRMS patients, was identified in this update and these further substantiated the conclusions from the Cochrane systematic review.

C.3 Background

This is an update of the systematic review by Munari et al and uses similar methodology described therein to assess the efficacy and safety of GA in the treatment of MS. (70) While we have summarised some of the data given in the review by Munari et al, the reader should refer to the published systematic review for more detailed discussion.

C.4 Objectives

The objective of this review was to update a systematic review that assessed the effects of GA in adults with MS. The main outcome measures of interest in the Munari et al review were:

- Clinical progression of disease in terms of sustained disability
- Frequency of clinical relapses
- Incidence of any adverse events
- Patient's quality of life

Secondary outcomes addressed were:

- Number of patients treated with steroids and number of steroid
- Courses administered during acute relapses or active disease progression
- Impact of treatment on hospital admissions and length of stay, in order to detect potential savings both in terms of healthcare resources and patient's time

C.5 Differences between this update and the original systematic review

The differences between this update and the systematic review of Munari et al were:

- The patient population included was 16-years of age and over.
- We restricted our search to find only studies that included RRMS patients, whereas, the Munari review included studies of any type of MS course (relapsing/remitting, relapsing/progressive, secondary progressive or primary progressive)
- We only included studies with the data on the outcome measures for (i) Disability progression: patients who progressed at 2-years and/or (ii) Patients with at least 1 exacerbation at 2 years and/or (iii) AEs.
- We only included studies of RRMS populations in the efficacy analyses, however studies of all types of MS were included in analyses of AEs.

C.6 Criteria for including studies

In the Munari et al review, all randomised or quasi-randomised controlled trials (RCTs) comparing GA and placebo in patients with definite MS were included. Non-controlled studies and studies where GA has been compared with interventions other than placebo were not included. Both double and single blind studies were eligible.

Patients of any age and either gender with MS of any disease severity were eligible for the review. Any patterns of MS course (relapsing/remitting, relapsing/progressive, secondary progressive or primary progressive) have been considered. MS patients receiving cytostatics, immunomodulators or immunosuppressants in the 6 months prior to study enrolment were excluded from the analysis.

All therapeutic schedules involving GA administration, irrespective of administration route, dosage, treatment duration and the interval between symptom onset and randomisation were considered as test treatment. Courses of steroids were permitted, provided they were administered without any restriction in both arms.

There were a number of differences in the criteria used in our update of this review and these are outline in section

C.7 Search strategy and results

The authors of the Munari et al review searched the Cochrane MS Group Studies Register (searched December 2004), CENTRAL 'The Cochrane Library Issue 4, 2004', MEDLINE (PubMed) (January 1966 to December 2004) and EMBASE (January 1988 to December 2004). Additionally they used hand searching to find the references quoted in the identified studies and of symposia reports (1990-2004) from the most important neurological associations and MS Societies in Europe and America. Contact was also made with researchers who were participating in studies of GA.

The Munari et al review identified initially 103 references up to June 2003 and 41 abstracts were provisionally selected to be read as published papers. Of these papers the authors included 17 papers, which related to 4 studies, in their review.

In total these 4 studies accounted for 646 patients, 320 of whom were allocated to GA and 326 to placebo. Three studies enrolled patients with RRMS whilst one study investigated the effect of GA in chronic-progressive (CP) MS.

The studies of RRMS patients included patients with an age range of 20 to 35 years, with at least two exacerbations in the 2 years before admission, provided they were not severely disabled (EDSS score had to be below 6) and/or emotionally unstable. The characteristics and critical appraisal of these studies was adapted from the publication of in section 5.5.2.2.

In our update, we searched MEDLINE, Medline in Process, CENTRAL and EMBASE (January 2001 to September 2006) with the OVID platform. In addition to these searches we consulted four UK Neurologists who had participated in studies in MS for expert advice.

The search strategies are given in Appendix E. We retrieved a total of 270 publications that comprised, respectively from Embase, Medline and Medline in process and Cochrane CENTRAL, 74, 162 and 34 publications.

Each abstract and title from these articles was appraised to decide on their suitability for inclusion based on the inclusion criteria (see sections C.5 and C.6). The reviewers identified 1 study by Filippi et al that was suitable for inclusion into the systematic review. (103) This study assessed an oral formulation of GA on clinical and MRI-monitored RRMS. The conclusion drawn from this study was that 5mg and 50mg GA daily administration did not affect relapse rate or MRI parameters. The article presented efficacy data in a way that was suitable for meta-analysis. Hence, the inclusion of this article did not change the results of the meta-analyses in the systematic review.

C.8 Main results from Munari et al

Munari et al concluded that GA did not show any significant effect on disability progression, measured as a sustained worsening in the EDSS. However, a slight decrease in the mean EDSS score, attributable to the results from one major study, was observed. No benefit was shown in CP MS patients (progression at two years: RR=0.69, 95% CI [0.33 to 1.46]).

Major toxicity associated with GA administration was not evident. The most common systemic AE was a transient and self-limiting patterned reaction of flushing, chest tightness, sweating, palpitations, anxiety (RR (95% CI), 3.40 (2.22 to 5.21), $p < 0.00001$]).

These results are still applicable to September 2006 because we could not identify any additional data to update these results.

C.9 Authors' conclusions

'Glatiramer acetate did not show any beneficial effect on the main outcome measures in MS, i.e. disease progression, and it does not substantially affect the risk of clinical relapses. Therefore its routine use in clinical practice is not currently supported.'

In this update, we conclude that the statements made in this review are still applicable to September 2006. This is because there was no new data available to further substantiate of refute the results of this review. However, one new study, with an oral formulation of glatiramer acetate, was identified that further substantiated the authors' conclusions, but in the publication of this study there was no data that was suitable for meta analysis.

C.10 Characteristics of included studies (adapted from Munari et al)

C.10.1 Bornstein 1987

Methods

- Randomised controlled trial.
- Patients have been enrolled in matched pairs with random assignment of either patient.
- Randomisation method not clearly specified.
- Intention-to-treat analysis.
- Double-blind, but patient's self-evaluation of either side effects or changes in neurologic status were reported
- to an unblinded clinical assistant.
- Treatment period: 24 months.
- Follow-up period: 24 months. Withdrawn criteria: unusable data (2 placebo)
- Withdrawals: placebo = 2 (dropouts for psychological reasons)
- Dropouts = 7:
- placebo = 4 (2 psychological reasons; 2 not stated), GA = 3 (1 exacerbation; 2 not stated).

Participants

- 50 patients: GA 25, placebo 25.
- Israel 1 centre.
- Sex: both.
- Age: 20-35

- Included (36%): definite MS with RR course, 2 exacerbations in the 2 years before admission, Kurtzke = 6, emotionally stable. Patients enrolled when 'clinically stable' and out of steroid treatment.
- Excluded (64%): age (23), low frequency of exacerbations (21), lack of documentation (19), psychologic profile (15), transition to chronic (8), distance from the clinic (3), pregnancy (1).

Baseline characteristics:

- 58% female
- mean age: GA 30.0 yrs, placebo 31.1 yrs
- mean EDSS: GA 2.9, placebo 3.2
- disease duration: GA 4.9 yrs, placebo 6.1 yrs.

Interventions

- Rx: GA 20 mg.
- Placebo: bacteriostatic saline.
- Subcutaneous GA or placebo self-administered daily.
- Co-interventions: unspecified steroid treatment during exacerbations; symptomatic medications (e.g.: cholinergic and spasmolytic drugs).

Outcomes

- Primary outcome: proportion of relapse-free patients at the end of follow-up.
- Secondary outcomes: frequency of relapses, change in EDSS scores from baseline, time to progression.
- Relapse defined as: patient symptoms accompanied by observed objective changes on the neurologic exam involving an increase of at least 1 point in the score for 1 of the 8 functional group of Kurtzke scale. Sensory symptoms alone not considered.
- Progression defined as: increase of at least 1 point EDSS maintained for at least 3 months.

Notes

- Jadad score = 3.
- Two different preparations of Copolymer-1 have been used in the study, but patients treated with either preparation cannot be identified throughout the study.
- Assumptions: 2 withdrawn in placebo group

Allocation concealment B – Unclear

C.10.2 Bornstein 1991

Not included in the updated review for efficacy since it contained patients with chronic progressive MS.

C.10.3 Comi 2001

Methods

- Randomised controlled trial.
- Randomisation stratified by centres with a pre-assigned computer-generated list.
- Intention-to-treat analysis.
- Although supposed unaware of treatment allocation, patient and physician blinding was not formally assessed as outcome measures focussed on MRI parameters. Treatment period: 9 months.
- Follow-up period: 9 months.
- Drop-outs: GA = 7 (3 adverse events, 1 moved away from study centre, 1 severe exacerbation, 4 withdrew consent; more than one causes are counted for the same patient), placebo = 7 (2 adverse events, 1 treatment believed ineffective, 1 poor compliance, 1 lost to follow-up, 2 refused to continue MRI monitoring)

Participants

- 239 patients: GA 119, placebo 120.
- Europe and Canada 29 centres.
- Sex: both.
- Age: 18-50.
- Included (49%): definite MS with RR course, a diagnosis of MS for at least 1 year, age 18-50 inclusive, EDSS of 0 to 5, at least 1 documented relapse in the preceding 2 years, at least 1 enhancing lesion in their screening brain MRI, clinically relapse-free and steroids-free in the 30 days before entry.
- Excluded (51%): previous use of GA or oral myelin, prior lymphoid irradiation, use of immunosuppressant or cytotoxic agents in the past 2 years, use of azathioprine, cyclosporine, interferons, deoxyspergualine, chronic corticosteroids during the previous 6 months. Concomitant therapy with an experimental drug for MS or for another disease. Serious intercurrent systemic or psychiatric illnesses; unwilling to practice reliable contraception during study; known hypersensitivity to Gadolinium-DTPA or unavailable to undergo repeat MRI studies. Currently on relapse or steroid treatment (13); unspecified requirement unmet (233).

Baseline characteristics:

- Unspecified gender distribution
- mean age: GA 34.1, placebo 34.0.
- mean EDSS: GA 2.3 placebo 2.4
- disease duration: GA 7.9 years, placebo 8.3 years

Interventions

- Rx: GA** 20 mg.
- Placebo: unspecified preparation
- Subcutaneous GA or placebo self-administered daily.
- Co-interventions: relapses could be treated by a standard dose of 1.0 g i.v. metilprednisolone for 3 consecutive days

Outcomes

- Primary outcome: total number of enhancing lesions on MRI.

- Secondary outcomes: total volume of enhancing lesions, number of new enhancing lesions, number of new lesions on T2-weighted images, %change of lesion volume on T2-weighted images, change in the volume of hypointense lesions on T1-weighted images.
- Tertiary outcomes: relapse rate, number of relapses, proportion of relapse-free patients
- Relapse defined as: appearance or reappearance of one or more neurologic symptoms, accompanied by abnormalities persisting for at least 48 hours and immediately preceded by a relatively stable or improving neurologic state of at least 30 days. A relapse was confirmed when patient's symptoms were accompanied by objective changes in neurologic examination consistent with at least 0.5 EDSS increase, 1 grade in the score of two or more functional systems, or 2 grades in one functional system. Transient neurologic deterioration associated with fever or infection in MS patients was not considered as relapse, nor was a change in bowel, bladder or cognitive function alone.

Notes

- Jadad score = 4.
- The Authors state that physician blinding was not formally assessed because primary and secondary outcome measures were MRI patterns.

Allocation concealment A – Adequate

C.10.4 Johnson 1995

Methods

- Randomised controlled trial.
- Central allocation at study office.
- Intention-to-treat analysis.
- Double-blind.
- Treatment period: 24 months (+ 11 in the extension phase).
- Follow-up period: 24 months (+ 11 in the extension phase).
- Withdrawals: GA = 19 (3 pregnancy, 1 progression, 2 serious adverse event, 3 transient self-limited systemic reactions, 10 not specified); placebo = 17 (2 poor protocol compliance, 1transient self-limited reaction, 14 not specified). Nine additional patients (GA= 2, placebo= 7) dropped out during the extension study.

Participants

- 251 patients: GA 125, placebo 126.
- USA 11 centres
- Sex: both.
- Age: 18-45

- Included (88%): criteria clinically definite MS or laboratory-supported definite with RR course, ambulatory, with an EDSS of 0.0 to 5.0, a history of at least 2 clearly defined and documented relapses in the 2 years prior to entry, onset of the first relapse at least 1 year before randomisation, neurologically stable and free from corticosteroid therapy for at least 30 days prior to entry
- Excluded (12%): treatment with GA or previous immunosuppression with cytotoxic therapy or lymphoid irradiation; pregnancy or lactation, IDDM, positive HIV/HTLV-1 serology, Lyme disease, required use of aspirin or chronic NSAID during study; unwilling to undergo adequate contraception.

Baseline characteristics:

- 73% female
- mean age: GA 34.6 yrs, placebo 34.3 yrs
- mean EDSS: GA 2.8, placebo 2.4
- disease duration: GA 7.3 yrs, placebo 6.6 yrs.

Interventions

- Rx: GA 20 mg.
- Placebo: not specified.
- Subcutaneous GA or placebo self-administered daily.
- Co-interventions: standard steroid protocol during exacerbations; conventional medication received at the time of randomisation

Outcomes

- Primary outcome: mean number of relapses.
- Secondary endpoints: proportion of relapse-free patients, time to first relapse after randomisation, proportion of patients with sustained disease progression and mean change in EDSS score. Relapse defined as: 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. A relapse was confirmed in neurologic examination consistent with at least 0.5 EDSS increase, 2 points on one of the seven functional when patient's symptoms were accompanied by objective changes systems, or 1 point on two or more of the functional systems
- Progression defined as: increase of at least 1 point EDSS maintained for at least 3 months

Notes

- Jadad score = 5.
- Authors carried out both an intention-to treat and an on-treatment analyses, claiming that results are comparable.
- This study has been extended for an additional 11 months until all 203 remaining patients (i.e.: excluding 36 already withdrawn and 12 who refused to participate in the extension study), have received 24 months of treatment. Clinical status of these 12 withdrawn between the early and the extension phase are no different from the remaining cohort. Extension study was carried out double blind.

Allocation concealment A - Adequate

C.11 Search strategy

The search strategy for the review is reported in Appendix E.

C.12 References included in this review

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Comi, 2001

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Appendix D Summary of supportive data for natalizumab

D.1 Summary of methodology: MS 201

D.1.1 Methods (MS 201)

The MS 201 study was a preliminary study that assessed whether natalizumab reduced the number of new brain lesions in MS patients and the time course of this reduction. It was conducted in the UK in nine different centres. The study was a randomised, double-blind, parallel-group, placebo-controlled study in patients with relapsing-remitting or secondary-progressive MS. Patients meeting the eligibility criteria entered a run-in period of four weeks and were then randomised to receive a first intravenous (IV) infusion of natalizumab 3.0 mg/kg or placebo, followed by a second infusion four weeks later. Patients were followed up for 24 weeks after the first infusion so the total duration of the study for each patient was 28 weeks.

In the study, randomisation was done centrally and medication and placebo were identical clear liquids, which were supplied in vials identical in appearance and labelling. Sealed randomisation codes for individual patients were supplied to the pharmacist or a named member of the study staff to facilitate blinding.

D.1.2 Participants (study MS 201)

The following criteria, for male or female patients aged 18 to 55 of weight up to 90 kg, were used to determine eligibility of patients into the run-in period:

- Clinically definite MS, if possible supported by laboratory findings, by criteria of Poser 1983. (105)
- Either relapsing-remitting or secondary-progressive MS.
- EDSS score between 2.0 and 6.0, increased to 7.0 upon recommencement of the study after drug reformulation.
- Two or more exacerbations in the past 18 months; at least four weeks since the onset of the last exacerbation.
- Fully informed, written consent.
- For patients to be randomised and to receive the first infusion of study drug or placebo four weeks after the screening visit, the patient must not have had an exacerbation of their MS during this run-in period. An MS exacerbation was defined as one or more new, or worsening of existing, MS symptoms lasting at least 48 hours.

Conversely, the following patients were excluded from participation:

- Women of child-bearing potential that would potentially become pregnant in the study period and pregnant of breast-feeding mothers.
- Normal T2 MRI scan at screening.
- Patients who were receiving, or who had received in the past six months, immunosuppressive drugs (including azathioprine, cyclo-phosphamide, and IFN-beta, but excluding methyl-prednisolone and prednisolone) for any reason.
- Use of methylprednisolone and/or oral prednisolone in the four weeks prior to the first (screening) visit.
- Treatment with anti-CD4 antibodies, other monoclonal antibodies, or total lymphoid irradiation at any time.
- Any concurrent major disorder that may have affected the interpretation of efficacy or safety information or which otherwise contraindicated participation in a clinical study of a new drug.
- Alcohol consumption greater than 21 units (315 mg) per week, or abuse of other drugs.
- Likely noncompliance with the protocol or any other reason that, in the investigator's opinion, made the patient unsuitable for inclusion in the study.
- Previous exposure to any product containing murine protein.

D.1.3 Patient Numbers (study MS 201)

A total of 99 patients were screened for entry into the study and 73 patients were randomised. Of those randomised, 72 (37 natalizumab and 35 placebo) received study medication. The ITT population was based on these 72 patients (Table 98), but efficacy analyses were performed on a modified ITT population that excluded two patients who received placebo prior to a reformulation of the study drug. The per-protocol population excluded the two patients reviewed above and an additional two patients that did not have sufficient MRI data. This population was therefore based on a total of 68 patients (37 natalizumab and 31 placebo). Three patients withdrew early from the study: one in each treatment group at their own request; and one patient in the placebo group due to an adverse event.

Table 98 Baseline characteristics of the MS 201 study population (data on file MS 201)

Parameter	Treatment Group	
	Natalizumab (n = 37)	Placebo (n = 35)
Age: Mean (range)	39.9 (24.6 – 52.1)	40.8 (25.4 – 55.1)
Sex		
Male	12 (32%)	14 (40%)
Female	25 (68%)	21 (60%)
Type of MS		
RRMS	25 (68%)	28 (80%)
SPMS	12 (32%)	7 (20%)

D.1.4 Outcomes (study MS 201)

The primary efficacy parameter was the number of new active lesions during the 12 weeks following the first treatment. Secondary efficacy parameters were the number of new active lesions during the second 12-week period following the first treatment and assessment of the numbers of new enhancing lesions, pre-existing enhancing lesions, persistent enhancing lesions, new and enlarging T2 lesions, new fast flair lesions and new hypo-intense T1 lesions. Clinical secondary efficacy parameters included the number of MS acute exacerbations, time to first exacerbation, proportions of patients showing improvement from baseline in EDSS, and total scores on the Guys neurological disability scale (GNDS) compared to baseline. Safety was assessed by adverse events, and included immune function profile and natalizumab and anti-natalizumab antibody assays.

D.1.5 Statistical analysis and definition of study groups (study MS 201)

Analyses of covariance were used to test treatment differences in the primary efficacy parameter, the numbers of new enhancing lesions, the numbers of pre-existing enhancing lesions and GNDS score. Logistic regression techniques and subsequently conventional Chi-squared tests were used to analyse the numbers of patients with at least one new T2 lesion, at least one enlarging T2 lesion and at least one new hypo-intense T1 lesion. The proportions of patients experiencing at least one acute exacerbation and EDSS scores were also analysed in the same way. The time to first acute exacerbation was compared between groups using survival analysis techniques.

D.2 Summary of methodology: MS 231

D.2.1 Methods (study MS 231)

Study MS 231 was a phase II, international, randomised, double-blind, placebo-controlled, parallel group, dose-finding study. It was conducted at 15 sites in the United States, 4 sites in Canada, and 7 sites in the United Kingdom. Patents were randomised in a 1:1:1 ratio into three treatment groups consisting placebo, 3 or 6 mg/kg natalizumab. Medication or placebo was given as once monthly IV infusions for 6 months and the 6-month treatment period was followed by a 6-month post-treatment safety follow-up phase. Efficacy was evaluated throughout the study and measures included MRI scans, EDSS, safety, antinuclear antibody testing and blood tests.

A computer generated randomisation code assigned eligible patients to treatment group and this was site stratified using a centralized interactive voice response system (IVRS). Codes were used via an IVRS to ensure blinding of medication and placebo throughout the study. Placebo was identical in colour and appearance to the study drug and procedures for 'unblinding' in the case of medical emergency were available.

D.2.2 Participants (study MS 231)

Patents included in this study were males and females 18 to 65 years of age with a

diagnosis of clinically or laboratory-supported definite relapsing remitting or secondary-progressive MS; a history of at least 2 MS exacerbations within the past 2 years; a baseline EDSS 2.0 and 6.5; a minimum of three lesions on T2-weighted MRI of the brain; no concomitant treatment with immunosuppressant agents; and clinically acceptable physical and neurological examinations and laboratory evaluations.

D.2.3 Patient numbers (study MS 231)

In study MS 203, 213 patients were randomised and dosed, of which, 144 (68%) had RRMS and 69 (32%) had SPMS. The three different treatment groups were balanced with respect to the MS subgroup and other baseline characteristics (except for gender). A summary of the patient characteristics is given in Table 99. The withdraw rate in the study was low and with 4, 6 and 12% respectively in the placebo, 3mg/kg and 6mg/kg treatment arms (Table 100).

Table 99 Baseline characteristics of the patient population in study MS 231, data on file MS 231

Parameter	Placebo	3 mg/kg	6 mg/kg	Total
No. of subjects dosed	71 (100)	68 (100)	74 (100)	213 (100)
Age (mean (SD))	43 (9.3)	43 (9.6)	45 (8.6)	44 (9.2)
Male (n (%))	25 (35)	21 (31)	15 (20)	61 (29)
Female (n (%))	46 (65)	47 (69)	59 (80)	152 (71)
Race				
White	61 (86)	63 (93)	64 (86)	188 (88)
Hispanic	4 (6)	2 (3)	3 (4)	9 (4)
Black	5 (7)	2 (3)	1 (1)	8 (4)
Asian	0	1 (1)	3 (4)	4 (2)
Other	1 (1)	0	3 (4)	4 (2)
Mean weight(kg)	73 (14.1)	72 (13.6)	70 (13.0)	72 (13.5)

Table 100 Summary of withdrawal patents from the MS 231 study, data on file MS 231

Parameter	Treatment arm (n (%))			
	Placebo	3mg/kg	6mg/kg	Total
No. of subjects dosed	71 (100)	68 (100)	74 (100)	213 (100)
No. of subjects who completed study	68 (96)	64 (94)	65 (88)	197 (92)
Total no. of subjects withdrawn	3 (4)	4 (6)	9 (12)	16 (8)
No. of subjects withdrawn during treatment phase (a)	2 (3)	1 (1)	6 (8)	9 (4)
Adverse event	1 (1)	0	2 (3)	3 (1)
Non-compliance or lost to follow-up	0	1 (1)	2 (3)	3 (1)
Protocol violation	0	0	0	0
Sponsor discontinued	0	0	0	0
Voluntary	1 (1)	0	2 (3)	3 (1)
Other	0	0	0	0
No. of subjects withdrawn during follow-up (b)	1 (1)	3 (4)	3 (4)	7 (3)
Adverse event	1 (1)	2 (3)	0	3 (1)
Non-compliance or lost to follow-up	0	0	0	0
Protocol violation	0	0	0	0
Sponsor discontinued	0	0	0	0
Voluntary	0	1 (1)	3 (4)	4 (2)
Other	0	0	0	0

a) Subjects who withdrew before completing the Month 6 visit.

b) Subjects who withdrew after completing the Month 6 visit

D.2.4 Outcomes (study MS 231)

The primary aim of this study was to examine the effect of two different natalizumab treatments compared to placebo, on brain lesion activity assessed by magnetic resonance imaging (MRI) in subjects with RRMS or SPMS.

Safety, tolerability, immunogenicity, efficacy (e.g. EDSS, MSFC, exacerbation frequency), pharmacokinetics and pharmacodynamics were secondary measures in this study.

D.2.5 Statistical analysis and definition of study groups (study MS 231)

The safety and efficacy analyses were to be performed on the ITT population, defined as all randomised subjects. The primary efficacy endpoint was also to be analysed using modified ITT and per-protocol populations. The modified ITT population was to include all randomised subjects who received at least one infusion of study drug and had at least one post-baseline MRI. Statistical tests used were: Wilcoxon-Mann-Whitney test, Cochran-Mantel-Haenszel test, log-rank test and analysis of variance.

D.2.6 MS 201: Main results

Study MS 201 was a Phase II, dose-comparison study. (104) MS 201 demonstrated that:

- Six IV infusions of 3 and 6 mg/kg given 4 weeks apart were associated with significantly fewer new Gd-enhancing lesions when compared to placebo (Table 101).
- Similar findings were observed on all other MRI parameters assessed from T1-weighted scans, including the volume of Gd-enhancing lesions and the number and volume of new T1-hypointense lesions.
- Similar effects were also seen on the number and volume of new lesions on T2-weighted scans.
- Furthermore, there was a reduction of about 50% in the number of patients in the natalizumab group who experienced acute MS exacerbations, with fewer patients requiring treatment of relapse with IV steroids.
- There were no differences in terms of efficacy between the dose groups.

Table 101 Pertinent results from the Study MS 201: new active lesions, EDSS and acute exacerbations

Outcome	NAT 3.0 mg/kg (n = 37)	Placebo (n = 31)	Absolute reduction	Relative Risk reduction (95% CI)
Number (sd) of new active lesions during first 12 weeks after first dose	1.9 (3.6)	3.5 (4.9)	1.8 (0.1, 3.6)	0.46
Mean (sd) change in EDSS at 12 weeks †	-0.08 (0.60)	0.32 (0.80)	0.40 (0.05, 0.75)	1.25
Number (proportion) of subjects who experienced at least one acute MS exacerbation during the first 12 weeks after first dose	9 (0.24)	10 (0.30)	NS	NS

NAT = natalizumab. † Mean change in EDSS should be interpreted with caution, as EDSS is an ordinal scale and not a continuous measure.

D.2.7 MS 231: Main results

The MS 231 study was also a phase II study that included 213 patients assigned in approximately equal proportions to natalizumab 3 or 6 mg/kg or to placebo. An analysis of the results from this study revealed that natalizumab treatment was associated with (Table 102):

- less new GD-enhancing lesions
- a lower proportion of patients suffering at least one acute MS exacerbation during the 6-month treatment period

Table 102 Pertinent results from the Study MS 231: new lesions, EDSS and exacerbations

Outcome	NAT 3.0 mg/kg (n = 68)	NAT 6.0 mg/kg (n = 74)	Placebo (n = 71)	Absolute reduction (CI)	P-value (versus placebo)
Number (sd) of new gd-enhancing lesions (months 1-6)	0.7 (2.14)	1.1 (2.69)	9.6 (27.40)	3.0 mg/kg: 8.9 (2.3, 15.5) 6.0 mg/kg: 8.6 (2.2, 14.9)	<0.001* <0.001*
Mean (sd) change in EDSS at 6 months †	-0.14 (0.77)	-0.03 (0.79)	0.03 (0.90)	NS	NS
Number (proportion) of subjects who experienced at least one acute MS exacerbation during the 6 month treatment period	13 (0.19)	14 (0.19)	27 (0.38)	3.0 mg/kg: 0.19 (0.04, 0.34) 6.0 mg/kg: 0.19 (0.05, 0.34)	0.016 ** 0.016 **

NAT = natalizumab. † Mean change in EDSS should be interpreted with caution, as EDSS is an ordinal scale and not a continuous measure. * Based on Wilcoxon-Mann Whitney test. ** Based on Fisher's exact test.

Appendix E Search strategies for updating of clinical systematic reviews

E.1 Medline and Medline in Process

1. (Multiple Sclerosis or Myelitis, Transverse or Demyelinating Diseases or Encephalomyelitis, Acute Disseminated).me.
2. (multiple sclerosis or transverse myelitis or optic neuritis or devic or adem or neuromyelitis optica).mp. [mp=ti, ot, ab, nm, hw]
3. 1 or 2
4. Clinical Study.pt.
5. Randomized Controlled trial.pt.
6. Multicenter Study.pt.
7. Controlled Clinical Study.pt.
8. Clinical Studies.me.
9. Cross-Over Studies.me.
10. Single-Blind Method.me.
11. Double-Blind Method.me.
12. Random Allocation.me.
13. Follow-Up Studies.me.
14. Prospective Studies.me.
15. Placebos.me.
16. (placebo$ or multicentr$ or comparative study or comparative studies).mp. [mp=ti, ot, ab, nm, hw]
17. (random$ or clinical study$).mp. [mp=ti, ot, ab, nm, hw]
18. (single or double or trebl or triple).mp. [mp=ti, ot, ab, nm, hw]
19. (mask$ or blind$ or cross over or crossover or follow up).mp. [mp=ti, ot, ab, nm, hw]
20. 18 and 19
21. 4 or 5 or 6 or 7 or 8 or 9 or 10 or 11 or 12 or 13 or 14 or 15 or 16 or 17 or 20
22. 3 and 21
23. (interferon beta or interferon beta or Avonex or Rebif or Beta?eron).mp. [mp=ti, ot, ab, nm, hw]
24. (glatiramer acetate or Copaxone).mp. [mp=ti, ot, ab, nm, hw]
25. 22 and 23
26. limit 25 to english language

27. limit 26 to yr="2001 - 2007"
28. 22 and 24
29. limit 28 to english language
30. limit 29 to yr="2001 - 2007"

E.2 EMBASE

1. random$.ti,ab.
2. factorial$.ti,ab.
3. (crossover$ or crossover$ or cross-over$).ti,ab.
4. placebo$.ti,ab.
5. (doubl$ adj blind$).ti,ab.
6. (singl$ adj blind$).ti,ab.
7. assign$.ti,ab.
8. allocat$.ti,ab.
9. volunteer$.ti,ab.
10. crossover procedure.sh.
11. double-blind procedure.sh.
12. randomized controlled trial.sh.
13. single-blind procedure.sh.
14. or/1-13
15. exp ANIMAL/ or NON HUMAN/ or exp ANIMAL EXPERIMENT/
16. exp HUMAN/
17. 16 and 15
18. 15 not 17
19. 14 not 18
20. exp *demyelinating disease/
21. *encephalomyelitis/
22. 21 and acute disseminated.mp. [mp=title, abstract, subject headings, heading word, drug trade name, original title, device manufacturer, drug manufacturer name]
23. acute disseminated encephalomyelitis.ti,ab.
24. multiple sclerosis.ti,ab.
25. *myelooptic neuropathy/
26. neuromyelitis optica.ti,ab.
27. (adem or devic).ti,ab.
28. or/22-27
29. 19 and 28
30. (interferon beta or interferon beta or Avonex or Rebif or Beta?eron).mp. [mp=title, abstract, subject headings, heading word,

drug trade name, original title, device manufacturer, drug manufacturer name]

31. (glatiramer acetate or Copaxone).mp. [mp=title, abstract, subject headings, heading word, drug trade name, original title, device manufacturer, drug manufacturer name]
32. 29 and 30
33. limit 32 to (english language and yr="2001 - 2007")
34. 29 and 31
35. limit 34 to (english language and yr="2001 - 2007")

E.3 Cochrane CENTRAL

E.3.1 Interferon beta search strategy

1. MeSH descriptor Multiple Sclerosis explode all trees
2. MeSH descriptor Myelitis, Transverse explode all trees
3. MeSH descriptor Demyelinating Autoimmune Diseases, CNS explode all trees
4. MeSH descriptor Encephalomyelitis, Acute Disseminated explode all trees
5. multiple sclerosis or transverse myelitis or optic neuritis or devic or adem or neuromyelitis optica
6. (#1 OR #2 OR #3 OR #4 OR #5)
7. interferon beta or interferon beta or Avonex or Rebif or Beta?eron
8. (#6 AND #7)

E.3.2 Glatiramer Actetate search strategy

1. MeSH descriptor Multiple Sclerosis explode all trees
2. MeSH descriptor Myelitis, Transverse explode all trees
3. MeSH descriptor Demyelinating Autoimmune Diseases, CNS explode all trees
4. MeSH descriptor Encephalomyelitis, Acute Disseminated explode all trees
5. multiple sclerosis or transverse myelitis or optic neuritis or devic or adem or neuromyelitis optica
6. (#1 OR #2 OR #3 OR #4 OR #5)
7. glatiramer acetate or Copaxone
8. (#6 AND #7)

Appendix F Critical Appraisals of the natalizumab studies included in this submission

F.1 Critical appraisal: AFFIRM

Polman 2006 (AFFIRM)	
Study Summary	This study was a randomised, multi-centre, placebo-controlled clinical study. The primary objective of this study was to determine the effect of natalizumab in relapsing multiple sclerosis patients. The duration of this study was two years.
Number of patients randomised	942 (natalizumab n = 627; placebo n = 315)
Withdrawals	86 patients withdrew of which 39 patients discontinued the treatment but completed follow-up and 3 Patients from the placebo-arm were not treated.
Jadad score	5
Methods of generation of the random allocation	Patients were randomly assigned in a 2:1 ratio with the use of a computer-generated block randomization schedule and a multi-digit identification number.
Concealment of allocation at randomisation	Each subject's treatment assignment was determined using an IVRS program and delivered to the patient via an interactive voice-response system.
Blinding of study participants and investigators	This was a described as a double-blinded study where patients were unaware of the treatment. . Patients were provided with identical vials, labelled in such a way to ensure the identity of the treatment remained blinded. The study personnel, sponsor personnel and investigator advisory were also blinded. Evaluation of MRI's following screening were carried out by blinded physicians/technicians.
Completeness of intervention and follow-up	86 withdrawals were reported in this study, of which 39 patients completed through to follow-up.
Methods used to compensate for missing outcome data.	Missing data from subjects that missed a stage of the study was accounted for using the principle of last observation carried forward (LOCF), whereby the previous studies' results were carried forward and averaged with the non-missing value.
Was a justification of sample size provided	Sample sizes were specifically calculated using data from Biogen Idec's AVONEX® phase III study, NS26321-01. Sample size was based on two-sided tests with an experiment-wise alpha of 0.05 and 90% power. The 900 subjects sample size provided at least 92% power. Full justification of the sample size is provided in the protocol.
Was the design parallel-group or cross-over? Indicate for each cross-over study whether a carry-over effect is likely	This study was a parallel-group study.
Was the RCT conducted in the UK (or were one or more centres of the multinational RCT located in the UK)? If not, where was the RCT conducted, and is clinical practice likely to differ from UK practice?	99 clinical centres in Europe, North America, Australia and New Zealand enrolled patients for the study. Clinical practice in these countries is unlikely to differ from UK practice; the dispersion of the study is unlike to affect the results of the study.
How do the included in the RCT participants compare with patients who are likely to receive the intervention in the UK? Consider factors known to affect outcomes in the main indication, such as demographics, epidemiology, disease severity, setting.	The countries studied within this study are similar in epidemiology, disease severity and demographics to the UK. It is known that patients suffering from MS tend to be more inclined to come from temperate regions i.e. Europe, that from tropical regions. This study focuses on patients from the more temperate regions (Europe, North America, New Zealand and Australia) and therefore the epidemiology is unlikely to affect the outcomes of the study.

Polman 2006 (AFFIRM)	
For pharmaceuticals, what dosage regimens were used in the RCT? Are they within those detailed in the Summary of Product Characteristics?	The study specifies that patients were administered with 300mg infusions of natalizumab (or placebo) every four weeks up to 116 weeks. This supports the advised dosage regimen detailed in the Summary of Product Characteristics.
Were the study groups comparable?	The study specifies no significant differences in baseline characteristics between the treatment groups therefore the study groups are comparable.
Were the statistical analyses used appropriate?	A standard analysis was carried out in this study. Hazard ratios were calculated.
Were there any confounding factors that may attenuate the interpretation of the results of the RCT(s)?	Baseline characteristics are not significantly different between the study groups. No confounding factors have been noted.
Comments	This is a well-conducted study providing extensive details on the blinding process and methodology of the study.

F.2 Critical appraisal: SENTINEL

Rudick 2006 (SENTINEL)	
Study Summary	This study was a randomized, double blinded, placebo-controlled, phase III clinical study. This two-year study was designed to determine the effect of interferon beta-1a in conjunction with natalizumab as a form of treatment for relapsing-remitting multiple sclerosis as oppose to interferon beta-1a alone.
Number of patients randomised	1171 patients (interferon beta-1a + 300mg natalizumab, n = 589; placebo, n = 582)
Withdrawals	168 patients withdrew from the study (interferon beta-1a + natalizumab, n = 73; interferon beta-1a alone, n = 95). 64 patients discontinued the treatment but completed through to follow-up.
Jadad score	5
Methods of generation of the random allocation	Patients were randomly assigned in a 1:1 ratio with the use of a computer-generated schedule and provided with a multi-digit identification number, implemented by an interactive voice response system (IVRS).
Concealment of allocation at randomisation	Patients were supplied with randomisation codes implemented by the IVRS.
Blinding of study participants and investigators	This study was described as a double-blinded study whereby the patients, all study personnel, sponsor personnel involved in the conduct of the study, and members of the investigator advisory committee were blinded. The treatment provided was concealed in identical vials and labelled such that the identity of the treatment was kept hidden
Completeness of intervention and follow-up	168 patients withdrew; 64 discontinued the treatment (but completed through to follow-up. Full details of the disposition of patients during the study was reported.
Methods used to compensate for missing outcome data.	Missing data from the subjects that missed a stage of the study was accounted for using the principle of last observation carried forward (LOCF), whereby the previous studies' results were carried forward and averaged with the non-missing value. Full details are available in the report.
Was a justification of sample size provided	Sample sizes were specifically calculated using data from Biogen Idec's AVONEX® phase III study, NS26321-01. Sample size was based on two-sided tests with an experiment-wise alpha of 0.05 and 90% power. The 1200 subjects sample size provided at least 92% power. Full justification of the sample size is provided in the protocol.
Was the design parallel-group or cross-over? Indicate for each cross-over study whether a carry-over effect is likely	This study was a parallel-group study.
Was the RCT conducted in the UK (or were one or more centres of the multinational RCT located in the UK)? If not, where was the RCT conducted, and is clinical practice likely to differ from UK practice?	124 clinical centres in Europe and the united states enrolled patients for the study. Clinical practice in these countries is unlikely to differ from UK practice; the dispersion of the study is unlike to affect the results of the study.
How do the included in the RCT participants compare with patients who are likely to receive the intervention in the UK? Consider factors known to affect outcomes in the main indication, such as demographics, epidemiology, disease severity, setting.	The countries studied within this study are similar in epidemiology, disease severity and demographics to the UK. It is known that patients suffering from MS tend to be more inclined to come from temperate regions i.e. Europe, that from tropical regions. This study focuses on patients from the more temperate regions (Europe and United States of America) and therefore the epidemiology is unlikely to affect the outcomes of the study.
For pharmaceuticals, what dosage regimens were used in the RCT? Are they within those detailed in the Summary of Product Characteristics?	The patients were administered with 300mg infusions every 4 weeks as well as 30μg of AVONEX by IM injection weekly for up to 16 weeks. This supports the advised dosage regimen in the Summary of Product Characteristics.

Rudick 2006 (SENTINEL)	
Were the study groups comparable?	There were no significant differences in demographic or disease-related baseline characteristics between the two treatment arms, with the exception of the duration of disease (median, seven years in the combination-therapy group and eight years in the group assigned to interferon beta-1a alone; P = 0.02).
Were the statistical analyses used appropriate?	A standard analysis was carried out in this study. Hazard ratios were calculated.
Were there any confounding factors that may attenuate the interpretation of the results of the RCT(s)?	The study indicated that the duration of disease characteristic in the two treatment arms was significantly different (median, seven years in the combination-therapy group and eight years in the group assigned to interferon beta-1a alone; P = 0.02), however this is not highly significant in the interpretation of the results.
Comments	This study was well conducted. Full details of blinding and methodology have been reported; all the results have been accounted for.

F.3 Critical appraisal: MS 201

Miller 2004 (MS 201)	
Study Summary	This study was a randomized, double-blinded, placebo-controlled clinical study of patients with multiple sclerosis. The primary objective of this study was to determine the effect of natalizumab in patients with relapsing-remitting or secondary-progressive Multiple Sclerosis as well as assessing the safety, tolerability and pharmacokinetics of Natalizumab in these patients over a 24 week period.
Number of patients randomised	73 patients, only 72 received study medication (natalizumab, n = 37; placebo, n = 35)
Withdrawals	3 patients (natalizumab, n = 1; placebo, n = 2)
Jadad score	5
Methods of generation of the random allocation	This study was a multi-centre study. Individuals' details i.e. patients weight were sent off to Élan (Europe) from the individual centres along with randomized lists generated by an independent statistician. Vials were then produced containing either natalizumab or the placebo, clearly labelled with the randomized allocated number.
Concealment of allocation at randomisation	Patients were allocated with randomisation codes.
Blinding of study participants and investigators	This study was a double-blinded study. Patients were provided with identical vials, clearly labelled with a multi-digit code, corresponding to each patient. These vials contained either natalizumab or the placebo in the form of clear identical liquids. MRI films were dispatched directly and were not seen by investigators at the individual centres.
Completeness of intervention and follow-up	This study has reported full details on the numbers of patients that withdrew from each treatment arm, as well as the reasons for withdrawal.
Methods used to compensate for missing outcome data.	Patients with missing MRI scans were looked at individually and an estimated number of new lesions was determined by taking into account the scan results preceding and following the missing scan. Two of the patients had insufficient data to produce an estimated result and the data was left as "missing".
Was a justification of sample size provided	Sample size was determined on the assumption of significance at 5% and a power of 80%. Full details of the sample size determination is found in the study.
Was the design parallel-group or cross-over? Indicate for each cross-over study whether a carry-over effect is likely	This was a parallel-group study.
Was the RCT conducted in the UK (or were one or more centres of the multinational RCT located in the UK)? If not, where was the RCT conducted, and is clinical practice likely to differ from UK practice?	All 9 clinical centres were based in the UK.
How do the included in the RCT participants compare with patients who are likely to receive the intervention in the UK? Consider factors known to affect outcomes in the main indication, such as demographics, epidemiology, disease severity, setting.	All participants included in the RCT were based in the UK.
For pharmaceuticals, what dosage regimens were used in the RCT? Are they within those detailed in the Summary of Product Characteristics?	Patients were injected with an intravenous infusion at a dose of 3.0mg/kg which was administered on each of the two study days (week 0 and week 4). This dosage supports the dosage regimen detailed in the Summary of Product Characteristics.
Were the study groups comparable?	The two treatment groups were comparable with regards to demographic characteristics, MS history and screening physical examination.

Miller 2004 (MS 201)	
Were the statistical analyses used appropriate?	A standard analysis was carried out in this study. Hazard ratios were calculated.
Were there any confounding factors that may attenuate the interpretation of the results of the RCT(s)?	There was a significant difference in types of MS amongst the patients within the two treatment arms, however this was regarded as not significant to affect the outcome of the results. There was a significant different between the numbers of males and females in the treatment arms but, again, this was not thought to attenuate the interpretation of the results.
Comments	This study was well conducted. Full details on the completeness of intervention and follow-up was provided along with detailed information of the study design.

F.4 Critical appraisal: MS 231

Miller 2003 (MS 231)	
Study Summary	This study was a randomized, multi-centre, double-blinded, placebo-controlled clinical study designed to examine the effect of natalizumab (3 or 6mg/kg), compared to placebo, on brain lesion activity in subjects with relapsing-remitting or secondary-progressive multiple sclerosis. This phase II study appears to have been studied over a period of 2 years.
Number of patients randomised	214 patients including one erroneously randomized patient (placebo, n = 71; 3mg/kg natalizumab, n = 68; 6mg/kg natalizumab, n = 74)
Withdrawals	16 withdrawals (placebo, n = 3; 3mg/kg natalizumab, n = 4; 6mg/kg natalizumab, n = 9)
Jadad score	5
Methods of generation of the random allocation	This study was a multi-centre study, patients were randomized in a 1:1:1 ratio with the use of a site-stratified blocked randomization schedule. Patients were supplied with a random multi-digit code.
Concealment of allocation at randomisation	Patients were allocated with a randomized multi-digit code, implemented using a centralized Interactive Voice Response System (IVRS).
Blinding of study participants and investigators	This study was a double-blinded study. Patients were provided the treatment in identical 20mL vials containing either placebo or natalizumab. The pharmacist providing the drug to the patient was also blinded. Reports containing information on the white blood cell count was concealed from the personnel and investigators. Blinded Evaluating Investigators conducted EDSS evaluations.
Completeness of intervention and follow-up	All the study subjects were accounted for. 16 patients withdrew from the study, 9 patients withdrew during the treatment phase and 7 patients withdrew during the follow-up.
Methods used to compensate for missing outcome data.	Missing results from the MRI scans (primary endpoint results) were replaced by calculating an average number of lesions on available scans over the 6-month treatment period. Missing secondary endpoint values due to missed visits were accounted for by inputting on a last observation carried forward (LOCF) basis. The study reported full details on accounting for missing data.
Was a justification of sample size provided	The sample size estimate was based upon using the Wilcoxon-Mann-Whitney rank-sum test. Assuming an estimated 10% dropout rate between randomization and study completion, for a 2-sided test at the 5% level of significance, a sample size of 73 subjects (per group) was required for 80% power. Full details of determination of the sample size are provided within the protocol.
Was the design parallel-group or cross-over? Indicate for each cross-over study whether a carry-over effect is likely	This study was a parallel-group study.
Was the RCT conducted in the UK (or were one or more centres of the multinational RCT located in the UK)? If not, where was the RCT conducted, and is clinical practice likely to differ from UK practice?	This study was a multi-centre study conducted in the United States, Canada and the United Kingdom. Clinical practice is unlikely to differ amongst the countries.
How do the included in the RCT participants compare with patients who are likely to receive the intervention in the UK? Consider factors known to affect outcomes in the main indication, such as demographics, epidemiology, disease severity, setting.	The countries studied within this study are similar in epidemiology, disease severity and demographics to the UK. It is known that patients suffering from MS tend to be more inclined to come from temperate regions i.e. Europe, that from tropical regions. This study focuses on patients from the more temperate regions (Canada, United Kingdom and United States of America) and therefore the epidemiology is unlikely to affect the outcomes of the study.
For pharmaceuticals, what dosage regimens were used in the RCT? Are they within those detailed in the Summary of Product Characteristics?	Patients were administered, via intravenous infusions, with 3mg/kg natalizumab, 6mg/kg natalizumab or placebo. The 3mg/kg natalizumab is within the detailed dosage regimen in the Summary of Product Characteristics, however the 6mg/kg does not comply.
Were the study groups comparable?	The study groups are comparable; groups are balanced across the demographic characteristics with the exception of gender (female to male ration is 2:1)

Miller 2003 (MS 231)	
Were the statistical analyses used appropriate?	Unclear
Were there any confounding factors that may attenuate the interpretation of the results of the RCT(s)?	There were no significant confounding factors that may affect the interpretation of the results.
Comments	This study was well conducted, an extensive detail on the methodology has been provided.

Appendix G Independent critical appraisals of IFN-beta and GA studies included in systematic review updates

G.1 Interferon studies covered in the Rice review (73)

IFNB MS, 1996	
Study Summary	This study was a randomized, multi-centre, double-blinded, placebo-controlled study designed to test the efficacy of interferon-β-1b in patients with relapsing-remitting multiple sclerosis. Patients received placebo, 1.6 MIU IFNB or 8 MIU IFNB self-administered everyday. This study was carried out over a period of 2 years.
Number of patients randomised	372 patients were randomised (placebo, n = 123; 1.6 MIU IFNB, n = 125; 8 MIU IFNB, n = 124)
Withdrawals	65 patients discontinued treatment during the first 2 years (placebo, n = 23; 1.6 MIU IFNB, n = 18; 8.0 MIU IFNB, n = 24). 122 patients did not complete the third year (including 22 patients who chose not to continue when the study was extended). Withdrawal was due to lack of efficacy, excessive use of steroids, toxicity, 1 patient due to suicide, and other adverse events. This study has clearly reported patient withdrawal.
Jadad score	4
Methods of generation of the random allocation	Not reported
Concealment of allocation at randomisation	Not reported
Blinding of study participants and investigators	Identical vials containing either the IFNB treatment or placebo were prepared; both vials contained a similar amount of human albumin and dextrose. All personnel at each study site were blinded to treatment categories Patients receiving the IFNB are more prone to experience to side effects e.g. flu-like symptoms, headache, nausea, and skin reactions at the injection site. 50% of the IFNB treatment group had visible side effects. Hence blinding may have been compromised this study because of this.
Completeness of intervention and follow-up	Patient withdrawal (reported above). The report stated that a systematic follow-up of dropouts was not performed.
Methods used to compensate for missing outcome data.	A modified "intent-to-treat" analysis was used, to avoid any systematic influence on outcome by dropouts who behave differently for a given outcome measure than do those remaining in the study. Efficacy measures were analyzed separately for dropouts and completers. There was a lack of detail provided in the report regarding this.
Was a justification of sample size provided	This study has not reported a justification of sample size, however, the study has mentioned that the dropout rate did not exceed that anticipated at the study's inception.
Was the design parallel-group or cross-over? Indicate for each cross-over study whether a carry-over effect	This study was a parallel-group vs. placebo study.

IFNB MS, 1996	
is likely	
Was the RCT conducted in the UK (or were one or more centres of the multinational RCT located in the UK)? If not, where was the RCT conducted, and is clinical practice likely to differ from UK practice?	This study was conducted in 11 different medical centres in the United States and Canada. Medication was self-administered.
How do the included in the RCT participants compare with patients who are likely to receive the intervention in the UK? Consider factors known to affect outcomes in the main indication, such as demographics, epidemiology, disease severity, setting.	The patients in this study were accrued from the United States and Canada; the demographics, epidemiology, disease severity are very similar between the two countries and therefore it is unlikely that these factors could have affected the outcome of the study.
For pharmaceuticals, what dosage regimens were used in the RCT? Are they within those detailed in the Summary of Product Characteristics?	Patients were administered with either 1.6 MIU IFNB or 8.0 MIU IFNB every other day. The recommended dose of Betaferon in patients suffering from relapsing-remitting multiple sclerosis or from secondary progressive multiple sclerosis is 250 microgram (8.0 million IU), contained in 1 ml of the reconstituted solution. The SPC also recommends titration of the medication. The dose regime used in this study is within the range specified in the SPC.
Were the study groups comparable?	The study has reported the study groups as comparable. There were no significant baseline differences between the study groups besides the higher female population in each group (2:1, female: male).
Were the statistical analyses used appropriate?	Analysis was based on Intent-to treat. ANOVA was used to analyse treatment group differences. The Cochran-Mantel-Haenszel chi-square test was used to analyse categorical variables. A two-tailed Fisher's exact test was used for categorical data. The log rank statistic test was also used. The statistical tests used in this study seem to be appropriate.
Were there any confounding factors that may attenuate the interpretation of the results of the RCT(s)?	There were no significant confounding factors that may have attenuated the interpretation of the results.
Comments	This study was well conducted, with a sufficient sample size. More detail is required on the randomisation process, and justification of sample size. Blinding methods may be invalid due to side effects portrayed by the treatment arm.

Knobler, 1993	
Study Summary	Patients all had definite RRMS and were randomised into 4 different interferon beta treatments and placebo. This was a dose finding study, which included a placebo with a follow-up period. Sample size was very small. After 6 months on the dose finding regimes, most patients were given 8mU interferon beta 3 times per week. A response was probably observed for the medication, but the sample sizes were to small for significance to be seen. Safety data up to six years of follow-up was given.
Number of patients randomised	30 patients (male or female) randomised into 5 groups of 6 patients each.
Withdrawals	1 patient dropped out because they became aware of the dosage. Withdraw rates were reported where 12 patients withdrew from the study during treatment.
Jadad score	4
Methods of generation of the random allocation	Not described
Concealment of allocation at randomisation	Patients and investigators had no prior knowledge of the injection volume and dosage group to which patients were assigned.
Blinding of study participants and investigators	Betaseron drug and placebo were identical in appearance. Medication was self administered by patients and tags removed prior to dispensing. For clinical examinations one neurologist worked independently of the other to either do a neurological examination and verify exacerbations or to evaluate clinical tests. It is difficult to maintain blindness because dosage for IFN-beta is related to side effects and this study, in part, aimed to address this.
Completeness of intervention and follow-up	Withdraws are described above. All completed the first 24 weeks. In the follow up period 6-months to 3 years and 3-ears to 6-years explanation was not given for withdraws.
Methods used to compensate for missing outcome data.	Unclear
Was a justification of sample size provided	Not specified, but this is a pilot study (dose finding)
Was the design parallel-group or cross-over? Indicate for each cross-over study whether a carry-over effect is likely	Parallel group design versus placebo
Was the RCT conducted in the UK (or were one or more centres of the multinational RCT located in the UK)? If not, where was the RCT conducted, and is clinical practice likely to differ from UK practice?	Conducted in the USA at 3 university centres. It is unlikely that practice will differ significantly from the UK. Medication was self administered.
How do the included in the RCT participants compare with patients who are likely to receive the intervention in the UK? Consider factors known to affect outcomes in the main indication, such as demographics, epidemiology, disease severity, setting.	Both countries are Western industrialised, and there is likely to be significant genetic overlap between the two. This is not likely to be a problem.
For pharmaceuticals, what dosage regimens were used in the RCT? Are they within those detailed in the Summary of Product Characteristics?	The SPC recommends dosage starting from 62.5 mg and titrated up to 250 mg (8 million IU). In this study dosage was 0.8 to 16 million IU, with patients transferred, generally, to 8 million after 6 months. Hence, the dosage regime is consistent with practise according to the SPC.
Were the study groups comparable?	Yes, demographic characteristics were stated to be comparable between the treatment groups, but given they are so small this might be refutable.
Were the statistical analyses used appropriate?	The authors controlled for between site differences. Cochran-Mantel-Haenszel, ANOVA and Kaplan-Meier were used in analysis

	which seemed appropriate.
Were there any confounding factors that may attenuate the interpretation of the results of the RCT(s)?	The sample sizes for each treatment group were very small which might make unforeseen confounding factors problematic. However, this should be reflected in the inference to test for significance.
Comments	Study appeared to be well planned and written up. Given it was a pilot study, much useful information was drawn from it that would need to be substantiated with larger studies.

MSCRG, 1996	
Study Summary	This study was a randomized, double-blinded, placebo-controlled, multi-centre, phase III study designed to evaluate the efficacy of Interferon-β-1a (IFN-β-1a) as a treatment for exacerbating-remitting multiple sclerosis (ERMS). Patients were administered with weekly intramuscular injections. This study was carried out over a period of 4 years with a 2 year treatment period and a 2 year follow-up.
Number of patients randomised	301 patients were randomized to receive weekly injections of either IFN-β-1a (n=158) or placebo (n=143)
Withdrawals	2 patients withdrew from the placebo arm and 7 patients from the interferon-β-1a due to adverse events. 1 patient in the interferon-β-1a treatment arm died from pulmonary embolism and cardiac arrhythmia (unrelated to the study drug).
Jadad score	5
Methods of generation of the random allocation	Efron's biased coin method was used for randomization. The randomization schedule was generated at the Danish Multiple Sclerosis Research Centre (DMSC).
Concealment of allocation at randomisation	The randomisation schedule was forwarded to the clinical centre data coordinator. Four clinical centres (Buffalo, Cleveland, Portland and Washington) sequentially assigned the next ID number from the randomization schedule to the patients following registration.
Blinding of study participants and investigators	Only the DMSC had access to randomisation schedules containing treatment arm assignments and listing subject names. The vials of treatment were labelled with ID and lot number – no information on the treatment contained was provided. The randomization schedule was generated before patient accrual therefore names of patients were available to the staff labelling the vials. Opaque double sealed envelopes were sent to the principle investigators to be opened in the event of a medical emergency.
Completeness of intervention and follow-up	93% of patients completed the treatment as scheduled.
Methods used to compensate for missing outcome data.	Unclear
Was a justification of sample size provided	The study reports a justification of sample size; calculations assumed a 2 year sustained progression rate of 50% for patients treated with placebo and 33% for patients treated with IFN-β-1a. The study sample was calculated in order to allow a statistical power of 80%.
Was the design parallel-group or cross-over? Indicate for each cross-over study whether a carry-over effect is likely	This study was a parallel-group design vs. placebo.
Was the RCT conducted in the UK (or were one or more centres of the multinational RCT located in the UK)? If not, where was the RCT conducted, and is clinical practice likely to differ from UK practice?	This multi-centre study was conducted in the US. Clinical practice is unlikely to have a significant difference from UK practice.
How do the included in the RCT participants compare with patients who are likely to receive the intervention in the UK? Consider factors known to affect outcomes in the main indication, such as demographics, epidemiology, disease severity, setting.	The study was multicentre in the USA with a relatively large sample size. The study population is likely to reflect the UK patient population quite well. Statistics related to epidemiology, disease severity, and demographics are likely to be similar.
For pharmaceuticals, what dosage regimens were used in the RCT? Are they within those detailed in the Summary of Product Characteristics?	Treatment consisted of 6.0×10^6 IU (30µg) IFN-β-1a administered weekly. Acetaminophen, 650 mg was administered every 6 hours starting immediately before and continuing for 24 hours after each study injection. This supported the detailed dosage in the Summary of Product Characteristics.
Were the study groups comparable?	The study does not state that the study groups were comparable however, there are no significant differences between the demographical characteristics besides gender (female, n = 221; male, n = 80)

MSCRG, 1996	
Were the statistical analyses used appropriate?	The study reports the use of the Mantel-Cox stratified log-rank test in a Kaplan-Meier failure time analysis, Mantel-Haenszel method, Mann-Whitney rank-sum test, Fischer's exact test, multivariate analysis of variance analysis (MANOVA) and univariate analysis of variance analysis (ANOVA) for analysis, which seemed appropriate.
Were there any confounding factors that may attenuate the interpretation of the results of the RCT(s)?	There were no confounding factors that may attenuate the interpretation of the results of the RCTs.
Comments	This is a well-conducted study with extensive detail on methodology, blinding, concealment of randomisation and allocation.

OWIMS, 1999	
Study Summary	This study compared 2 different doses of beta (1a) interferon to placebo in RRMS patients over 48 weeks. The outcome measure for this study was MRI related data. The results are consistent with MRI related benefit at low dose in MS, but highlight the limited clinical effect. The only significant clinical effect was steroid use, whereas for MRI related parameters results were highly significant.
Number of patients randomised	293
Withdrawals	All withdraws (both at 24 and 48 weeks) were outlined in the publication. Withdraws appeared to be proportional to dosage of medication, with 13 withdrawing from the high dose β interferon.
Jadad score	5
Methods of generation of the random allocation	Computer generated done centrally 1:1:1 stratified.
Concealment of allocation at randomisation	Randomisation codes were delivered to instigator in sealed envelopes that were to be opened in emergency situations. There were no reported incidence of breaking the concealment.
Blinding of study participants and investigators	Randomisation codes were used. Two physicians were involved: one for administration and one for neurological assessment. Physicians were blind with respect to adverse event profiles, and patients instructed to cover injection sites an refrain from discussing symptoms. But given injection site adverse reactions it will have been difficult to maintain true double blinding.
Completeness of intervention and follow-up	All patients were accounted for and explained. 97 of 100 completed in the placebo; 87 of 95 in the 22μg IFN-beta group and 85 of 96 in the 44μg group.
Methods used to compensate for missing outcome data.	ITT analysis was performed. Data from patients that withdrew was subjected to censoring depending on their tie on the study.
Was a justification of sample size provided	Yes, study was powered at 80% to detect a 50% reduction in no of combined active lesions at week 24.
Was the design parallel-group or cross-over? Indicate for each cross-over study whether a carry-over effect is likely	Parallel group
Was the RCT conducted in the UK (or were one or more centres of the multinational RCT located in the UK)? If not, where was the RCT conducted, and is clinical practice likely to differ from UK practice?	This study was done in 11 centres 5 countries including the UK. Results are applicable to the UK.
For pharmaceuticals, what dosage regimens were used in the RCT? Are they within those detailed in the Summary of Product Characteristics?	Study used 22 or 44μg (micrograms) IFN-beta-1a. The SPC for Rebif specifies 22μg.
Were the study groups comparable?	Baseline patient characteristics showed no differences between treatments.
Were the statistical analyses used appropriate?	ANOVA was used to assess no of combined active lesions at week 24 and a model fitted to adjust for factors such as centre and baseline no of combined active lesions. A generalised linear model was used to analyse relapse count. Cox Proportional hazards and logistic regression models were used for time to endpoints and binary outcomes respectively. These seemed appropriate.
Were there any confounding factors that may attenuate the interpretation of the results of the RCT(s)?	These were accounted for in the analyses.
Comments	Well written study. Withdraws and adverse events were well covered and study was easy to follow. Although the study attempted to maintain blinding throughout the study, the ability to maintain a double blind study, given injection site reactions is

	questionable.

PRISMS 1998	
Study Summary	All patients had clinically defined or laboratory-supported RRMS of at least 1 year duration. Patients were randomised into three different treatment arms: interferon beta 1a (22μg), interferon beta 1a (44μg), and placebo. Treatment was self-administered, subcutaneous injection, three times weekly for 2 years. The primary hypothesis of this study was that interferon β-1a would lower the relapse rate. This study reports 2 year data and provides an analysis of patients who undergo biannually and monthly MRI scans. Note that all patients are included in the biannually analysis and 260 patients undergo monthly MRIs.
Number of patients randomised	560 adult patients (male or female) were randomised into 3 treatment groups.
Withdrawals	58 patients withdrew from the study. 4 patients experienced disease progression (placebo = 3; IFNβ (22μg) = 1); 17 patients withdrew due to an adverse event (placebo = 2; ; IFNβ (22μg) = 6; IFNβ (44μg) = 9). Two patients died from unrelated causes during the study (placebo = 1 and ; IFNβ (22μg) = 1). Patient numbers were accounted for.
Jadad score	4
Methods of generation of the random allocation	The randomisation list was computer-generated by Serono Biometrics and stratified by centre which was appropriate.
Concealment of allocation at randomisation	The study drug was packed accordingly for concealment and delivered to the centres so that treatment allocation remained concealed.
Blinding of study participants and investigators	Total volume of subcutaneous injection was 0.5 ml and the study medication was self-administered. Blinding of participants was not described in detail. Authors state that all personnel involved in the study were unaware of treatment. Injection sites were covered during neurological exams to mask local site reactions.
Completeness of intervention and follow-up	Withdraws are described above. Of the 560 patients randomised, 533 (95%) of patients completed 1 year of treatment and 502 (90%) completed 2 years of treatment. However 2 year data was available for 533 (95%) of patients.
Methods used to compensate for missing outcome data.	Analysis was by intention to treat. All outcome data were included. A statistical method was used to carry the last observation forward, taking into account time spent in the study.
Was a justification of sample size provided	The study had a power of 80% to detect a mean difference of 0.64 in the mean number of relapse between the IFNβ (22μg) and placebo group. A sample size of 100 participants per treatment arm was required.
Was the design parallel-group or cross-over? Indicate for each cross-over study whether a carry-over effect is likely	Parallel group design versus placebo
Was the RCT conducted in the UK (or were one or more centres of the multinational RCT located in the UK)? If not, where was the RCT conducted, and is clinical practice likely to differ from UK practice?	The study was conducted in 22 centres in 9 countries (including the UK). All countries were industrialised and western. It is likely that practise in this study is representative of that in the UK.
How do the included in the RCT participants compare with patients who are likely to receive the intervention in the UK? Consider factors known to affect outcomes in the main indication, such as demographics, epidemiology, disease severity, setting.	The study sampled from a broad patient population and with a large sample size. Additionally, participants were included from the UK. It is likely that the results from this study are applicable to the UK population.
For pharmaceuticals, what dosage regimens were used in the RCT? Are they within those detailed in the Summary of Product Characteristics?	The SPC recommended INFβ to be given at 44mμ, three times per week by subcutaneous injection. A lower dose (22μg) is recommended for patients that cannot tolerate higher dose. Hence, the dosage regime is consistent with practise according to the SPC.

Were the study groups comparable?	Yes, demographic characteristics were stated to be comparable between the treatment groups.
Were the statistical analyses used appropriate?	Authors used a Cox proportional hazards models, logistic regression, ANOVA and χ^2 test which were appropriate.
Were there any confounding factors that may attenuate the interpretation of the results of the RCT(s)?	There were no confounding factors that may attenuate the interpretation of the results of the RCTs.
Comments	Study appeared to be well planned and written up. Baseline data is reported in detail as is the final analysis.

G.2 Glatiramer acetate studies covered in the Munari review (70)

Bornstein, 1987	
Study Summary	This was a double blind, randomised pilot study of 50 RRMS patients of self administered COP1 (GA). 6 of 23 patients in the placebo and 14 of 24 in the COP 1 group suffered no exacerbations. Results suggest benefit for COP1, but the sample sizes are small.
Number of patients randomised	Study patients were matched according to sex, number of exacerbations and degree of disability. The random assignment for each pair was determined by the assignment of the first patients. 48 patients in 24 matched pairs and 2 unmatched individuals were randomised.
Withdrawals	Withdrawals are poorly reported, but all patients were accounted for in the study (3 withdraws).
Jadad score	3
Methods of generation of the random allocation	Unclear
Concealment of allocation at randomisation	unclear
Blinding of study participants and investigators	Efforts were made to maintain blinding including limiting discussion of examining neurologist and patient in discussing side effects. A test was conducted to examine blinding success, that suggested side effects may have enabled patients and researchers to correctly guess treatment to some extent. Hence blinding may have been compromised because of side effects.
Completeness of intervention and follow-up	unclear
Methods used to compensate for missing outcome data.	Attempted ITT analysis where possible, two patients receiving 2 dropped out. Data on patients lost to follow-up were censored at the time of withdraw.
Was a justification of sample size provided	Not stated, but this was a pilot study so this may have been inappropriate
Was the design parallel-group or cross-over? Indicate for each cross-over study whether a carry-over effect is likely	Parallel group with matched pairs of patients.
Was the RCT conducted in the UK (or were one or more centres of the multinational RCT located in the UK)? If not, where was the RCT conducted, and is clinical practice likely to differ from UK practice?	Study was conducted in the USA and Israel, and patients self administered. Study methodology and patient population is likely to be applicable to UK.

For pharmaceuticals, what dosage regimens were used in the RCT? Are they within those detailed in the Summary of Product Characteristics?	20 mg in 1 ml daily for 2 years was used in the study. SPC for Copaxone recommends 20mg injections. Hence dose used in this study is consistent with SPC.
Were the study groups comparable?	Patients were matched as pairs with respect to treatment (24 pairs matched and 1 pair unmatched).
Were the statistical analyses used appropriate?	Multiple logistic regression was used to study co-variants.
Were there any confounding factors that may attenuate the interpretation of the results of the RCT(s)?	MLR was used to adjust for covariates and pairing at randomisation should have decreased risk for this.
Comments	This was a pilot study with small sample size. It appeared to be well reported and written.

Bornstein, 1991	
Study Summary	chronic progressive MS patients were randomised into placebo or GA. The primary endpoint was progression (EDSS)at 12 and 24 months. The results for these endpoints were not significant P=0.088.
Number of patients randomised	106.
Withdrawals	86 patients completed study requirements. 10 from placebo and 10 from GA withdrew.
Jadad score	4
Methods of generation of the random allocation	Randomised block design mentioned
Concealment of allocation at randomisation	Only the statistician and clinical assistant were aware of assignment
Blinding of study participants and investigators	Patients were coded and codes not broken during the study. 2 neurologists, working separately, assessed exacerbation and clinical parameters. Blinding was assessed after the study, where about a half of the patients guessed their assignments.
Completeness of intervention and follow-up	81% finished the study the remaining patients were withdraws and an explanation was given for withdraw.
Methods used to compensate for missing outcome data.	A decision was made by PI whether to count withdraws as confirmed progressions prior to breaking codes. Data on patients lot to follow-up were censored at the time of withdraw.
Was a justification of sample size provided	unclear
Was the design parallel-group or cross-over? Indicate for each cross-over study whether a carry-over effect is likely	Parallel group
Was the RCT conducted in the UK (or were one or more centres of the multinational RCT located in the UK)? If not, where was the RCT conducted, and is clinical practice likely to differ from UK practice?	Study was performed in 2 centres in the USA and the results applicable to the UK. (Western industrialised country with genetic overlap)
For pharmaceuticals, what dosage regimens were used in the RCT? Are they within those detailed in the Summary of Product Characteristics?	Patients were given 64 vials (15mg GA in 0.75 ml solution). Injection was 1 vial per day, which was less that the SPC specified (20mg/day).
Were the study groups comparable?	No significant differences observed between groups for base line characteristics.
Were the statistical analyses used appropriate?	Multiple logistic model was used to examine factors contributing to progression. Proportional hazards model was used to examine time to progression. These seemed appropriate.
Were there any confounding factors that may attenuate the interpretation of the results of the RCT(s)?	Analyses were used to adjust data where necessary,
Comments	Study was straightforward and well written. It was a follow up to a previous study. However the dosage was less and it was unclear why this lower dose was used.

Comi 2001	
Study Summary	All patients who had relapsing-remitting multiple sclerosis diagnosed for at least 1 year. An EDSS score of 0 to 5 was required with at least one documented relapse in the preceding 2 years and at least one enhancing lesion on their screening brain MRI. This was a double blind, placebo-controlled, randomised study lasting nine months. The aim of this study was to determine whether treatment with glatiramer acetate is associated with a measurable effect on the inflammatory aspect of the disease and to define the time course of the evolution of any effect. The primary outcome measure was the total number of enhancing lesions. In this study treatment with glatiramer acetate showed a significant reduction in total number of enhancing lesions compared with placebo. The reporting of withdrawals is difficult to follow.
Number of patients randomised	239 patients were randomised to treatment with placebo (n = 120) or glatiramer acetate (20mg; n = 119).
Withdrawals	Although the authors state that 7 patients withdrew from each treatment arm, details of the withdrawals are given for 16 patients. It is not known if this is due to reporting for more than one cause. Five patients withdrew due to adverse events (placebo = 2; glatiramer acetate = 3). One patient in the glatiramer acetate arm withdrew due to severe disease exacerbation.
Jadad score	4
Methods of generation of the random allocation	The randomisation list, stratified by centre was computer-generated by the TEVA statistical data management department.
Concealment of allocation at randomisation	Concealment of allocation was not specified but it was stated that all personnel involved in the study were unaware of treatment allocation.
Blinding of study participants and investigators	Blinding of participants is not described. Authors state that all personnel involved in the study were unaware of treatment. Authors also state that patients and physician blinding were not formally assessed because the primary and secondary outcome measures were MRI parameters. Also patients and treating neurologists were asked not to discuss safety issues with the examining neurologist.
Completeness of intervention and follow-up	Withdraws are described above. Although details of withdrawals are reported these are not clear. Of the 1309 planned MRI session in the glatiramer acetate group, 1237 (94.5%) were available for analysis. The comparable proportion in the placebo group was 96.3%. No reason for this is given.
Methods used to compensate for missing outcome data.	An intention-to-treat analysis was performed, with last observation carried forward method to account for early discontinuation and missing data.
Was a justification of sample size provided	The sample size was projected based on literature data and on simulations modelled using a Poisson cyclic variable. For a treatment effect greater than 30% a 9-month study with 85 patients would provide more than 85% power to detect a significant difference in the primary outcome.
Was the design parallel-group or cross-over? Indicate for each cross-over study whether a carry-over effect is likely	Parallel group design versus placebo
Was the RCT conducted in the UK (or were one or more centres of the multinational RCT located in the UK)? If not, where was the RCT conducted, and is clinical practice likely to differ from UK practice?	This study was conducted in 29 centres in Europe and Canada. It is not explicated states whether the UK was included. Clinical practice is unlikely to have a significant difference from UK practice.
How do the included in the RCT participants compare with patients who are likely to receive the intervention in the UK? Consider factors known to affect outcomes in the main indication, such as demographics, epidemiology, disease severity, setting.	It is known that patients suffering from MS tend to be more inclined to come from temperate regions i.e. Europe, than from tropical regions. This study focuses on patients from the more temperate regions and therefore the epidemiology is unlikely to affect the outcomes of the study.

For pharmaceuticals, what dosage regimens were used in the RCT? Are they within those detailed in the Summary of Product Characteristics?	The recommended dosage in the SPC for glatiramer acetate is 20mg administered as a subcutaneous injection daily. Hence, the dosage regime is consistent with practice according to the SPC.
Were the study groups comparable?	Yes, baseline demographics and clinical characteristics did not differ significantly between the treatment groups.
Were the statistical analyses used appropriate?	Authors used a Cox proportional hazards models, logistic regression, ANOVA, two-sided t-test, or Mann-Whitney test and χ^2 test which seemed appropriate.
Were there any confounding factors that may attenuate the interpretation of the results of the RCT(s)?	There were no confounding factors that may attenuate the interpretation of the results of the RCTs.
Comments	Study appeared to be well planned and written up. Safety data and withdrawal rates are not clearly reported.

Johnson, 1995	
Study Summary	This study was a randomised, multi-centre, open-label, placebo-controlled, phase III study designed to study the effect glatiramer acetate (GA). Patients were randomised to receive either 20 mg of GA or placebo by daily subcutaneous injection. This study was carried out over a period of 2 years. The primary endpoint for this study was a difference in MULTIPLE SCLEROSIS relapse rate. Authors concluded that GA can significantly and beneficially alter the course of RRMS in a well-tolerated fashion.
Number of patients randomised	251 patients were randomised (GA, n = 125; placebo, n = 126)
Withdrawals	There were a total of 56 withdrawals (details below)
Jadad score	4
Methods of generation of the random allocation	This study was a multi-centre study of 11 universities. A centralised randomisation scheme was used but details are not reported.
Concealment of allocation at randomisation	Unclear
Blinding of study participants and investigators	Medication was distributed to each centre by an independent data management and coordination centre. The medication was supplied in single-dose vials. Medication was self-administered.
Completeness of intervention and follow-up	The study was carried out in two stages. At the completed 24-month controlled phase, 19 patients had withdrawn from the GA treatment arm and 17 patients withdrew from the placebo arm. At the 36-month controlled-phase another 2 patients dropped out from the GA treatment arm and 7 patients from the placebo arm. In total, 24/125 patients withdrew from the GA treatment arm and 32/126 patients withdrew from the placebo arm. Withdrawal was either due to disease progression or adverse events.
Methods used to compensate for missing outcome data.	Data was excluded if patients didn't complete 6 months of treatment, failed to complete 2 years (730 days) of treatment, and patients who missed over 5% of consecutive study medication doses or 10% of total doses during the study.
Was a justification of sample size provided	A justification of the sample size is not reported.
Was the design parallel-group or cross-over? Indicate for each cross-over study whether a carry-over effect is likely	Parallel-group vs. placebo
Was the RCT conducted in the UK (or were one or more centres of the multinational RCT located in the UK)? If not, where was the RCT conducted, and is clinical practice likely to differ from UK practice?	The RCT was conducted in the United States of America at 11 universities. Clinical practice is unlikely to differ from UK practice.
How do the included participants in the RCT compare with patients who are likely to receive the intervention in the UK? Consider factors known to	The study was carried out in the United States. This country is similar in epidemiology, disease severity and demographics to the UK. There is unlikely to be any significant difference between the patients accrued in the study and UK patients (if the study was to be carried out here).

Johnson, 1995	
affect outcomes in the main indication, such as demographics, epidemiology, disease severity, setting.	
For pharmaceuticals, what dosage regimens were used in the RCT? Are they within those detailed in the Summary of Product Characteristics?	Patients were supplied with 20mg/day of GA. This supports the dosage detailed in the Summary of Product Characteristics.
Were the study groups comparable?	Both study groups had considerably more females (2/3:1). However there was no significant difference between the two study groups and therefore were comparable.
Were the statistical analyses used appropriate?	Statistical analysis in this study included the Student's *t*-test for continuous variables, the chi-squared test and the Kaplan-Meier approach which seemed appropriate.
Were there any confounding factors that may attenuate the interpretation of the results of the RCT(s)?	There were no confounding factors that may attenuate the interpretation of the results of the RCT.
Comments	Reports were written detailing individual centre results. The study has been well written, however, lacks detail in the randomization process and sample size justification.

Appendix H Systematic review of natalizumab economic evaluations

A systematic review of economic evaluations for natalizumab in the treatment of multiple sclerosis

Heron Evidence Development Ltd, Letchworth, Hertfordshire

Date of Most Recent Substantive Amendment: 04/11/06

H.1 Introduction

Natalizumab is valuable in the treatment of highly active RRMS as it offers high efficacy and substantial reduction in clinical and MRI measures of MS disease activity. It should be considered for first line monotherapy use in patients with rapidly evolving severe RRMS and as the first option for patients who have failed β interferon therapy. This review aims to collect and assess economic evaluations that have been undertaken to assess the cost effectiveness of natalizumab as treatment of MS.

H.2 Methods

We searched Medline, Medline in Process, EMBASE and NHS EED databases up to the end of week 2 September 2006 including all years covered by each database but limiting to those articles published in the English language. The search strategies used to search the databases are given in sections H.5, for the respective databases. Specifically, the searches were designed to find any economic evaluations related to MS and natalizumab.

Abstracts of articles retrieved by the literature searches were inspected and included or excluded according to pre-defined eligibility criteria listed in Table 1.

Table 103 Eligibility criteria of studies

Criterion	Detail
Study design	Full economic evaluations: cost-benefit analyses cost-utility analyses cost-effectiveness analyses also: cost-minimisation analyses cost-consequence analyses
Intervention	Natalizumab
Comparator	Standard care

H.3 Results

H.3.1 Literature Search Results

Four abstracts were retrieved from the literature search. Of these, the reviewer could identify no articles that met the inclusion criteria for this review.

H.4 Discussion

Up to week 2 September, 2006 there were no published economic evaluations examining the cost effectiveness of natalizumab in the treatment of MS that met

the eligibility criteria. The lack of any published economic evaluations of natalizumab in multiple sclerosis is likely to be due to its recent licensing status (June 2006).

H.5 Search strategies

H.5.1 Medline and Medline in Process

1. (Multiple Sclerosis or Myelitis, Transverse or Demyelinating Diseases or Encephalomyelitis, Acute Disseminated).me.

2. (multiple sclerosis or transverse myelitis or optic neuritis or devic or adem or neuromyelitis optica).mp. [mp=title, original title, abstract, name of substance word, subject heading word]

3. 1 or 2

4. Economics/

5. "costs and cost analysis"/

6. Cost allocation/

7. Cost-benefit analysis/

8. Cost control/

9. Cost savings/

10. Cost of illness/

11. Cost sharing/

12. "deductibles and coinsurance"/

13. Medical savings accounts/

14. Health care costs/

15. Direct service costs/

16. Drug costs/

17. Employer health costs/

18. Hospital costs/

19. Health expenditures/

20. Capital expenditures/

21. Value of life/

22. exp economics, hospital/

23. exp economics, medical/

24. Economics, nursing/

25. Economics, pharmaceutical/

26. exp "fees and charges"/

27. exp budgets/

28. (low adj cost).mp.

29. (high adj cost).mp.

30. (health?care adj cost$).mp.

31. (fiscal or funding or financial or finance).tw.

32. (cost adj estimate$).mp.

33. (cost adj variable).mp.

34. (unit adj cost$).mp.

35. (economic$ or pharmacoeconomic$ or price$ or pricing).tw.

36. or/4-35

37. natalizumab.mp.

38. Tysabri.mp.

39. 37 or 38

40. 3 and 36 and 39

H.5.2 Embase

1. Socioeconomics/

2. Cost benefit analysis/

3. Cost effectiveness analysis/

4. Cost of illness/

5. Cost control/

6. Economic aspect/

7. Financial management/

8. Health care cost/

9. Health care financing/

10. Health economics/

11. Hospital cost/

12. (fiscal or financial or finance or funding).tw.

13. Cost minimization analysis/

14. (cost adj estimate$).mp.

15. (cost adj variable$).mp.

16. (unit adj cost$).mp.

17. or/1-16

18. exp *demyelinating disease/

19. *encephalomyelitis/

20. 19 and acute disseminated.mp. [mp=title, original title, abstract, name of substance word, subject heading word]

21. acute disseminated encephalomyelitis.ti,ab.

22. multiple sclerosis.ti,ab.

23. *myelooptic neuropathy/

24. neuromyelitis optica.ti,ab.

25. (adem or devic).ti,ab.

26. or/20-25

27. natalizumab.mp.

28. Tysabri.mp.

29. 27 or 28

30. 17 and 26 and 29

H.5.3 NHS EED

1. multiple AND sclerosis

2. MeSH Multiple Sclerosis, Relapsing-Remitting

3. relapsing AND remitting

4. relapsing-remitting

5. #1 or #2 or #3 or #4

6. natalizumab or Tysabri

7. 5 and 6

Appendix I R code for MSM

```
############# BEGIN

## Presented here is the R-code used to generate the transition matrices for
## the SOT and RES populations base on the data from the AFFIRM study

# Read in data
df <- read.csv("C:\\local path\\bsckpt-cj.csv", na.strings="-10")

# Remove data for collected at date of symptoms and
# unscheduled visits
df <- df[df$timep!="DATE OF SYMPTOM",]
df <- df[df$timep!="UNSCHEDULED",]

# Add EDSS states greater than 7 to 7 then round up to nearest EDSS state
df <- df[df$edss <= 7,]
df$edss[df$edss > 7] <- 7
df$edss <- ceiling(df$edss) + 1

# Make variable with number of observations per patient
nobspt <- table(df$patid)[match(df$patid, sort(unique(df$patid)))]

# remove those with only one observation
df <- df[nobspt>1,]

# order dataset by time and subject
df <- df[order(df$patid, df$days),]

# convert time to years
df$years <- df$days / 365.25

# Open MSM library
library(msm)

# Generate state tables
statetable.msm(edss, patid, df)
statetable.msm(edss, patid, df[df$h_naive=="Y",])

# Get qmatrix to generate initial conditions

qmatrix <- rbind(c(0,  0.5,0,  0,  0,  0,  0,  0  ),
                 c(0.5,0,  0.5,0,  0,  0,  0,  0  ),
                 c(0,  0.5,0,  0.5,0,  0,  0,  0  ),
                 c(0,  0,  0.5,0,  0.5,0,  0,  0  ),
                 c(0,  0,  0,  0.5,0,  0.5,0,  0  ),
                 c(0,  0,  0,  0,  0.5,0,  0.5,0  ),
                 c(0,  0,  0,  0,  0,  0.5,0,  0.5),
                 c(0,  0,  0,  0,  0,  0,  0.5,0  ))

# To use crudeinits.msm to estimate initial values, assign output of
# crudeinits.msm to a variable and use that variable as the qmatrix argument
# to msm.

q.in <- crudeinits.msm(edss ~ years, subject=patid, data=df, qmatrix)
# set row names
rownames(q.in) <- colnames(q.in) <- 0:7 # label states as 0-7 not 1-8, then
these labels will appear in the msm output.

# Generate transition matrix for SOT subgroup

msm.11 <- msm(edss ~ years, subject=patid, qmatrix=q.in,
data=df[df$prtnum=="C-1801",], control=list(trace=1,fnscale=20),
method="BFGS")

# Generate transition matrix for RES subgroup

msm.12 <- msm(edss ~ years, subject=patid, qmatrix=q.in[-8,-8],
data=df[df$h_naive=="Y",],control=list(trace=1,fnscale=20), method="BFGS")

## Print results
round(pmatrix.msm(msm.11,t=1),4)
round(pmatrix.msm(msm.12,t=1),4)

############# END
```

Appendix J The Expanded Disability Status Scale (EDSS)

Reproduced from Kurtzke 1983. (116)

The EDSS is an ordinal scale which is used to measure impairment and disability in individuals with MS. The Functional System (FS) scale is incorporated within the overall framework of the EDSS.

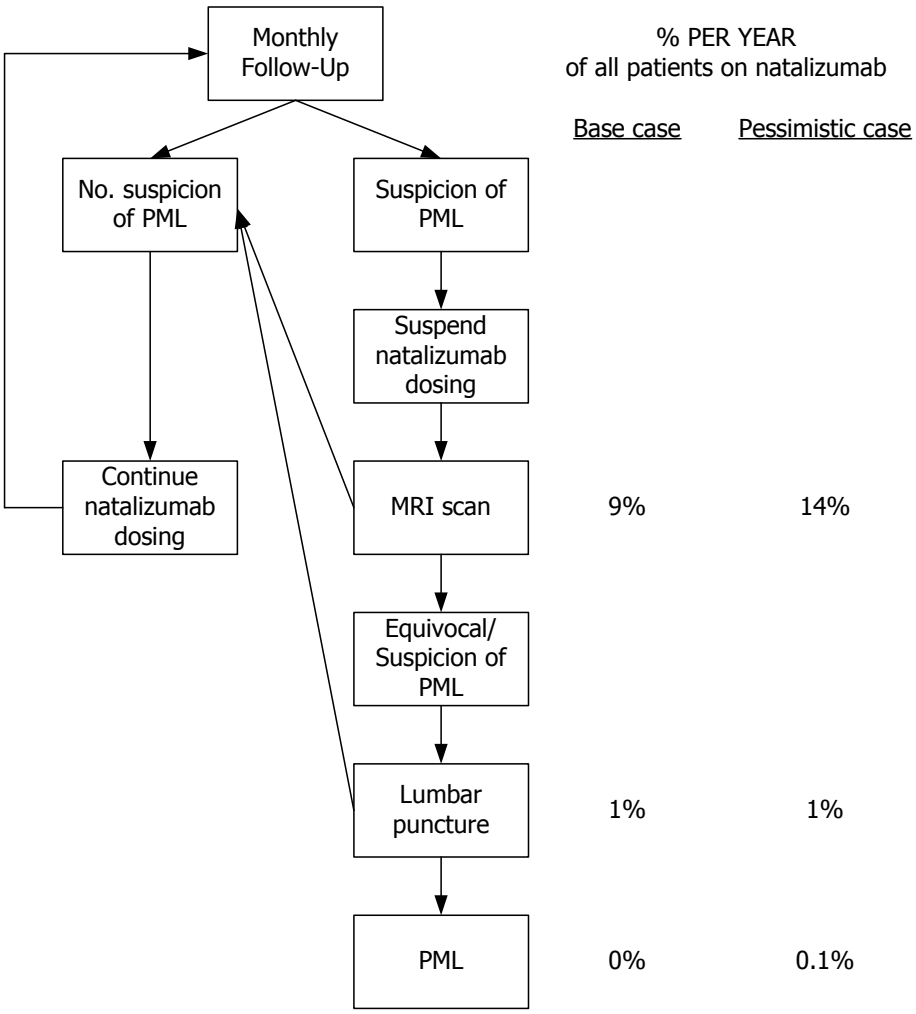
A brief description of each EDSS score is provided in Table 104.

Table 104 Description of EDSS values, Kurtzke 1983 (116)

0.0	Normal Neurological Exam
1.0	No disability, minimal signs on 1 FS
1.5	No disability minimal signs on 2 of 7 FS
2.0	Minimal disability in 1 of 7 FS
2.5	Minimal disability in 2 FS
3.0	Moderate disability in 1 FS; or mild disability in 3-4 FS, though fully ambulatory
3.5	Fully ambulatory but with moderate disability in 1 FS and mild disability in 1 or 2 FS; or moderate disability in 2 FS; or mild disability in 5 FS
4.0	Fully ambulatory without aid, up and about 12hrs a day despite relatively severe disability. Able to walk without aid 500 meters
4.5	Fully ambulatory without aid, up and about much of day, able to work a full day, may otherwise have some limitations of full activity or require minimal assistance. Relatively severe disability. Able to walk without aid 300 meters
5.0	Ambulatory without aid for about 200 meters. Disability impairs full daily activities
5.5	Ambulatory for 100 meters, disability precludes full daily activities
6.0	Intermittent or unilateral constant assistance (cane, crutch or brace) required to walk 100 meters with or without resting
6.5	Constant bilateral support (cane, crutch or braces) required to walk 20 meters without resting
7.0	Unable to walk beyond 5 meters even with aid, essentially restricted to wheelchair, wheels self, transfers alone; active in wheelchair about 12 hours a day
7.5	Unable to take more than a few steps, restricted to wheelchair, may need aid to transfer; wheels self, but may require motorized chair for full day's activities
8.0	Essentially restricted to bed, chair, or wheelchair, but may be out of bed much of day; retains self care functions, generally effective use of arms
8.5	Essentially restricted to bed much of day, some effective use of arms, retains some self care functions
9.0	Helpless bed patient, can communicate and eat
9.5	Unable to communicate effectively or eat/swallow
10.0	Death

Appendix K PML surveillance pathway

Assumptions concerning proportion of natalizumab treated patients that will require investigation to exclude PML.



Patients experiencing severe relapse (defined as relapse requiring corticosteroid treatment) whilst on natalizumab. In the AFFIRM study (4) this was 18% of patients over the two year study period, which is approximately 9% of patients per year

All patients that experience a relapse whilst on natalizumab. In the AFFIRM study (4) this was 28% of patients over the two year study period, which is approximately 14% of patients per year

In a safety study performed by Yousry et al (6), which evaluated patients treated with natalizumab, using MRI and CSF testing to exclude PML, 33 out of 2917 (1.1%) patients that had an MRI scan were referred to an Adjudication Committee because the MRI scan indicated the possibility of PML

No cases of PML were observed in clinical studies using natalizumab monotherapy in RRMS patients

Estimated risk of PML in study by Yousry et al (6) was 1/1000. This risk is based on analysis of all patients that received natalizumab and discounts the fact that no patients receiving natalizumab as monotherapy have developed PML. It there represents a pessimistic assumption.

References

(1) Natalizumab Summary of Product Characteristics. 2006 May 4.

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