



Natalizumab and Tyruko (natalizumab biosimilar) for
treating highly active relapsing-remitting multiple
sclerosis after at least one disease modifying therapy
[ID6369]

Final Protocol

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1 Plain Language Summary

What is the problem?

Multiple sclerosis (MS) is a relatively common lifelong condition that can affect the brain and the spine, causing symptoms like problems with vision, balance, movement, thinking, and bladder or bowel control. It usually starts in early adult life, and often slowly gets worse over time, but the course of disease varies per person.

It is not clear what causes MS, but some factors have been linked with an increased risk, like genetic abnormalities, vitamin D levels, inflammation, smoking and viral infections. There are a variety of treatments available to help manage symptoms, slow the progress of disease, and improve quality of life.

There are different types of MS, but most patients have specific type called relapsing remitting MS (RRMS). With this type of MS, patients usually have “relapses” – periods when their symptoms get worse or new symptoms develop. These relapses can last up to several weeks or months. Symptoms can disappear after a relapse, although some usually continue, causing ongoing disability for the patients. Drugs to treat MS try to reduce how often a patient has a relapse, but some people will continue to have relapses after starting their treatment. These patients have a specific form of RRMS known as “highly active disease” and will often need to switch to a different drug to improve their symptoms.

What are we trying to find out?

We want to know whether a drug called natalizumab (Tysabri) and similar drug known as natalizumab biosimilar (Tyruko) are effective and safe for patients with highly active RRMS, when compared with other drugs already in use for these patients. We also want to know whether using these drugs is a good use of NHS money.

What are we going to do?

We will review existing research and develop cost-effectiveness models to answer these questions.

2 Decision Problem

2.1 Technologies and population of interest for this appraisal

The technologies of interest for this appraisal are Natalizumab (Tysabri, Biogen) and natalizumab biosimilar (Tyruko, Sandoz). Natalizumab (Tysabri) has a marketing authorisation for subcutaneous and intravenous administration, whereas natalizumab biosimilar (Tyruko) has a licence for intravenous administration only. Both drugs have been licensed as single disease modifying therapy (DMT) in adults with highly active relapsing remitting multiple sclerosis for the following people:

- People with rapidly evolving severe RRMS 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 recent MRI.

OR

- People with highly active disease despite a full and adequate course of treatment with at least one disease modifying therapy

NICE already recommends natalizumab as a first-line treatment option for people with rapidly evolving severe relapsing–remitting multiple sclerosis (NICE TA127;¹ Table 3) covering the first part of the population above. This appraisal therefore focuses only **on highly active relapsing-remitting multiple sclerosis after at least one disease modifying therapy**. Table 2 in section 2.3.4 provides a summary of how different subtypes are classified.

2.2 Comparators for this appraisal

The comparator for this appraisal is standard care without natalizumab or natalizumab biosimilar. This includes the following interventions (see Table 3):

- Glatiramer acetate
- Interferon beta 1a
- Interferon beta 1b
- Alemtuzumab
- Cladribine tablets
- Fingolimod
- Ocrelizumab. *The NICE scope² suggested that this should only be if alemtuzumab is contraindicated. However, our clinical advisors suggested that this is not reflective of this drug is used in clinical practice and so we will not apply this restriction for our appraisal.*
- Ofatumumab
- Ponesimod
- Autologous haematopoietic stem cell transplantation

3 Background

3.1 Multiple sclerosis

Multiple sclerosis (MS) is a chronic, inflammatory, neurological autoimmune condition that affects the central nervous system (CNS), which includes the brain and spinal cord.³ MS usually presents in early adult life and is the most common cause of non-traumatic disabling disease in young adults.³⁻⁵ In MS, the immune system mistakenly attacks the protective covering of nerve fibres called myelin, causing inflammation and damage. This disrupts the normal flow of electrical impulses along the nerves. Inflammation can also lead directly to damage to axons, leading to their degeneration or loss. Axonal loss contributes significantly to the neurological symptoms and disability observed in people with MS.

The symptoms of MS vary widely and can include bladder and bowel dysfunction, cognitive changes, gait disturbance, fatigue, muscle weakness, numbness or tingling, difficulty with coordination and balance, and problems with vision.^{3, 4} It is not clear what causes MS, but a number of theories have been proposed. These include the “outside in” and “inside out” pathways. With the “outside in” model it is hypothesised that an unknown factor triggers the autoimmune response peripherally (outside the CNS), instigating the immune system to begin to invade the CNS, starting the process of demyelination characteristic of MS. The “inside out” model suggest that primary damage of the myelin as the cause of MS, leading to an autoimmune attack which results in further inflammatory demyelination.⁶ A number of factors have been associated with the risk of developing MS, these include genetic abnormalities, environmental factors such as vitamin D or ultraviolet B light (UVB) exposure, obesity, smoking and viral infection.^{6, 7} More recently a compelling link has been established between Epstein-Barr virus (EBV) and MS – being negative of EBV protects against MS, whereas active infection doubles the risk of developing MS.^{7, 8} A number of genes have been found to be associated with MS. The main genetic risk is with the HLA-DRB1*15, although genome wide association studies have identified over 150 single nucleotide polymorphisms that are associated with the development of MS.⁵

MS has a significant impact on individuals' quality of life and imposes a substantial burden on healthcare systems and society as a whole.⁴ A recent cross-sectional study of almost 17 000 participants with MS from across 16 countries found that work capacity declined from 82% to 8%, and that quality of life declined from normal population values to less than zero, indicating that the negative aspects of an individual's life outweigh the positive impacts, as disability became more severe with advancing disease.⁴ MS may reduce life expectancy with a recent study estimating life expectancy to be 75.9 years in an MS population compared to 83.4 years in a population matched on sex, age, and region.⁹ While there is currently no cure for MS, treatments are available to help manage symptoms, slow disease progression, and improve quality of life for individuals with MS.

3.2 Epidemiology of MS

MS is estimated to have a global prevalence of over 2.8 million cases (35.6 per 100 000 population), although this may be an underestimate due to the lack of data from large populations including China and India.¹⁰ Incidence and prevalence is increasing in both developed and developing countries.¹⁰

Estimates of incidence vary across studies, with higher prevalence rates observed in regions further from the equator, particularly in Europe, North America, and parts of Australasia.^{5, 7} A 2020 multi-national study reported a pooled incidence rate across 75 studies that provided data as 2.1 per 100 000 persons/year.¹⁰ The prevalence of MS tends to increase with distance from the equator, although there are exceptions to this pattern.⁷ The reasons for this geographic variation are not fully understood but may involve a combination of genetic, environmental, and lifestyle factors. Distance from the equator is also associated with UVB exposure which stimulates vitamin D production – low levels of vitamin D have been associated with MS.⁷ Migration studies have shown that migrants from low risk countries (e.g. the West Indies) to Europe remain at low risk of developing MS, however children born to migrants in Europe are at high risk.⁷ This suggests that environment overrules genetics, suggesting that prevention should focus on environmental risk factors.

In the United Kingdom (UK), MS is a relatively common neurological condition, with an estimated prevalence of around 130 cases per 100,000 population, with an estimated 7,000 new cases each year.¹¹ The prevalence of MS in the UK is among the highest in Europe. MS affects people of all ages, but it is most commonly diagnosed in young adults, typically between the ages of 20 and 40. Women are about two to three times more likely to develop MS than men, although in the early 1900s the sex ratio was almost equal.⁷ A reason for this change may be the changing prevalence of smoking in women over time – before the first world war very few women smoked. The incidence and prevalence of MS in the UK have been increasing over time, although this trend may be partially attributed to improvements in diagnostic methods and increased awareness of the condition.

3.3 Clinical pathway

3.3.1 Clinical presentation

MS is usually first suspected when a patient presents with what is known as a “clinically isolated syndrome” (CIS), this occurs as result of lesions in the brain or spinal cord and presentation will depend on the location of the lesion. The most frequent presentations include unilateral optic neuritis, brainstem syndromes (e.g. intranuclear ophthalmoplegia, vertigo, hearing loss, facial sensory disturbance) and focal sensory disturbance (e.g. limb paresthesias) although many other presentations exist.^{7, 12}

3.3.2 Diagnosis of multiple sclerosis

The diagnosis of multiple sclerosis (MS) is primarily a clinical diagnosis, supported by investigations including imaging and cerebrospinal fluid (CSF) analysis. The key features required for a diagnosis of MS are dissemination in time and space – this involves looking for

evidence of disease activity affecting different parts of the CNS across different points in time. Differential diagnosis of MS can be challenging, particularly in the early stages, as many other disorders have similar clinical presentations and paraclinical findings to MS.¹³ The 2022 NICE guidelines on the diagnosis and management of MS recommend that people suspected of having MS should be referred for diagnosis by a consultant neurologist or specialist under their supervision.¹⁴

Diagnostic criteria have evolved over time from the first criteria proposed by Jean-Martin Charcot as early as 1868¹⁵ to the most recently published 2017 McDonald criteria.¹⁶ The McDonald criteria were first developed by an international committee of neurologists and published in 2001.¹⁷ These were updated in 2005, 2010 and most recently in 2017¹⁶ – these are the current criteria recommended for diagnosis of MS by NICE. Table 1 provides an overview of the 2017 McDonald criteria for diagnosing MS. These follow the principle of aiming to detect evidence of dissemination in time and space.

Table 1 2017 Revised McDonald criteria for diagnosing MS¹⁶

Number of attacks at clinical presentation	Number of lesions with objective clinical evidence	Additional data needed for diagnosis of MS
≥2	≥2	None
≥2	1 + clear cut historical evidence of a previous attack involving a lesion in a distinct anatomical location	None
≥2	1	Dissemination in space demonstrated by additional clinical attack implicating a different CNS site <i>OR</i> by MRI
1	≥2	Dissemination in time demonstrated by an additional clinical attack <i>OR</i> by MRI <i>OR</i> demonstration of CSF-specific oligoclonal bands
1	1	Dissemination in space demonstrated by an additional clinical attack implicating a different CNS site <i>OR</i> by MRI <i>AND</i> Dissemination in time demonstrated by an additional clinical attack <i>OR</i> by MRI <i>OR</i> demonstration of CSF-specific oligoclonal bands

Magnetic resonance imaging (MRI) can be used to detect changes in white matter lesions in the brain. It is not sufficiently accurate to be used alone for the diagnosis of MS, but can be helpful in addition to clinical features.¹⁸ CSF analysis involves detection of oligoclonal bands as a surrogate marker of dissemination in space.¹⁹ The presence of oligoclonal bands (bands of immunoglobulin) provides evidence of local immunoglobulin synthesis which occurs most commonly in MS, but can also be found in other conditions and so the finding is not specific for the diagnosis of MS.²⁰ Findings of elevated CSF protein or significant pleocytosis or the

presence of neutrophils is not typical of MS and so suggests an alternative diagnosis. The McDonald 2017 criteria allow for a greater role of MRI and CSF than previous versions, allowing for an earlier diagnosis of MS. This is particularly important as new, earlier aggressive treatments become available for MS; it is important to identify patients with MS so that they can receive treatment as soon as possible, but it is equally important that people are not wrongly diagnosed with MS and given inappropriate treatment with these aggressive treatments.²¹ Visually evoked potentials have previously been suggested as useful for the diagnosis of MS, with an abnormal VEP suggesting a second lesions if the clinical presentation did not include the visual pathway. However, these are not included in the more recent diagnostic criteria due to insufficient evidence.²²

3.3.3 Measurement of progression

Disease activity and progression are measured using MRI activity, incidence of relapses and short-term (3-6 month) progression in disability.¹² MRI measures of disease activity include the development of new T2 lesions, enlarging T2 lesions, and gadolinium-enhancing lesions. Disability is measured using the Expanded Disability Status Scale (EDSS) – this quantifies the accumulation of permanent disability. Scores range from 0 (no disability) to 10 (death) and are measured in incremental units of 0.5 (from EDSS 1). Scores are based on measures of impairment across the eight functional symptoms:²³

1. Pyramidal Functions: weakness or difficulty in moving limbs
2. Cerebellar Functions: ataxia, loss of coordination, or tremor
3. Brain Stem Functions: problems with speech, swallowing, and nystagmus (involuntary eye movement)
4. Sensory Functions: numbness or loss of sensations
5. Bowel and Bladder Functions
6. Visual (or Optic) functions
7. Cerebral (or Mental) Functions
8. Other Functions (neurologic findings)

To provide an accurate and reliable evaluation of confirmed disease progression (CDP), two consecutive examinations should be carried out by the same physician at least 6 months apart. Although EDSS is commonly used it does not capture some important aspects of the impact of MS, particularly on quality of life. It is also prone to bias as it is a subjective measure and so open to investigator bias and is also heavily influenced by mobility.

3.3.4 Classification of MS

MS presents on a continuum from relapsing to progressive disease, with distinctions currently made between different types of disease. Some see this as an artificial distinction as they force cases into distinct boxes, which does not reflect the continuum of illness.⁷ Most cases of MS (85-90%) are characterised by relapses followed by periods of remission – known as “relapsing remitting MS” (RRMS). A relapse generally develops over a period of hours to days, then reaches a plateau lasting several weeks, followed by a period of gradual recovery. The nature of the relapse is dependent on the region of the CNS affected by the

acute demyelinating lesion, and also by the extent of the inflammation.⁵ Although initial relapses can lead to complete recovery, there is often some damage left behind by the relapse, with overall disability increasing slightly after each relapse.²⁴ As neuronal damage increases, recovery from disability becomes incomplete leading to further disability.⁷ RRMS is further subcategorised depending on disease activity and response to treatment as summarised in Table 2. The population of interest for this appraisal is “highly active disease” (highlighted blue in the table).

Table 2 Overview of subclassifications of RRMS²⁵

Classification	Definition
Active disease	≥Two clinically significant relapses within the last 2 years. (Any motor relapse, any brainstem relapse, a sensory relapse if it leads to functional impairment, a relapse leading to sphincter dysfunction, optic neuritis, intrusive pain lasting more than 48 hours)
Highly active disease	No consensus definition; previous appraisals for NICE have used different definitions. We will use the following definition for this appraisal: <i>Unchanged or increased clinical or radiological evidence of disease activity despite treatment with at least one DMT</i>
Rapidly evolving severe (RES) disease	≥Two disabling relapses in 1 year and MRI changes (one or more gadolinium-enhancing lesions or a significant increase in T2 lesion load compared with a previous MRI). A disabling relapse is defined as any relapse which fulfils one or more of the following criteria: • Affects the patient’s social life or occupation, or is otherwise considered disabling by the patient • Affects the patient’s activities of daily living as assessed by an appropriate method • Affects motor or sensory function sufficiently to impair the capacity or reserve to care for themselves or others • Needs treatment/hospital admission.²⁵

After 10-15 years RRMS typically develops into “secondary progressive MS” (SPMS), characterised by a gradual progression from discrete relapses to disease that progresses slowly.²² A smaller proportion have a progressive onset from the start, known as “primary progressive MS” (PPMS). The proportion of patients with PPMS has decreased over time, but this may be an artificial change, caused by patients being more commonly labelled as having RRMS so that they are eligible for some of the newer treatments,⁷ or be a result of better ascertainment of relapses leading to more people being identified as having RRMS. PPMS is more common in those presenting in later life (over age 60 years).⁵

3.3.5 Management of MS

Management of MS typically involves a multidisciplinary approach, including medical treatment to manage symptoms and modify disease progression, rehabilitation therapies, and support services to address the physical, cognitive, and emotional challenges associated with the condition. The pathway may vary depending on the subtype of MS, disease severity, individual patient factors, and treatment goals. The MS treatment pathway is dynamic and individualized, requiring ongoing collaboration between patients, healthcare

providers, and interdisciplinary teams to optimize outcomes and quality of life for individuals living with MS. NICE guidelines recommend that people with MS should have a comprehensive review of all aspects of their care at least once a year.^{12, 14}

Symptomatic management focuses on alleviating symptoms associated with MS, such as fatigue, mobility problems, spasticity, oscillopsia, emotional lability, pain, cognitive and memory problems, ataxia, tremor and dystonia. Symptomatic treatments may include medications, physical therapy, occupational therapy, speech therapy, cognitive rehabilitation, assistive devices, and lifestyle modifications.¹⁴ Acutely, relapses are often treated with corticosteroids and, sometimes, plasma exchange.²⁶

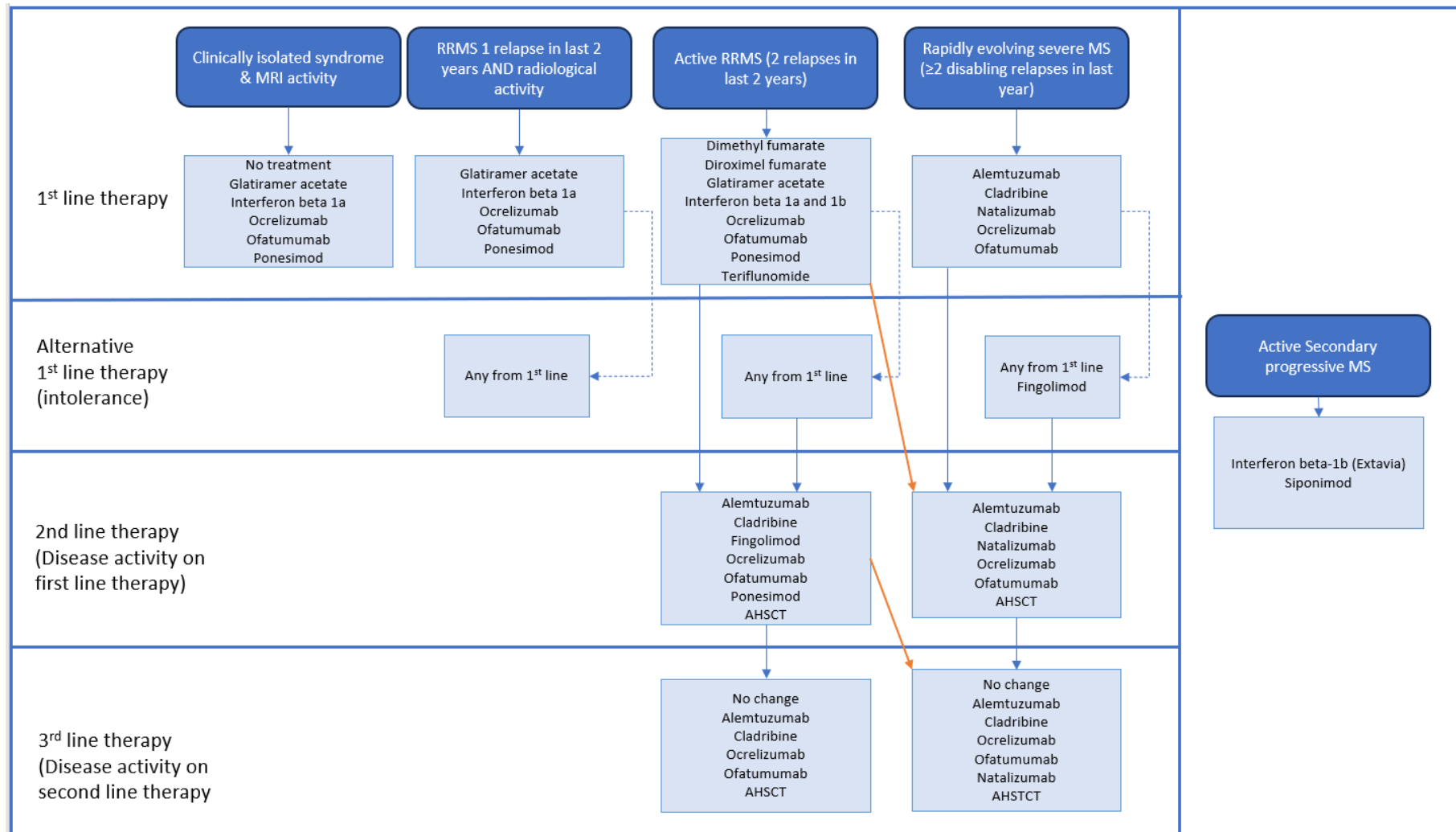
Disease-modifying therapies (DMTs) are the cornerstone of treatment for relapsing forms of MS. DMTs aim to reduce the frequency and severity of relapses, delay disability progression, and decrease the number of lesions observed on MRI scans.¹² They work by modifying the course of MS by suppressing or modulating immune function. Various DMTs are available, including injectable medications, oral agents, and infusion therapies, each with different mechanisms of action and side effect profiles. Interferon beta-1b was the first DMT to be approved by the Federal Drugs Agency (FDA) in 1993. This was followed by interferon beta-1b and glatiramer acetate. These drugs were generally well tolerated and have a modest impact on the frequency of relapses.²⁷ Prior to this a variety of immunosuppressive agents were used to treat MS including azathioprine, methotrexate, mycophenolate mofetil, intravenous immunoglobulin, and corticosteroids.²⁷

More recently many MS specific DMTs have become available.²⁷ Table 3 provides an overview of the DMTs that have been appraised by NICE. It also highlights which DMTs are included in the scope for this appraisal – interventions and comparators are shown in cells shaded blue in the table, interventions are also highlighted in bold. NHS England have developed a treatment algorithm for DMTs within the NHS. Different treatment options are recommended based on initial presentation.²⁸ The recommendations for RRMS are summarized in Figure 1. An additional treatment option is *autologous haematopoietic stem cell transplantation*. This involve collecting a patient's healthy stem cells from the blood or bone marrow before treatment, storing this and then giving it back to the patient after treatment. A growing body of evidence suggests that this can induce prolonged remission in patients with RRMS.²⁷

Patients who progress to SPMS are managed with Interferon beta-1b (Extavia) or Siponimod if they meet the following starting criteria:

- Patient is able to walk 10 m or more (EDSS less than 7.0)
- >18 years-old
- No contraindications
- Patient has been informed of and agreed to stopping criteria
- For Siponimod, there is also a requirement of active disease (relapses or imaging features of inflammatory activity).²⁹

Figure 1 NHS England treatment algorithm for MS DMTs



Orange arrows show treatment pathways for patients with active RRMS who develop RES

AHSCT: autologous haematopoietic stem cell treatment.

Table 3 Overview of DMTs for adults with MS together with details of marketing authorisation and NICE recommendations

Pale blue highlighting shows interventions and comparators included within the scope of this appraisal

Drug name	Mechanism of Action	Administration route and frequency	Marketing authorisation	Related NICE TA	NICE recommendation
Recommended for RRMS					
Glatiramer Acetate	Not fully known	SC injection, once daily or 3 times weekly	Relapsing forms of multiple sclerosis.	TA527 ³⁰	Recommended for treating RRMS
Interferon beta-1a	Not fully known	IM injection, once Weekly or SC injection, 3 times weekly	Relapsing multiple sclerosis. In clinical trials, this was characterised by two or more acute exacerbations (relapses) in the previous three years without evidence of continuous progression between relapses.	TA527 ³⁰	Recommended for treating RRMS
Peginterferon beta-1a	Not fully known	SC injection, every 2 weeks	Relapsing remitting multiple sclerosis.	TA624 ³¹	Recommended for treating RRMS
Interferon beta-1b (Extavia)	Not fully known	SC injection, every other day	Relapsing remitting multiple sclerosis and two or more relapses within the last two years.	TA527 ³⁰	Recommended for treating RRMS if person has had 2 or more relapses with past 2 years. <i>Currently not available in the UK</i>
Recommended for RRMS in specific situations or specific subtypes					
Ocrelizumab	Anti-CD20 mAb	IV infusion, every 6 months	Adult patients with relapsing forms of multiple sclerosis (RMS) with active disease defined by clinical or imaging features.	TA533 ³²	Recommended for active RRMS only if alemtuzumab is contraindicated or otherwise unsuitable
Natalizumab (Tysabri)	$\alpha 4\beta 1$ integrin inhibitor	IV infusion, every 4 weeks can also be given subcutaneously	Highly active RRMS: • Rapidly evolving severe RRMS defined by 2 or more disabling relapses in one year, and with 1	TA127 ¹	Recommended for rapidly evolving severe RRMS

Drug name	Mechanism of Action	Administration route and frequency	Marketing authorisation	Related NICE TA	NICE recommendation
			or more Gadolinium enhancing lesions on brain Magnetic Resonance Imaging (MRI) or a significant increase in T2 lesion load as compared to a previous recent MRI. OR Highly active disease despite a full and adequate course of treatment with at least one DMT		
Natalizumab biosimilar (Tyruko)	$\alpha 4\beta 1$ integrin inhibitor	IV infusion, every 4 weeks	Highly active RRMS: - Rapidly evolving severe RRMS 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 recent MRI. OR - Highly active disease despite a full and adequate course of treatment with at least one DMT	NA	Recommended as per Natalizumab (Tysabri) under NICE's biosimilar policy
Diroximel fumarate (Almirall)	Nuclear factor (erythroid derived 2)-like 2 pathway inhibitor	Oral, twice daily	Adult patients with relapsing–remitting multiple sclerosis.	TA794 ³³ TA320 ³⁴	Recommended for active RRMS only if they do <i>not</i> have highly active or rapidly evolving severe relapsing–remitting multiple sclerosis
Dimethyl fumarate	Promotes anti-inflammatory	Oral, twice daily	Indicated for the treatment of adult patients with relapsing remitting multiple sclerosis	TA320 ³⁴	Recommended for active RRMS, only if:

Drug name	Mechanism of Action	Administration route and frequency	Marketing authorisation	Related NICE TA	NICE recommendation
	activity and can inhibit expression of pro-inflammatory cytokines and adhesion molecules				they do not have highly active or rapidly evolving severe relapsing-remitting multiple sclerosis, and the manufacturer provides dimethyl fumarate with the discount agreed in the patient access scheme.
Cladribine	Not fully known	Oral, 4-5 days over 2-week treatment courses	Adult patients with highly active relapsing multiple sclerosis (MS) as defined by clinical or imaging features	NICE TA616 ³⁵	Recommended for highly active MS only if the person has rapidly evolving severe RRMS or disease that has responded inadequately to treatment with DMT
Recommended for previously treated RRMS					
Alemtuzumab	Anti-CD52 mAb	IV infusion, once daily	Adult patients with relapsing remitting multiple sclerosis (RRMS) with active disease defined by clinical or imaging features.	TA312 ³⁶	Recommended for highly active RRMS despite a full and adequate course of treatment with at least 1 disease-modifying therapy OR rapidly evolving severe RRMS
Fingolimod	Sphingosine-1-phosphate inhibitor	Oral, once daily	Indicated as single disease modifying therapy in highly active relapsing remitting multiple sclerosis for the following adult patient groups: • Patients with highly active disease despite a full and adequate course of treatment with at least one disease modifying therapy or	TA254 ³⁷	Recommended for highly active RRMS if they have an unchanged or increased relapse rate or ongoing severe relapses compared with the previous year

Drug name	Mechanism of Action	Administration route and frequency	Marketing authorisation	Related NICE TA	NICE recommendation
			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		despite treatment with beta interferon
Ofatumumab	Anti-CD20 mAb	SC injection, every 4 weeks	Adult patients with relapsing forms of multiple sclerosis (RMS) with active disease defined by clinical or imaging features.	TA699 ³⁸	Recommended for previously treated active RRMS, only if alemtuzumab is contraindicated or otherwise unsuitable
Ponesimod	Sphingosine-1-phosphate inhibitor	Oral, once daily	Adult patients with relapsing forms of multiple sclerosis (RMS) with active disease defined by clinical or imaging features.	TA767 ³⁹	Recommended for previously treated active RRMS
Cladribine	Not fully known	Oral, 4-5 days over 2-week treatment courses	Adult patients with highly active relapsing multiple sclerosis (MS) as defined by clinical or imaging features	NICE TA616 ³⁵	Recommended for highly active MS only if the person has rapidly evolving severe RRMS or disease that has responded inadequately to treatment with DMT
Recommended for SPMS					
Siponimod	Sphingosine 1-phosphate receptor modulator	Oral, once daily	Adult patients with secondary progressive multiple sclerosis (SPMS) with active disease evidenced by relapses or imaging features of inflammatory activity.	TA656 ²⁹	Recommended as an option for treating SPMS with evidence of active disease (that is, relapses or imaging features of inflammatory activity)

Drug name	Mechanism of Action	Administration route and frequency	Marketing authorisation	Related NICE TA	NICE recommendation
Interferon beta-1b (Extavia)	Not fully known	SC injection, every other day	Patients with secondary progressive multiple sclerosis with active disease, evidenced by relapses.	TA527 ³⁰	Recommended for SPMS with continuing relapses
Recommended for PPMS					
Ocrelizumab	Anti-CD20 mAb	IV infusion, every 6 months	Adult patients with early primary progressive multiple sclerosis (PPMS) in terms of disease duration and level of disability, and with imaging features characteristic of inflammatory activity.	TA585 ⁴⁰	Recommended for treating early PPMS with imaging features characteristic of inflammatory activity
Not recommended					
Interferon beta-1b (Betaferon)	Not fully known	SC injection, every other day	• Patients with a single demyelinating event with an active inflammatory process, if it is severe enough to warrant treatment with intravenous corticosteroids, if alternative diagnoses have been excluded, and if they are determined to be at high risk of developing clinically definite multiple sclerosis. • Patients with relapsing-remitting multiple sclerosis and two or more relapses within the last two years). • Patients with secondary progressive multiple sclerosis with active disease, evidenced by relapses.	TA527 ³⁰	Not recommended
Ozanimod	Sphingosine 1-phosphate receptor modulator	Oral, once daily	Adult patients with relapsing remitting multiple sclerosis (RRMS) with active disease as defined by clinical or imaging features	TA706 ⁴¹	Not recommended for treating active RRMS

4 Aim and Objectives

The overall aim of this assessment is to appraise the clinical and cost effectiveness of natalizumab (Tysabri) and natalizumab biosimilar (Tyruko) within their marketing authorisations for treating highly active RRMS after at least one disease modifying therapy.

We defined the following objectives to address the overall aim:

1. Conduct a systematic literature review (SLR) of treatments for highly active RRMS after at least one disease modifying therapy
2. Conduct a network meta-analysis to estimate the clinical effectiveness and safety of treatments for highly active RRMS after at least one disease modifying therapy
3. Develop an economic model to assess the cost-effectiveness of treatments for highly active RRMS after at least one disease modifying therapy

5 Systematic literature review methods

A SLR will be conducted to summarise the effectiveness of treatments for relapsing-remitting multiple sclerosis after at least one disease modifying therapy. The SLR will follow the principles outlined in the Centre for Reviews and Dissemination (CRD) guidance for undertaking reviews in health care and the NICE Health Technology Evaluations Manual.^{42, 43} and will be reported according to the PRISMA NMA statement.⁴⁴

5.1 Selection criteria

Studies that meet the following criteria will be eligible for inclusion:

5.1.1 Participants

The population of interest for this appraisal is people with highly active RRMS who have received at least one previous DMT (see section Table 3). We do not anticipate identifying studies for all interventions of interest in this specific sub-population, or expect to only find sub-analyses of existing trials which may have low power to detect differences and be more prone to bias than full trials. Inclusion for the SLR will therefore be broadened to include all studies in patients with RRMS. Studies will be included if at least 90% of the participants have RRMS or if data can be extracted for this sub-population of interest.

5.1.2 Interventions

The two interventions of interest for this appraisal are **natalizumab** and **natalizumab biosimilar**. To allow comparison with standard care we will also include trials that evaluate:

- Glatiramer acetate
- Interferon beta 1a
- Interferon beta 1b
- Alemtuzumab
- Cladribine tablets
- Fingolimod
- Ocrelizumab

- Ofatumumab
- Ponesimod
- Autologous haematopoietic stem cell transplantation

Studies will be required to compare one of the interventions above to an alternative intervention. We will exclude studies that only compared different doses, modes of administration, or manufacturers of the same intervention, unless these are needed to create a connected network. Where available, we will select studies that compare eligible interventions to create connected networks, so that only studies that are informative for the network are included.

5.1.3 Outcomes

Studies that report data on any of the following outcomes will be eligible for inclusion:

- Relapse rate
- Severity of relapse
- Disability (for example, expanded disability status scale [edss])
- Disease progression
- Symptoms of multiple sclerosis (such as fatigue, cognition, and visual disturbance)
- Freedom of disease activity (for example lesions on mri scans)
- Mortality
- Adverse effects of treatment
- Health-related quality of life.

5.1.4 Study design

We will restrict inclusion to randomised controlled trials.

No language or publication restrictions will be applied.

5.2 Study identification

5.2.1 Studies included in existing TAs

The first step in identifying studies will be to extract studies used by companies to make the case for clinical effectiveness in previous appraisals. We will also extract associated reports cited in the clinical effectiveness section of the company submission. These will be added to EndNote and exported to Microsoft Access for assessment (see section 4.3.2).

5.2.2 Literature searches

Additional studies will be identified using bibliographic and non-bibliographic search methods following guidance in the NICE technology appraisal manual.⁴³

Bibliographic searching

The following databases will be searched:

- MEDLINE (Ovid)
- EMBASE (Ovid)

The search strategy will be written by one researcher and checked by another. It will take the following form:

1. Terms for relapsing remitting MS
2. Terms for Intervention listed in section 4.1.4
3. The Cochrane Highly Sensitive Search Strategy for identifying randomized trials in MEDLINE: sensitivity- and precision-maximizing version (2008 revision) supplemented with the Cooper P3 filter.^{45, 46}
4. 1 and 2 and 3

The bibliographic search strategy will not be limited by date of publication or by language. A draft search strategy is reported in Appendix 10.1.

Non-bibliographic search methods

Completed and ongoing trials will be identified through searches of the following trial registries:

- ClinicalTrials.gov via www.clinicaltrials.gov
- WHO International Clinical Trials Registry Platform (ICTRP) via www.who.int/clinical-trials-registry-platform

Once eligible studies have been identified, the study's web page on the trials registry resource will be re-checked for data (published results) or linked publications.

Whilst SLRs are not eligible for inclusion, we will retain any SLR identified if published in the last three years (2021-current) and which aligns with our scope. We will check the studies included in each review to identify any studies not identified by our searches.

NICE will request submissions from Companies with technologies in scope for this appraisal (See Table 3). We will check the submissions for studies (and study data) which align with our inclusion criteria. Studies will be tabulated to show where they contribute to our review or why they were excluded.

Managing the searches

Search results will be exported to EndNote 20 for de-duplication. We will compare the studies and study reports from the mapping of TAs to our search results. Search results will be exported to Microsoft Access for screening.

5.3 Review strategy

5.3.1 Title and abstract screening

Titles and abstracts from the literature searches will be screened independently by two reviewers. At this stage all records that evaluate one of the interventions of interest in the broad population of patients with RRMS will be retrieved. Full copies of all reports considered potentially relevant will be obtained and move to the inclusion assessment stage. Studies included in existing TAs will move straight to the inclusion assessment stage.

Full text inclusion assessment

Full text studies, including all reports included in existing TAs, will be assessed for inclusion against the criteria specified in section 4.1. This stage will be completed by one reviewer and checked by a second reviewer. Any disagreements will be resolved by consensus or discussion with a third reviewer. Studies excluded at this stage will be documented, together with reasons for exclusion.

5.3.2 Mapping reports to studies

All reports of studies that meet the review inclusion criteria will progress to the mapping stage. This stage aims to identify and link reports of the same study and identify which reports should be prioritised for extraction for each outcome. To aid identification of linked reports and to determine which reports to select for data extraction we will extract the following information from each study:

- Study name
- NCT ID number
- Interventions evaluated
- Outcomes reported
- Follow-up times reported

We will identify a “primary report” for each study. This will be the study that reports the most complete trial data and results. Other reports will be labelled as secondary reports and will be linked to the primary report using the endnote IDs.

5.3.3 Data extraction

Data will be extracted using standardised data extraction forms developed in Microsoft Access. Data extraction forms will be piloted on a small sample of papers and adapted as necessary. Data will be extracted by one reviewer and checked in detail by a second reviewer. Any disagreements will be resolved by consensus or discussion with a third reviewer.

Baseline data

Data will be extracted on the following:

- Study design
- Study phase

- Funding sources (public, industry, mixed)
- Full text or conference abstract
- NCT number
- Study location
- Population
 - Criteria used to diagnose MS
 - RRMS subtype
 - Previous treatment
- Intervention
 - Treatment name
 - Mode of administration
 - Dose
 - Duration
- Comparator
 - Treatment name
 - Mode of administration
 - Dose
 - Duration
- Number of participants (eligible, randomised and treatment)
- Age
- Sex
- Ethnicity
- EDSS score
- Time from diagnosis of MS to study entry
- Relapse rate at baseline

Results data

Where possible results data will be extracted for both the sub-population of interest (highly active RRMS) and for the overall RRMS population. Data will be extracted for the longest follow-up period available. We will extract data on the following outcomes:

Time to event outcomes:

- Confirmed disability progression at 3 months (CDP3)
- Confirmed disability progression at 6 months (CDP6)

In line with the data typically used for NMA in RRMS, we will extract hazard ratios (HR) and 95% confidence intervals, and numbers of events.^{47, 48} If reported, Kaplan-Meier plots will be digitized and IPD reconstructed using the Guyot method.⁴⁹ These reconstructions will be used to test the proportional hazards assumption which will underly the NMA of hazard ratios and models based on numbers of events. If HRs are not reported, we will extract any other summary effect estimates available (odds ratios (OR), risk ratios (RR)) or number of patients with events), and HRs will be estimated with a hazard rate analysis of event

frequencies in relation to time at risk (when follow-up time is available), or from 2x2 tables of event numbers using complementary log-log (cloglog) transformations, assuming proportional hazards.⁵⁰

Rate outcomes

- Annualised relapse rate

We will extract rate ratios together with 95% CIs and p-values for comparisons between groups together with details on the methods of analysis, any variables controlled for in the analysis and the test statistic. We will also extract the total number of relapse events, the total exposure time (calculated as person-years with 1 year = 56 weeks), the follow-up time, and the number of patients at risk.

Dichotomous outcomes:

- Symptoms of multiple sclerosis (such as fatigue, cognition, and visual disturbance)
- Freedom of disease activity (for example lesions on MRI scans)
- Mortality
- Discontinuation due to adverse events
- Any adverse events (AEs)
- Serious (grade 3 or 4) adverse events (any and treatment related)

Where available, treatment related adverse events will be extracted in preference to non-cause-specific adverse events. If these data are not available, non-cause specific adverse events will be extracted.

We will extract data on the number of patients with events and/or number of events and total number of patients in each treatment arm. Summary effect estimates (e.g. odds ratio (OR) or relative risk (RR)) together with 95% CIs and p-values for comparisons between groups together with details on the methods of analysis, any variables controlled for in the analysis and the test statistic will be extracted.

Continuous outcomes:

- Severity of relapse
- Disability (for example, expanded disability status scale [EDSS])
- Health-related quality of life

We will extract means/medians together with ranges, standard deviations (SD), standard errors (SE) and/or confidence intervals (CIs) for the outcome at baseline and at the latest follow-up point, or follow-up time that is most similar across studies. Summary effect estimates (e.g. mean difference (MD)) together with 95% CIs and p-values for comparisons between groups together with details on the methods of analysis, any variables controlled for in the analysis and the test statistic will be extracted. Where the required data are not reported in a similar format across studies, we will calculate the required data from the information presented. For example, estimate the standard deviation if only p-values or

confident intervals are reported. Where data are only reported graphically, data will be extracted from the graphs where possible.

5.4 Quality assessment strategy

The methodological quality of included RCTs will be assessed using the updated Cochrane Risk of Bias Tool (ROB-2).⁵¹ Any disagreements will be resolved by consensus or discussion with a third reviewer.

5.5 Synthesis methods

5.5.1 Network Meta-Analysis

To compare the efficacy and safety of treatment options simultaneously using the available trial information, Bayesian Network Meta-Analyses (NMA) will be conducted. NMA strengthens inference concerning the relative effect of two treatments by including both direct and indirect comparisons while respecting randomisation. Most treatments will not have been compared in head-to-head RCTs, and NMA allows for the use of indirect information to make that comparison. General details of the method are given in NICE Decision Support Unit Technical Support Document 2.⁵² Interventions with different doses will be considered as separate nodes. An exception will be for interferons which will be grouped as described in Section 4.5.3 and this follows the approach of TA767 on posenimod.³⁹

Vague priors will be used for Bayesian estimation of all treatment effect parameters.

The results of the NMA will also be used to inform the economic model, as described in Section 5.5.1.

5.5.2 Populations

We will conduct our NMA on all feasible outcomes in the following populations:

1. Highly active RRMS (or studies with at least 90% participants in this group) who have received at least one previous DMT.
2. Any RRMS, including studies with at least 90% of participants with RRMS.

A sensitivity analysis will be conducted on population 1 where treatments that are disconnected are included through an “Any RRMS” study from population 2.

5.5.3 Synthesis of time-to-event outcomes

The following endpoints will be analysed as time-to-event outcomes:

- CDP3
- CDP6

The reported hazard ratios on these outcomes will be converted to the log hazard ratio scale (i.e. a log link). The standard error for the log hazard ratio will be calculated by assuming

normality on the log scale and assuming the upper and lower 95% confidence intervals are separated by $2 \times 1.96 \times SE$.

If the log hazard ratio of an event on arm k relative to arm 1 in trial i is denoted y_{ik} and its standard error se_{ik} ($k \geq 2$) we use the Normal likelihood

$$y_{ik} \sim N(\theta_{ik}, se_{ik}^2)$$

Using the identity link the linear predictor is

$$\theta_{ik} = \delta_{ik}$$

If a trial i has more than 2 arms we must account for correlation between hazard ratios.⁵³

We therefore model the absolute log hazard rate for each arm h_{ik} with standard error hse_{ik}^2 as

$$h_{ik} \sim N(\theta_{ik}, hse_{ik}^2)$$

With link function

$$\theta_{ik} = \mu_i + \delta_{i,bk} I_{k \neq 1}$$

Where μ_i represents the log hazard rate on baseline arm $k = 1$.

For a random-effects model the trial-specific log hazard ratios come from a common distribution:

$$\delta_{i,bk} \sim N(d_{t_{ib}t_{ik}}, \sigma^2)$$

Where $d_{t_{ib}t_{ik}}$ is the treatment effect of the treatment t_{ik} in arm k over treatment t_{ib} in the control arm b and σ^2 is the across trials treatment effect heterogeneity variance, assumed the same for all treatment comparisons. For a fixed-effects model, we simply set

$$\delta_{i,bk} = d_{t_{ib}t_{ik}}$$

which is equivalent to setting the between-trial heterogeneity to zero thus assuming homogeneity of the underlying true treatment effects.

If the random effects models do not converge due to lack of data, we will employ predictive distributions for the heterogeneity variance σ^2 as informative priors.^{54, 55}

If a connected network cannot be formed for either CDP3 or for CPD6 but a network on studies that report either CPD3 or CDP6 (i.e., CDP3/6) is connected, a multivariate Normal likelihood will be used to analyse as a joint outcome. Effects of treatments disconnected on CDP6 can be estimated if connected on CDP3, and vice versa.

If necessary to connect the network, interferons will be pooled as a class of treatments using a hierarchical class-based model in which exchangeable effects are drawn from a class-level distribution rather than assuming a single, pooled treatment effect. This follows the approach of TA767 on posenimod.¹⁴

5.5.4 Synthesis of dichotomous outcomes

The following endpoints will be synthesised as dichotomous outcomes:

- Symptoms of multiple sclerosis (such as fatigue, cognition, and visual disturbance)
- Freedom of disease activity (for example lesions on MRI scans)
- Mortality
- All-cause discontinuation

- Discontinuation due to adverse events

We follow NICE DSU TSD 2 guidelines to analyse the number of patients with an event (or absence of an event, in the case of freedom of disease activity) r_{jk} out of patients n_{jk} on arm k of trial i as

$$r_{jk} \sim \text{Binomial}(p_{jk}, n_{jk})$$

Where the probability of event p_{jk} is mapped by the logistic link function

$$\text{logit}(p_{jk}) = \theta_{ik} = \mu_i + \delta_{i,bk} I_{k \neq 1}$$

Fixed and random effects models for the trial-specific log odds ratios $\delta_{i,bk}$ are as in Section 4.5.3. Treatment effects will be estimated on the odds ratio scale.

5.5.5 Synthesis of count outcomes

The following outcomes will be analysed as count outcomes:

- Annualised Relapse Rate (ARR)
- Any adverse events (AEs)
- Serious (grade 3 or 4) AEs (any and treatment related)

Note that AE outcomes are commonly reported as number of events in total, rather than number of patients with ≥ 1 event, so cannot be modelled as dichotomous outcomes.⁵⁶

We follow NICE DSU TSD 2 recommendations to model count outcomes as a Poisson process with a constant hazard rate. Total number of events r_{jk} over exposure E_{jk} are modelled with log link and Poisson likelihood

$$r_{jk} \sim \text{Pois}(\lambda_{jk} E_{jk})$$

The exposure E_{jk} is the product of timepoint by number of patients. Where λ_{jk} is the constant event rate arm k of trial i is linked to linear predictor scale with a log transformation

$$\theta_{jk} = \log(\lambda_{jk})$$

The model then proceeds as for other outcomes.

5.5.6 Synthesis of continuous outcomes

The following will be analysed as continuous outcomes:

- Severity of relapse
- Disability (for example, expanded disability status scale [EDSS])
- Health-related quality of life

We will follow NICE DSU TSD 2 and analyse these with an identity link function and Normal likelihood (i.e., the model of Section 4.5.3 but without a log transform). Treatment effects will be summarised as mean differences.

5.5.7 Model assessment and selection

Model selection between fixed and random effects will be based on the Deviance Information Criterion (DIC), with a difference of 3-5 points being meaningful.^{57, 58} For models with similar DIC we will select the simplest model (lowest effective number of parameters)

as this supports interpretability. The total residual deviance, as described in NICE DSU TSD 2, will be calculated, and compared to the number of datapoints as an overall assessment of goodness-of-fit.⁵² Studies with high residual deviance will be qualitatively assessed (E.g., for differences in line of therapy, disease severity, year of publication, concomitant medications) and sensitivities excluding them will be considered.

NMA assumes that all effect modifiers are balanced across studies both within (homogeneity) and between (consistency) treatment comparisons.

We will assess impact of effect modifiers using aggregate data network meta-regression, as described in NICE DSU TSD 3.⁵⁹ We will conduct meta-regression only for the outcomes CDP3/6 and ARR. This will assume a single regression coefficient for all non-placebo treatments on their treatment effects relative to placebo. Potential effect modifiers include demographics (e.g., age, gender) and disease characteristics (e.g., line of therapy, type of previous treatment, severity at baseline, active or highly active). A final list of covariates to explore will be decided on completion of the SLR.

For any networks of evidence with closed loops of direct and indirect evidence we will assess consistency in the final selected model by comparing model fit of the NMA model with the Unrelated Mean Effects (UME) model.⁶⁰ Dev-dev plots of the residual deviance contribution of individual data points in consistency vs UME models will be used to identify any discrepant data-points.

5.5.8 Predicting absolute outcomes

The economic model will require absolute outcomes rather than relative treatment effects. For example, if relapses were included, an absolute ARR would be required rather than the hazard ratios relative to placebo estimated using the methods of Section 4.5.8. A baseline natural history model will therefore be fit to the placebo arms of trials identified by the SLR. This will follow the methods of NICE DSU TSD 5 and utilise the same link function and likelihood as the NMA but model only single outcomes with no treatment effects.

Placebo or general “standard of care” estimates of absolute outcomes (e.g. CDP3/6 or ARR) may also be sourced from the targeted literature review of observational evidence described in Section 5.3.3. As example, beta-interferons and glatiramer acetate potentially describe standard of care and 10-year effectiveness results are available from the UK multiple sclerosis risk-sharing scheme (RSS).⁶¹ These sources may be combined through a Bayesian meta-analysis or multiparameter evidence synthesis (MPES).⁶²

5.5.9 Model Implementation

Data preparation will be conducted in the R programming language.⁶³ The NMA models will be fitted in a Bayesian framework using either the OpenBUGS software, interfaced with R using R2OpenBUGS, or the R package ‘multinma’.^{58, 64} Sufficient chains and Markov Chain Monte Carlo (MCMC) samples will be used for burn-in and sampling. Convergence will be

assessed by visual inspection of the trace plots and the Brookes-Gelman-Rubin (BGR) Rhat statistic, which will be reported for model parameters.⁵⁸

5.5.10 Summary of results

Results would be summarised as the mean and median of the posterior distribution of the treatment effect with Bayesian 95% credible intervals (CrI) to represent uncertainty. The 95% CrI would be calculated as the lower 2.5th and upper 97.5th percentile of the MCMC samples.

The results of the NMA will be presented in terms of cross tables with relative treatment effect estimates between all interventions of interest with 95% CrI for all outcomes presented.

One of the advantages of NMA is that it allows for the ranking of interventions. Based on the results of the NMA, we can calculate the probability of each treatment taking a particular rank as well as the probability that treatment is best. 'Rankograms' as will be presented which illustrate the probability that each treatment occupies each rank. Cumulative rankograms will also be presented, which illustrate the probability that each treatment occupies each rank or higher (e.g., probability of being ranked 2nd or 1st; probability of being ranked 3rd, 2nd or 1st; etc.).

6 Economic model

An economic model will be developed to compare the cost-effectiveness of treatments for highly active RRMS after at least one disease modifying therapy.

6.1 Decision question for modelling

The target population for our economic evaluation will be highly active RRMS who have received at least one previous DMT. As the evidence on this population is limited, we will use evidence in any RRMS (including studies with at least 90% of participants with RRMS) to fill any gaps. This aligns with the planned NMA sensitivity analysis (Section 4.5.2).

The interventions will be Natalizumab (Tysabri), delivered subcutaneously or intravenously, and intravenous natalizumab biosimilar (Tyruko). Comparators are aligned with those of the overall appraisal (Section 1.2):

- Glatiramer acetate
- Interferon beta 1a
- Interferon beta 1b
- Alemtuzumab
- Cladribine tablets
- Fingolimod
- Ocrelizumab
- Ofatumumab
- Ponesimod

- Autologous haematopoietic stem cell transplantation

Only comparators with efficacy and safety data, as identified by the SLR described in Section 4, necessary for the economic model will be assessed.

We will align with recommendations of the NICE reference case. We therefore take an NHS and NHS and personal and social services (PSS) perspective and lifetime horizon. Health benefits will be measured using Quality Adjusted Life Years (QALYs). Discounting will be applied to both costs and benefits at the annual 3.5% rate.

The model and cost-effectiveness analysis will be fully probabilistic with any specific parameter or structural sensitivity analyses also probabilistic.^{65, 66}

6.2 Models used in relevant TAs

We reviewed the economic models used in relevant NICE TAs. These were the TAs for comparators in Section that were categorised as "Recommended for RRMS in specific situations or specific subtypes" or "Recommended for previously treated RRMS" in Table 3.

6.2.1 TA767 Ponesimod

TA767 2022³⁹ assessed the cost-effectiveness of Ponesimod (Ponvory, Janssen) for RRMS at first or second line. The Markov model simulates a cohort of patients over a lifetime progressing through 10 RRMS & 10 SPMS EDSS health states leading up to death. The natural history of disability progression for RRMS patients was based on the British Columbia Multiple Sclerosis registry.⁶⁷ Annual relapse rates by disability⁶⁸ were based on population data from the burden of illness 2005 UK MS Survey⁶⁹ and patient data from a prospective study.⁷⁰ Conversion from RRMS to SPMS was based on data from the London Ontario MS database.⁶⁸ The placebo arm of the AFFIRM trial was used to modify the natural history for the HA RRMS subgroup.¹

The model inputs for patients on treatment with Ponesimod were reported by OPTIMUM & OPTIMUM-LT trials. The CDP-3 & CDP-6 outcomes modify disability progression, the ARR to estimate the number of relapses, and the proportion experiencing AEs. The model accounts for treatment waning, discontinuation, and excess mortality due to MS. Health state costs⁷¹ and utilities⁶⁹ were included. Disutilities were applied for disability, relapse, AEs, and caregivers. The EAG was critical of the model not allowing for treatment switching or sequencing and considered this to be an oversimplification of clinical practice, they acknowledged limitations maybe due to the availability of data.

6.2.2 TA699 Ofatumumab

TA699 2021³⁸ assessed the cost-effectiveness of Ofatumumab (Kesimpta, Novartis) for RRMS at first or second line. The Markov model simulates a cohort of patients over a lifetime progressing through 10 RRMS & 10 SPMS EDSS health states leading up to death. The natural history of disability progression for RRMS patients was based on the British

Columbia Multiple Sclerosis registry.⁶⁷ Annual relapse rates by disability⁶⁸ were based on population data from the burden of illness 2005 UK MS Survey⁶⁹ and patient data from a prospective study.⁷⁰ Conversion from RRMS to SPMS was based on data from the London Ontario MS database⁶⁸ supplemented by data from the EXPAND trial. The HA RRMS subgroup was modelled but not considered suitable for decision making.

The model inputs for patients on treatment with Ofatumumab were reported by ASCLEPIOS I & II trials. The CDP-3 & CDP-6 outcomes modify disability progression, the ARR to estimate the number of relapses, the proportion experiencing AEs, and quality of life data. The model accounts for treatment discontinuation, and excess mortality due to MS. Health state costs were included,⁷¹ and disutilities were applied for disability, relapse, AEs, and caregivers. The EAG was critical of the model not having incorporated loss of treatment effectiveness, they accepted treatment discontinuation as a proxy to waning as in TA533.

6.2.3 TA616 Cladribine

TA616 2019³⁵ assessed the cost-effectiveness of Cladribine tablets (Mavenclad, Merck Serono) for RES RRMS at first or second line and HA RRMS (SOT RRMS) at second line. The Markov model simulates a cohort of patients over a lifetime progressing through 10 RRMS & 10 SPMS EDSS health states leading up to death. The natural history of disability progression for RRMS patients from the British Columbia Multiple Sclerosis registry⁶⁷ adjusted to account for higher probability of progression on the RES and SOT subgroups using CDP-6 from CLARITY.

The model inputs for patients on treatment with Cladribine tablets were from an NMA and Meta-regression that included the key trials CLATIRY & CLARITY-EXT. The CDP-3 & CDP-6 outcomes modify disability progression, the ARR to estimate the number of relapses, the proportion experiencing AEs and quality of life data. The model accounts for treatment discontinuation, and excess mortality due to MS. Health state costs⁷¹⁻⁷³ and utilities^{69, 72} were included, and disutilities were applied for disability, relapse, AEs, and caregivers. The EAG was critical of the company assuming loss of treatment effectiveness to be delayed for Cladribine tablets, they accepted treatment discontinuation as a proxy to waning to as in previous appraisals.

6.2.4 TA533 Ocrelizumab

TA533 2018³² assessed the cost-effectiveness of Ocrelizumab (Ocrevus, Roche) for RRMS at first or second line. The multi—state Markov model simulates a cohort of patients over a lifetime progressing through 20 RRMS & 10 SPMS EDSS health states leading up to death. The natural history of disability progression for RRMS patients was based on the British Columbia Multiple Sclerosis registry.⁶⁷ Annual relapse rates by disability were based on population data from the burden of illness 2005 UK MS Survey⁶⁹ and patient data from a prospective study.⁷⁰ Conversion from RRMS to SPMS was based on data from the London Ontario MS database.⁶⁸ The placebo arm of the AFFIRM trial was used to modify the natural history for the HA RRMS subgroup.

The model inputs for patients on treatment with Ocrelizumab were reported by OPERA I & II trials. The CDP-3 & CDP-6 outcomes modify disability progression, the ARR to estimate the number of relapses, the proportion experiencing AEs and quality of life data. The model accounts for treatment discontinuation, and excess mortality due to MS. Health state costs were included,⁷¹ and disutilities were applied for disability, relapse, AEs, and caregivers. The EAG was critical of the model not having incorporated loss of treatment effectiveness which in clinical practice would lead to patients switching on to other treatments, they accepted treatment discontinuation as a proxy.

6.2.5 TA312 Alemtuzumab

TA312 2014³⁶ assessed the cost-effectiveness of Alemtuzumab (Lemtrada, Sanofi) for Active RRMS at first line RES RRMS at first or second line and HA RRMS at second line. The multi-state Markov model simulates a cohort of patients over a lifetime progressing through 10 RRMS & 9 SPMS EDSS health states leading up to death. The natural history of disability progression for RRMS patients and converting to SPMS states was based on the London Ontario MS database.⁶⁸ Annual relapse rates by disability were based on population data from the burden of illness UK MS Survey⁶⁹ and patent data from two prospective studies.^{70, 74}

The model inputs for patients on treatment with Alemtuzumab were from an NMA specific to the RRMS and RES RRMS and HA RRMS subgroups that included the key trials CAMMS223, CARE-MS I & II. The SAD-3 & SAD-6 outcomes modify disability progression, the ARR to estimate the number of relapses, the proportion experiencing AEs and quality of life data. The model accounts for treatment discontinuation, and excess mortality due to MS. Health state costs,^{71, 73, 75} were included and disutilities were applied for disability, relapse, AEs, and caregivers. The EAG was critical of the company assuming no loss of treatment effectiveness for Alemtuzumab, clinical advice was that patients would be offered alternative treatments after discontinuation but as treatment switching was not implemented in the model, the committee concluded it was appropriate to model long-term treatment waning.

6.2.6 TA254 Fingolimod

TA254 2012³⁷ assessed the cost-effectiveness of Fingolimod (Gilenya, Novartis) for HA RRMS at second line. The Markov model simulates a cohort of patients over a lifetime progressing through 10 RRMS & 10 SPMS EDSS health states leading up to death. The natural history of disability progression for RRMS patients and converting to SPMS states was based on the London Ontario MS database.⁷⁶ Annual relapse rates by disability were based on population data from the burden of illness UK MS Survey⁶⁹ and patient data from a prospective study.⁷⁰

The model inputs for patients on treatment with Fingolimod versus Avonex were reported on the TRANSFORMS & FREEDOMS trials. An NMA was undertaken to estimate relative treatment effects of other beta interferons. The SAD-3 & SAD-6 outcomes modify disability

progression, the ARR to estimate the number of relapses, the proportion experiencing AEs. The model accounts for treatment discontinuation, and excess mortality due to MS. Health state costs,¹ utilities⁶⁹, were included and disutilities were applied for disability, relapse, AEs, and caregivers. The model has many limitations which were critiqued by the EAG and are summarised in Table 5, they called for a new decision model, one that better reflects clinical practice in future appraisals of Multiple Sclerosis.

6.2.7 TA127 Natalizumab

TA127 2007¹ assessed the cost-effectiveness of Natalizumab (Tysabri, Biogen Idec) for RES RRMS at first or second line. The multi-state Markov model simulates a cohort of patients over a lifetime progressing through 10 RRMS & 10 SPMS EDSS health states leading up to death. The natural history of disability progression for RRMS patients and converting to SPMS states was based on the London Ontario MS database.⁷⁶ Annual relapse rates by disability were based on population data from the burden of illness UK MS Survey⁶⁹ and patient data from a prospective study.⁷⁰ The placebo arm of the AFFIRM trial was used to modify the natural history for the HA RRMS subgroup.

The model inputs were obtained from a number of sources. The Hazard ratios for disability progression and annual relapse of RES RRMS patients on treatment with Natalizumab was obtained from the AFFIRM trial and converted to risk ratios. The risk ratios for disability progression and annual relapse for patients on beta interferon or glatiramer acetate were obtained from pairwise meta-analyses, data from two Cochrane reviews.^{77, 78} The analyses derived relative treatment effects contrasting the risk ratios from the ITT and RES Natalizumab groups versus either of the beta interferon or glatiramer acetate ITT groups' risk ratios. The risk ratios for disability progression could be multiplied directly with the natural history transition matrices. However the relapse risk ratios describe had to be transformed into relative relapse rates using the annualised relapse rate from the placebo groups in AFFIRM from the RES RRMS sub group, and the ITT main group as a proxy for the SOT RRMS subgroup. Health state costs and utilities⁶⁹, were included and disutilities were applied for disability, relapse, AEs, and caregivers. The ERG was critical of the company excluding the SENTINEL trial SOT RRMS subgroup data from the model, especially that it was relied on for the marketing authorisation.

6.2.8 Common criticisms

1. Treatment sequencing and variable treatment waning was an issue in all of the reviewed submissions (TA767, TA699, TA616, TA533, TA312, TA254 and TA127) to varying degrees. These TAs explain that clinical practice is to switch patients to alternative treatments if their current drug is no longer effective. The ERGs have accepted treatment discontinuation as proxy for loss of effectiveness over time, despite lack of evidence on waning from the key trials this is because treatment switching was not modelled in any of these submissions.

2. Previous models (TA767) have modelled relative risk of death being applied to each EDSS health state, taken from Pokorski (1997) which demonstrated that risk of death because of multiple sclerosis was primarily dependent on disability. But this dataset is quite old and has been criticised by clinicians for this reason.
3. Previous models in Multiple sclerosis have had limited ability to accurately reflect the course of the condition. In TA767 and TA699 an implausible number of patients were found in high EDSS states contrary to what would be observed in clinical practice. In TA699 and TA127 issues with converting from RRMS to SPMS were discussed. In TA254 and TA127 issues with unrealistic disability progression when treatment effects were applied to the natural history was discussed.

6.3 Identification of existing evidence

We will undertake a systematic search for economics evaluations and studies reporting HRQoL data following the guidance of the CRD and NICE handbooks.

6.3.1 Planned searches for economic evidence

We will search the following bibliographic databases, using the search strategy reported in Appendix 10.1.3:

- MEDLINE (MEDALL) via Ovid
- Embase via Ovid
- EconLit via EBSCOHost
- NHS EEDs via CRD (noting that we search the archive, as the resource is no longer updated)

We will search the ISPOR Presentations Database via <https://www.ispor.org/heor-resources/presentations-database/search> limited 2020-current, to identify conference proceedings reported in the last four calendar years.

We will check the reference lists of studies included at full-text.

Studies identified in the clinical or HRQoL review (described in Section 5.3.2), where relevant to this review, will be checked for inclusion against our inclusion criteria.

6.3.2 Planned searches for evidence on HRQoL

We will search the following bibliographic databases, using the search strategy reported in Appendix 10.1.4:

- MEDLINE (MEDALL) via Ovid
- Embase via Ovid
- EuroQoL Website

Studies identified in the clinical or HRQoL review, where relevant to this review, will be checked for inclusion against our searches.

We plan for a targeted literature review (TLR) to identify studies reporting prevalence data. This search will be undertaken in MEDLINE (MEDALL) via Ovid. The syntax is reported in Appendix 10.1.5

6.3.2.1 *Managing the searches*

Search results will be exported to EndNote 20. We will deduplicate the studies and study reports from the mapping of TAs to our search results. Search results will be exported to Microsoft Access for screening.

6.3.3 Targeted literature review for placebo or standard of care outcomes

A targeted search will be required to identify placebo or standard of care estimates of absolute outcomes from observational studies as long-term large-sample data are unlikely to be located in the randomised studies. These will cover outcomes on both RRMS and possibly SPMS. We indicate a sample search approach for secondary searches, if required, in Appendix 10.1.2 as guided by DSU document two.⁵² We will search MEDLINE via Ovid with a date limit of 10 years.

6.4 Model structure

To overcome the key criticisms of the previous manufacturer models for RRMS submitted to NICE (Section 5.1.1), we will adopt an individual-level discrete-event simulation (DES) model.⁷⁹ This will make it possible to model treatment sequences and enable treatment-specific waning patterns. The inflexibility of cohort Markov models made it difficult to accurately reflect the course of MS, leading to implausible numbers of patients in the high EDSS states.³⁹ The flexibility of DES will better reflect the natural course of MS, and ease the inclusion of new standardised mortality rates by EDSS (TA767).^{39, 80} Modelling individual patients will also make it easier to allow treatment stopping rates to be higher in the first year of treatment than in subsequent years, following EAG recommendations in TA616.³⁵ Our model structure was influenced by the recent Dutch clinical guidelines models on RRMS which was a microsimulation accounting for treatment sequences.⁸¹⁻⁸⁴ However, rather than using a DES, this microsimulation used an underlying multistate structure defined by EDSS and SPMS status, similar to the Markov models used in previous NICE submissions (Section 5.2). Our justification for adopting event-based rather than state-based modelling is that the targeted of RRMS treatment is to reduce the events of relapse and disability progression, rather than to directly affect EDSS severity or SPMS status. A DES is therefore better tailored to RCT data and the focus of RRMS treatment.

The proposed model is illustrated in Figure 2. The attributes of the DES will represent important demographic and disease characteristics. The modelled disease characteristics will include the EDSS ($\in (0, \dots, 9)$) and SPMS status to thus capture health state information of previous RRMS Markov models (Section 5.1). Age and gender will be modelled as

demographic attributes and will determine the rate of background mortality. Treatment status is also included and described in more detail below.

Event rates will depend on some or all of these attributes. If a patient has not yet progressed to SPMS, events will include increase in severity (i.e., EDSS increase), decrease in severity (i.e., EDSS reduction), progression to SPMS, relapse, adverse events, treatment change not driven by an event, and death. If a patient has progressed to SPMS, the events will include increase in severity (i.e., EDSS increase), relapse, adverse events, and death.

Treatment status will be a key attribute and the sequence of treatment is represented in Figure 3. The initial treatment will be any of the interventions/comparators in highly active RRMS (Section 5.3). Following this, rescue therapy and later line therapy will follow the currently recommended pathway described in Section 2.3.5. Patients can progress to SPMS on any line of RRMS therapy and are then assumed to receive an average 'basket' of approved therapies, as described in Section 2.3.5.

We will resolve competing risks using the "event-specific" approach, which requires sampling times for all competing events and simulating the event that is the first to occur.⁸⁵
⁸⁶ The alternatives (sampling the event to occur first and then the time-to-event; sampling the time-to-event and then the event) require data to be analysed in a joint manner, which is not possible in this setting as rates of (for example) CDP3/6, ARR, and adverse events can only be estimated independently.

Capacity issues, for example with limited availability of MRI machines, may be considered by including resource constraints into the simulation.

Progressive Multifocal Leukoencephalopathy (PML) is an important side effect of some MS drugs, particularly natalizumab and its biosimilar.^{87, 88} It is caused by suppression of the immune system which can cause the John Cunningham human polyomavirus (JC virus), to become active.⁸⁷ Biogen, the manufacturer of natalizumab, currently fund JC virus testing and report a risk of PML.⁸⁹ However, this testing and is not routinely done for the biosimilar and would need to be funded by the NHS. We will explore a sensitivity analysis where the cost of JC virus testing is included for the biosimilar but not for natalizumab.

Figure 2 Model diagram for cost-effectiveness DES model

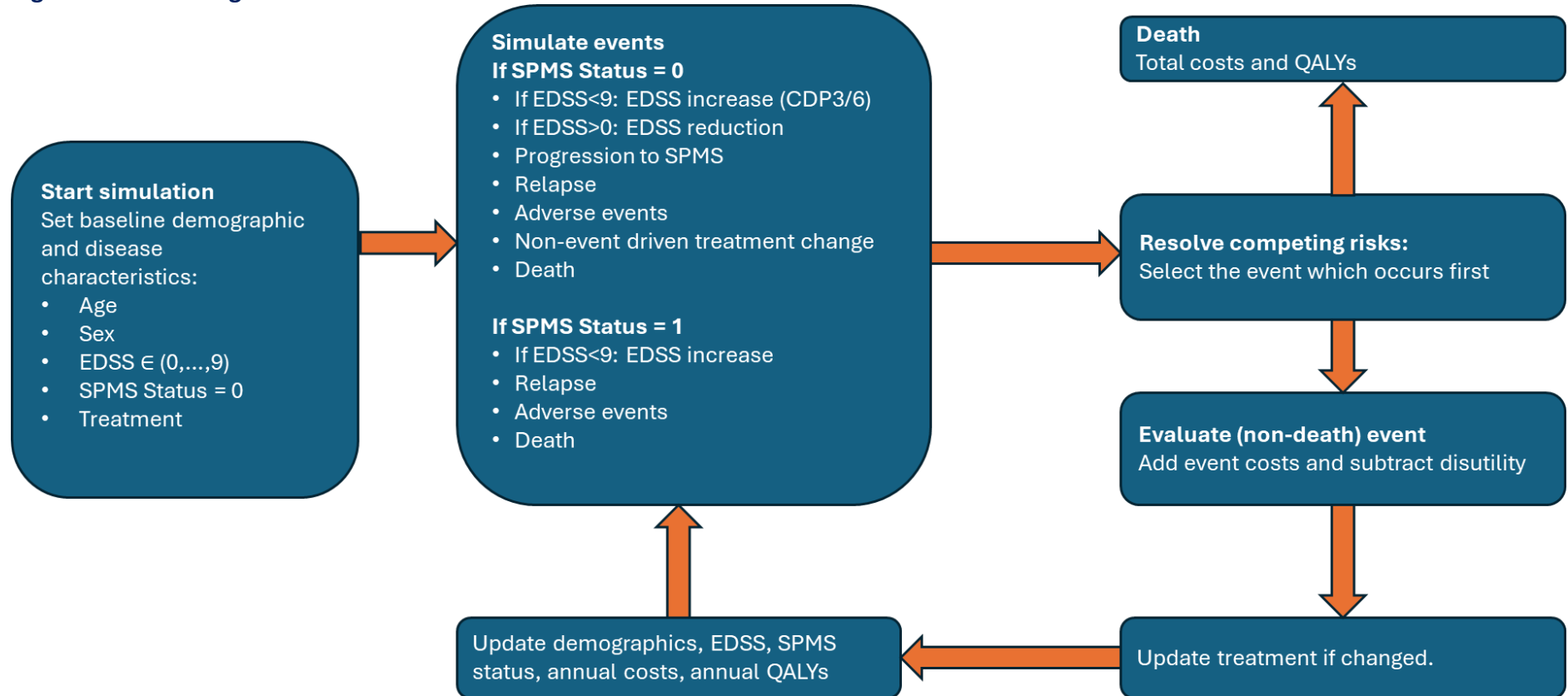
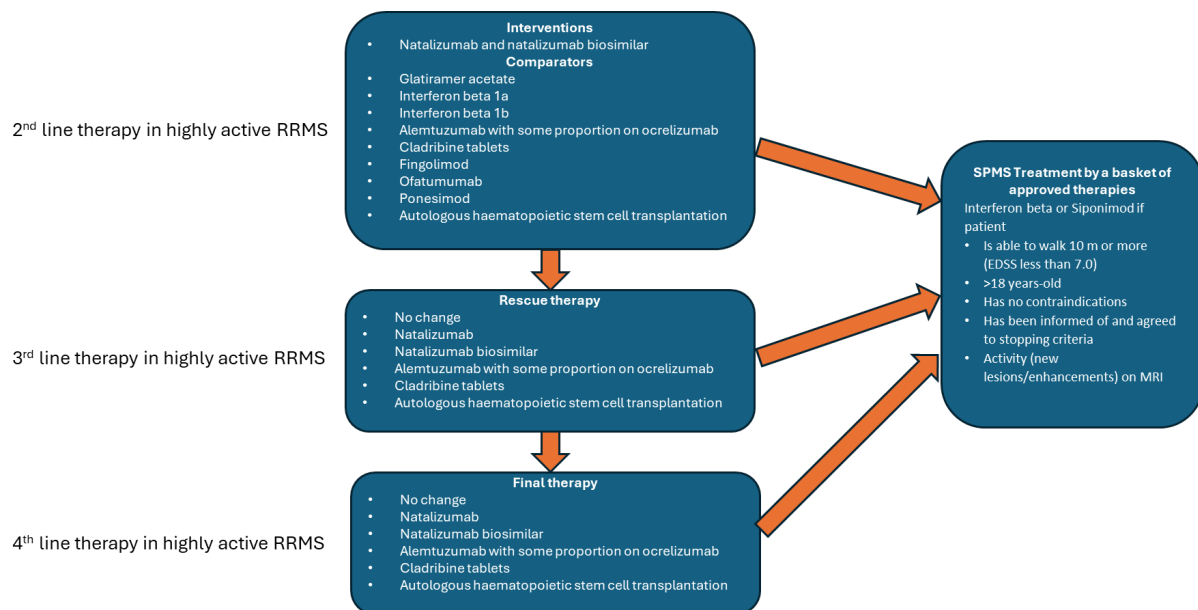


Figure 3 Treatment sequence in the cost-effectiveness DES model



6.5 Input data

6.5.1 Clinical outcomes and treatment effects

The event rates will be a combination of natural history (informed by the targeted literature review described in Section 5.3.3) and treatment effects. Treatment effects will come from the NMA described in Section 4.5. Events for patients with RRMS (i.e., SPMS status = 0) with treatment effects will be EDSS increase (i.e., CDP3, CDP6, or CDP3/6), relapse (i.e., ARR), adverse events, progression to SPMS, and mortality. EDSS decrease will be assumed not to be affected by treatment. Events for patients with SPMS (i.e., SPMS status = 1) will be assumed not to be affected by the RRMS treatment. The natural history data for these will represent outcomes on the basket of treatments described in Figure 3, and will be informed by targeted reviews described in Section 5.3.3.

Relapse rates in SPMS will be informed by our SLR but it is likely that rates will decrease with increasing severity, following EAG recommendations in TA699 and rates reported in TA527.^{30, 38} In TA767 For people who progressed to SPMS, people were assumed to transition through health states based on the London Ontario dataset.³⁹

Regarding the choice of CDP3, CDP6 or CDP3/6 for EDSS increase, in TA767 the EAG recommended that CDP6 was a more appropriate measure of disease progression following clinical advice that CDP3 may potentially overestimate progression due to natural fluctuations in the disease.³⁹ CDP6 was also preferred in other previous appraisals.³⁶

However, CDP3 may be preferred if the NMA on this outcome has greater number and quality of studies, and lower heterogeneity. Our final decision will be made following completion of the clinical SLR.

We will likely use treatment discontinuation as a proxy to waning to as in previous appraisals.

In TA767 the EAG considered the British Columbia dataset, which was used by the company, to be appropriate source for the active RRMS population for natural progression data. This Canadian observational study has been accepted in previous NICE RRMS appraisals, including the appraisal of TA493, TA527, TA533 and TA624.^{30-32, 90} The EAG in TA767, and the appraisals TA303 and TA312, noted the limitation of the alternative London Ontario dataset, that the study did not collect data on people whose disease had improved.^{36, 91}

In TA767 For the HA RRMS subgroup, the natural history transition matrix was based on a TA533, which reflected progression of participants in the placebo arm of the AFFIRM trial for natalizumab (for EDSS 0-6).^{32, 92} For EDSS 7-9 the company used values from the British Columbia database.

6.5.2 Utilities

Utilities associated with model attributes (i.e., age, gender, EDSS, SPMS status) will be derived from previous appraisals and the SLR on HRQoL described in Section 5.3.2. Disutilities for events (i.e., relapse, adverse events) will also be derived from these sources.

6.5.3 Costs and resource use

Drug costs will be derived from previous appraisals, the SLR on economic evidence described in Section 5.3.1, and PAS prices provided by NICE. Event costs will be derived from previous appraisals and the SLR.

6.6 Analyses

The model and cost-effectiveness analysis will be fully probabilistic with any specific parameter or structural sensitivity analyses also probabilistic.^{65, 66}

6.6.1 Validation

A lack of validation and transparency for cost-effectiveness models can be significant barrier to their acceptance by stakeholders and decision makers in HTA.⁹³

The International Society for Outcomes Research (ISPOR) and Society for Medical Decision Making (SMDM) taskforce on modelling have published significant guidelines on the need and methods for validation.^{94, 95} The taskforce identified five forms of validation: face validity, verification, cross validation, external validation, and predictive validation. Face validity of the RRMS model has been checked by clinical opinion and verification will be checked by a Bristol TAG validation checklist. Cross validation is conducted by comparing

the estimates of one model with those of others, but this will not be conducted as requires full access to multiple RRMS models. External validation requires the comparison of model estimates with reports from independent external data. Given concerns about estimated occupancy of high EDSS states in TA767 and TA699 and the conversion to SPMS in TA699 and TA127, this is of importance to our RRMS model.^{1, 38, 39} We will therefore conduct an informal external validation of estimated EDSS and SPMS status in the standard of care arm against long-term data identified by the searches in Section 5.3.3. Calibration to these sources will not be conducted as we will use instead include them in meta-analyses or MPES analysis of Section 4.5.8.

6.6.2 Cost-effectiveness analysis

Lifetime costs and QALYs will be estimated. These will be summarised for each intervention/comparator using their mean and 95% CrI. Incremental costs and QALYs, summarised by means and 95% CrI, will be calculated for each comparator compared to natalizumab and natalizumab biosimilar. Two cost-effectiveness planes comparing all comparators against each intervention will be generated. Pairwise cost-effectiveness analysis will be conducted using the ICER.

The primary analysis will be a multiple treatment comparison under the net benefit framework. Net benefit and, relative to each intervention, incremental net benefit will be calculated at willingness-to-pay of £20,000/QALY and £30,000/QALY. Their mean and 95% CrI will be calculated and the treatment with greatest net benefit will be interpreted as most cost-effective. Cost-effectiveness acceptability curves (CEAC) and cost-effectiveness acceptability frontiers (CEAF) will be generated.

A key sensitivity analysis will include a cost for JC testing on natalizumab biosimilar but not on natalizumab, as explained in Section 5.4.

6.6.3 Value of information analysis

Parameter uncertainty will be quantified using value of information analysis.⁹⁶ The per-person expected value of partial perfect information (EVPPI) will be estimated for each parameter and for groups of parameters of interest (e.g., efficacy, safety, utilities, and uncertain costs). Generalised additive models (GAM), Gaussian processes (GP), and, if found necessary, Multilevel Monte Carlo (MLMC) simulation will be used to estimate EVPPI.^{97, 98} The population EVPPI for parameters and groups of parameters will be estimated using UK incidence data for 2nd line highly active RRMS and a technology horizon decided in discussion with clinical advisers. The population EVPPI will be used to develop research recommendations.

6.7 Software

The model will be coded in the R programming language.^{63, 99, 100} The 'simmer' package may be used for the implementation of DES, 'BCEA' will be used for generating the CEACs and CEAFs, and both 'BCEA' and 'VOI' will be used for value of information analysis.¹⁰⁰

7 Handling information from the companies

All data submitted by the manufacturers/sponsors will be considered if received by the EAG no later than 20 August 2024. Data arriving after this date will not be considered. If the data meet the inclusion criteria for the review they will be extracted and quality assessed in accordance with the procedures outlined in this protocol. If the companies submit an NMA and economic model then the NMA and model structures, assumptions and parameter values from models submitted will be critiqued and the results compared to the equivalent results from the main RRMS model. Where there are differences between the results obtained, an effort will be made to provide a justification for the key driving factors influencing these differences.

Any confidential data **'CON'** will be highlighted in blue and underlined. Any data related to company confidential pricing such as patient access schemes **'PAS'** will be highlighted in green and underlined and labelled cPAS.

8 Competing interests of authors

Dr Claire Rice declares the following interests:

- Regular prescriber of MS disease modifying therapies in NHS MS clinics.
- Work with the MS Society as an expert panel reviewer on grant applications.
- Research grant funded by Sanofi looking at blood biomarkers of people with MS.
- Routinely involved in clinical trials other clinical studies of people on disease modifying therapies for MS including natalizumab but these are investigator-led and are not commercial studies.

Dr Emma Tallantyre declares the following interests:

- Honorarium from Roche / Novartis for consulting work in the last 12m.
- Expenses for attending educational meetings from Merck.
- Biogen honorarium for speaker fees but not in the last 24m.

Howard Thom owns shares in Clifton Insight which has received consulting fees from Amicus, Argenx, Baxter, Bayer, Daiichi-Sankyo, Eisai, Janssen, Lundbeck, Merck, Novartis, Novo Nordisk, Pfizer, and Roche.

9 Timetable/milestones

Milestone	Date to be completed
Draft protocol	19 April 2024
Final protocol	13 May 2024
Title and abstract screening	31 May 2024
Full text inclusion assessment	28 June 2024
Data extraction and risk of bias assessment	16 August 2024
Network meta-analysis of outcomes needed for economic model	13 September 2024
Network meta-analysis of other outcomes	30 September 2024
Shell DES model code	31 August 2024
Full parameterised DES model	30 September 2024
Draft assessment report	16 October 2024
Final assessment report	20 November 2024

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11 Appendices

11.1 Search strategies

11.1.1 Clinical Effectiveness

Database: Ovid (MEDALL)

Host: Ovid

Data parameters: 1946 to April 12, 2024

Date of search: 15 April 2024

#	Search terms	Results
1	Multiple Sclerosis, Relapsing-Remitting/ or (((("multiple sclerosis*" or MS) and (relap* or remit*)) or RRMS).ti,ab,kf,kw.	22675
2	Natalizumab/ or (natalizumab* or antegren* or tyruko* or tysabri* or "AN-100226*" or "AN 100226*" or AN100226* or "bg-0002" or "bg 0002" or bg0002 or "dst-356a1" or "dst 356a1" or dst356a1 or "pb-006" or "pb 006" or pb006 or "pbp-2002" or "pbp 2002" or pbp2002 or L04AA23 or 3JB47N2Q2P or "189261-10-7").ti,ab,kf,kw.	3344
3	(glatiramer* or copaxobene* or copaxone* or copemyl* or copolymer* or glatect* or galtipex* or glataxon* or glatimyl* or glatopa* or glaxaton* or marcyto* or myeloxen* or perscleran* or remurel* or sclerthon* or "tv 5010" or "tv-5010" or tv5010 or "COP 1" or "COP-1" or COP1 or "Copolymer-1" or (tv adj "5010") or u782c039qp or L03AX13 or U782C039QP or "28704-27-0" or "147245-92-9").ti,ab,kf,kw.	52717
4	*INTERFERON-BETA/ or ((INTERFERON adj2 (BETA* or fibroblast)) or avonex* or extavia* or feron* or fiblaferon* or fibrolast* or frone* or hemeferon* or naferon* or "bm 532" or "bm-532" or bm532 or "SNG 001" or "SNG-001" or SNG001 or "mr 21" or "mr-21" or mr21 or V9GU1EM8SF or "74899-71-1").ti,ab,kf,kf.	15753
5	ALEMTUZUMAB/ or (alemtuzumab* or campath* or lemtrada* or mabcambath* or mabkampat* or remniq* or "bxt 1523" or "bxt-1523" or bxt1523 or "gz 402673" or "gz-402673" or gz402673 or "ldp 03" or "ldp 103" or "ldp-103" or ldp103 or L04AA34 or 3A189DH42V or "216503-57-0").ti,ab,kf,kw.	4039
6	cladribine/ or (cladribine* or biodribin* or intocel* or leustat* or leustatin* or litak* or mavenclad* or movectro* or mylinax* or "RWJ 26251" or "RWJ-26251" or RWJ26251 or L04AA40 or 47M74X9YT5 or "4291-63-8").ti,ab,kf,kw.	2628
7	Fingolimod Hydrochloride/ or (fingolimod* or bonaxon* or chantico* or efigalo* or fenoxa* or fimodigo* or fingod* or "fty 720" or "fty-720" or fty720 or gilenia* or gilenya* or golpimec* or imusera* or inzolfi* or lognif* or "ro 7079904" or "ro-7079904" or ro7079904 or tascenso* or	4672

#	Search terms	Results
	"tdi 132" or "tdi-132" or tdi132 or L04AA27 or 3QN8BYN5QF or "162359-55-9").ti,ab,kf,kw.	
8	(ocrelizumab* or ocrevus* or rhumba* or "PR 070769" or "PR-070769" or PR070769 or "R 1594" or "R-1594" or R1594 or "RG 1594" or "RG-1594" or RG1594 or "RO 4964913" or "RO-4964913" or RO4964913 or L04AA36 or A10SJL62JY or "637334-45-3").ti,ab,kf,kw.	967
9	(ofatumumab* or arzerra* or kesimpta* or "HuMax CD20" or "HuMax-CD20" or HuMaxCD20 or "humac CD20" or "humac-CD20" or humacCD20 or "GSK 1841157" or "GSK-1841157" or GSK1841157 or "HSDB 8170" or "HSDB-8170" or HSDB8170 or "OMB 157" or "OMB-157" or OMB157 or L01FA02 or M95KG522R0 or "679818-59-8").ti,ab,kf,kw.	776
10	(ponesimod* or ponvory* or "ACT 128800" or "ACT-128800" or ACT128800 or "r 3477" or "r-3477" or r3477 or "rg 3477" or "rg-3477" or rg3477 or L04AA50 or 5G7AKV2MKP or "854107-55-4").ti,ab,kf,kw.	119
11	HEMATOPOIETIC STEM CELL TRANSPLANTATION/ or ((haematopoietic and stem and cell and transplant*) or (haematopoietic and stem and cell and therap*) or (hematopoietic and stem and cell and transplant*) or (hematopoietic and stem and cell and therap*) or (HSC adj1 (therap* or transplant*))).ti,ab,kf,kw.	79639
12	2 or 3 or 4 or 5 or 6 or 7 or 8 or 9 or 10 or 11	159476
13	randomized controlled trial.pt.	610719
14	controlled clinical trial.pt.	95511
15	random*.ti,ab,kf,kw.	1511789
16	placebo.ab.	247349
17	("Phase 3*" or "phase3*" or "phase III*" or P3* or "PIII*" or "Phase 2*" or "phase2*" or "phase II*" or P2* or "PII*").ti,ab,kw,kf.	406274
18	(trial or trail).ti,ab,kw,kf.	832384
19	13 or 14 or 15 or 16 or 17 or 18	2422314
20	1 and 12 and 19	2017

11.1.2 Clinical Effectiveness (targeted search)

Database: Ovid (MEDALL)

Host: Ovid

Data parameters: 1946 to April 12, 2024

Date of search: 15 April 2024

#	Search terms	Results
1	("Multiple Sclerosis Relapsing-Remitting" or "Relapsing-Remitting Multiple Sclerosis" or RRMS).ti,ab,kf.	8034
2	*Registries/ or ("Multiple Sclerosis regist*" or "MS regist*" or "Multiple Sclerosis database" or "MS database").ti,ab,kf,kw.	29479
3	(placebo* or (standard or (usual adj3 care)) or (treatment adj3 usual)).ti,ab,kf.	1413357
4	2 or 3	
3	Epidemiologic studies/	9524
4	exp case control studies/	1497493
5	exp cohort studies/	2594513
6	Case control.tw.	161303
7	(cohort adj (study or studies)).tw.	347739
8	Cohort analy\$.tw.	12924
9	Longitudinal.tw.	343066
10	Retrospective.tw.	804899
11	Cross sectional.tw.	557051
12	Cross-sectional studies/	498918
13	5 or 6 or 7 or 8 or 9 or 10 or 11 or 12 or 13 or 14	3885765
14	(2014* or 2015* or 2016* or 2017* or 2018* or 2019* or 2020* or 2021* or 2022* or 2023* or 2024*).dt,dp,ed,ep,yr.	14391773
15	1 and ((2 or (3 and 15 and 16)) and 17)	168

11.1.3 Cost effectiveness and economics

Database: Ovid (MEDALL)

Host: Ovid

Data parameters: 1946 to April 12, 2024

Date of search: 15 April 2024

#	Search terms	Results
1	Multiple Sclerosis, Relapsing-Remitting/ or *Multiple Sclerosis, Chronic Progressive/ or (RRMS or RMS or SPMS or ("multiple sclerosis*" or MS) adj5 (relap* or remit* or secondary or progres*))).ti,ab,kf,kw.	26539
2	exp "Costs and Cost Analysis"/	269763
3	exp Economics, Hospital/ or Financial management, hospital/	33087
4	Economics, Medical/	9276
5	economics, nursing/	4013
6	economics, pharmaceutical/	3130
7	(economic* or cost or costs or costly or costing or expense or expenses or financial or price or prices or pricing or pharmacoeconomic* or "pharmaco-economic*" or CEA or CUA or CBA or CMA).ti,ab,kf,kw.	1284212
8	exp "fees and charges"/	31430
9	exp budgets/	14198
10	(resource*1 and (allocation or utili* or usage or use*1)).ti,ab,kf,kw.	286318
11	(expenditure* not energy).ti,ab,kw.	38716
12	(value adj1 (money or monetary)).ti,ab,kw.	917
13	(budget* or fiscal or funding or financial or finance*).ti,ab,kw.	250196
14	("decision tree" or Markov or "semi Markov" or "partitioned adj2 survival" or "discrete event" or "conceptual* adj2 model*" or (decision adj2 model*) or "outcome model*" or "causal model*" or (simulat* adj2 model*) or "monte carlo" or "decision tree" or QALY*).ti,ab,kf.	169181
15	2 or 3 or 4 or 5 or 6 or 7 or 8 or 9 or 10 or 11 or 12 or 13 or 14	1851093
16	1 and 15	1640
17	(2014* or 2015* or 2016* or 2017* or 2018* or 2019* or 2020* or 2021* or 2022* or 2023* or 2024*).dt,dp,ed,ep,yr.	14378287
18	16 and 17	1481

11.1.4 HRQoL

Database: Ovid (MEDALL)

Host: Ovid

Data parameters: 1946 to April 12, 2024

Date of search: 15 April 2024

#	Search terms	Results
1	Multiple Sclerosis, Relapsing-Remitting/ or *Multiple Sclerosis, Chronic Progressive/ or (RRMS or RMS or SPMS or (("multiple sclerosis*" or MS) adj5 (relap* or remit* or secondary or progres*))).ti,ab,kf,kw.	21002
2	(15D or 15-D or 15 dimension).ti,ab,kw.	6285
3	(eq-5d or eq5d or eq-5 or eq5 or EQ-5D-Y or euro qual or euroqual or euro qual5d or euroqual5d or euro qol or euroqol or euro qol5d or euroqol5d or euro quol or euroquol or euro quol5d or euroquol5d or eur qol or eurqol or eur qol5d or eur qol5d or eur?qul or eur?qul5d or euro\$ quality of life or european qol or EQ-5D-3L).ti,ab,ot,hw,kw.	18680
4	(sf6 or sf 6 or SF-6D or short form 6 or short-form 6 or short-form six or shortform 6 or sf six or sfsix or shortform six or short form six).ti,ab,ot,hw,kw.	3554
5	(sf8 or sf 8 or sf-8 or short form 8 or shortform 8 or sf eight or sfeight or shortform eight or shortform eight).ti,ab,ot,hw,kw.	780
6	(sf10 or sf 10 or short form 10 or short-form 10 or short-form ten or shortform 10 or sf ten or sften or shortform ten or short form ten).ti,ab,ot,hw,kw.	163
7	(sf12 or sf 12 or short form 12 or short-form 12 or short-form twelve or shortform 12 or sf twelve or sftwelve or shortform twelve or short form twelve).ti,ab,ot,hw,kw.	8033
8	(sf16 or sf 16 or short form 16 or short-form 16 or short-form sixteen or shortform 16 or sf sixteen or sfsixteen or shortform sixteen or short form sixteen).ti,ab,ot,hw,kw.	41
9	(sf20 or sf 20 or short form 20 or short-form 20 or short-form twenty or shortform 20 or sf twenty or sftwenty or shortform twenty or short form twenty).ti,ab,ot,hw,kw.	460
10	(sf36 or sf 36 or short form 36 or short-form 36 or short-form thirty six or shortform 36 or sf thirtysix or sf thirty six or shortform thirtysix or shortform thirty six or short form thirty six or short form thirtysix or short form thirty six).ti,ab,ot,hw,kw.	31715

11	(health utilities index* or (hui or hui1 or hui2 or hui3 or hui4 or hui-4 or hui-1 or hui-2 or hui-3)).ti,ab,ot,hw,kw.	2373
12	("time trade off" or "time tradeoff" or "time trade-off" or TTO).ti,ab,ot,hw,kw.	2443
13	(standard gamble* or SG).ti,ab,ot,hw,kw.	15096
14	("discrete choice" or DCE).ti,ab,ot,hw,kw.	10473
15	(AQoL or "Assessment of Quality of Life").ti,ab,ot,hw,kw.	2435
16	Quality-Adjusted Life Years/	16270
17	(HRQoL or HRQL or HQL or HQOL or H QoL or hr QoL or QoL or (quality adj3 life) or quality time or HYE or HYES or (health* adj3 equivalent*)).ti,ab,ot,hw,kw.	484139
18	quality of life/	286289
19	value of life/	5824
20	uncertainty/	18835
21	(Disability adjusted life or Disability-adjusted life or health adjusted life or health-adjusted life or "years of healthy life" or healthy years equivalent or "years of potential life lost" or "years of healthlife lost").ti,ab,ot,kw.	6864
22	(HSUV* or health state* value* or health state* preference* or HSPV*).ti,ab,ot,kw.	569
23	(uncertain* or wellbeing or "well being" or "quality of wellbeing" or "index of wellbeing" or "index of well being" or rosser or "willingness to pay").ti,ab,kw.	391889
24	(utility* or disutili*).ti,ab,kw.	274580
25	(illness state*1 or health state* or health status or Quality adjusted life year* or QALY or QALD or DALY* or HALY* or YHL or HYES or YPLL or YHLL or qale or qtime or AQoL* or life year* or ICER or "incremental cost").ti,ab,ot,hw,kw.	226982
26	(burden and (disease or illness or caregiver or home)).ti,ab,kw.	146064
27	(lost adj2 (productivity or work or employment or earnings)).ti,ab,kw.	3517
28	2 or 3 or 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 18 or 19 or 20 or 21 or 22 or 23 or 24 or 25 or 26 or 27 [generic HRQoL filter]	1404015
29	(2014* or 2015* or 2016* or 2017* or 2018* or 2019* or 2020* or 2021* or 2022* or 2023* or 2024*).dt,dp,ed,ep,yr.	14378287
30	1 and 28 and 29	2239

11.1.5 Targeted search for prevalence data

Database: Ovid (MEDALL)

Host: Ovid

Data parameters: 1946 to April 12, 2024

Date of search: 17 April 2024

#	Search terms	Results
1	("Multiple Sclerosis Relapsing-Remitting" or "Relapsing-Remitting Multiple Sclerosis" or RRMS).ti,ab,kf.	8034
2	(epidemiology or epidemiological).ti,ab,kf.	459737
3	*Incidence/ or Incidence.ti,ab,kf.	954502
4	*Prevalence/ or Prevalence.ti,ab,kf.	834764
5	2 or 3 or 4	2028469
6	1 and 5	545

11.2 Details on economic models in previous relevant TAs

Table 4 Summary of economic evaluations of Highly Active Relapse Remitting Multiple Sclerosis technologies with marketing authorisation in the UK

TA (year) Intervention	Model type	Time horizon	Discount Rate	Population	Comparators	Outcomes and sources of data
TA767 (2022) Ponesimod (Ponvory, Janssen) ³⁹	Markov Cohort Model	Lifetime 50 years (annual cycles)	3.5 %	RRMS <u>Subgroup:</u> HA RRMS	<u>RRMS</u> • Beta interferons, • Dimethyl fumarate, • Glatiramer acetate, • Teriflunomide, • Ocrelizumab, • Peginterferon beta-1a • Ofatumumab. <u>HA RRMS</u> • Alemtuzumab • Fingolimod • Cladribine, • Ofatumumab and • Ocrelizumab (only if alemtuzumab is contraindicated or otherwise unsuitable)	<u>Intervention:</u> ARR, CDP-3, CDP-6, AEs from OPTIMUM, OPTIMUM-LT <u>Comparators:</u> ARR, DCP-3, CDP-6, All cause discontinuation from NMA (RRMS), NMA (HA RRMS) <u>Natural History:</u> RRMS transitions from the British Columbia Multiple Sclerosis registry, ⁶⁷ HA RRMS transitions from the AFFIRM trial. Converting from RRMS to SPMS from the London, Ontario MS database. ⁶⁸ ARR by EDSS ⁶⁸ Relative risk of relapse from the AFFIRM trial. Relative risk of death applied to EDSS states. ¹⁰¹

TA (year) Intervention	Model type	Time horizon	Discount Rate	Population	Comparators	Outcomes and sources of data
TA699 (2021) Ofatumumab (Kesimpta, Novartis) ³⁸	Markov Cohort Model	Lifetime 62 years (annual cycles)	3.5 %	RRMS <u>Subgroups:</u> HA RRMS & RES RRMS were not considered suitable for decision making	<u>RRMS</u> • Beta interferons, • Dimethyl fumarate, • Glatiramer acetate, • Teriflunomide, • Peginterferon beta-1a	<u>Intervention:</u> ARR, CDP-3, CDP-6, AEs , EQ-5D from ASCLEPIOS I, ASCLEPIOS II <u>Comparators:</u> ARR, DCP-3, CDP-6, All cause discontinuation from NMA (RRMS) <u>Natural History:</u> RRMS transitions from the British Columbia Multiple Sclerosis registry, ⁶⁷ . Converting from RRMS to SPMS from the London, Ontario MS database ⁶⁸ supplemented by the EXPAND trial. ARR by EDSS ⁶⁸ Relative risk of relapse from the AFFIRM trial. Relative risk of death applied to EDSS states. ¹⁰¹

TA (year) Intervention	Model type	Time horizon	Discount Rate	Population	Comparators	Outcomes and sources of data
TA616 (2019) Cladribine tablets (Mavenclad, Merck Serono) ³⁵	Markov Cohort Model	Lifetime 50 years (annual cycles)	3.5 %	RES RRMS SOT RRMS	<u>RES RRMS</u> • Alemtuzumab • Natalizumab • Daclizumab (contra indicated to alemtuzumab) <u>SOT RRMS</u> • Alemtuzumab • Fingolimod • Daclizumab (contra indicated to alemtuzumab)	<u>Intervention & Comparators relative treatment effects:</u> ARR, DCP-3, CDP-6, relapse free patients, AEs (grades 3 or 4), discontinuation due to AEs, all cause discontinuation from NMA & Meta-regressions per sub- group (RES RRMS, SOT RRMS) <u>Intervention:</u> EQ-5D from ASCLEPIOS I <u>Natural History:</u> RRMS transitions from the British Columbia Multiple Sclerosis registry, ⁶⁷ . Faster rates of progression for the SOT RRMS & RES RRMS groups based on CLARITY. Converting from RRMS to SPMS from the London, Ontario MS database ⁶⁸ supplemented by the EXPAND trial. ARR independent of EDSS, year1 pbo arm of CLARITY, subsequent years as a function of time from the British Columbia Multiple Sclerosis registry. ¹⁰² Relative risk of death from a meta-analysis of SMRs. ¹⁰³

TA (year) Intervention	Model type	Time horizon	Discount Rate	Population	Comparators	Outcomes and sources of data
TA533 (2018) Ocrelizumab (Ocrevus, Roche) ³²	Multi- state Markov Cohort Model	Lifetime 50 years (annual cycles)	3.5 %	RRMS <u>Subgroups:</u> HA RRMS RES RRMS	<u>RRMS</u> • Alemtuzumab, • Beta interferons, • Dimethyl fumarate, • Glatiramer acetate, • Natalizumab, • Fingolimod. <u>HA RRMS</u> • Alemtuzumab • Fingolimod <u>RES RRMS</u> • Alemtuzumab • Natalizumab	<u>Intervention:</u> ARR, DCP-3, CDP-6, AEs, EQ-5D from OPERA I - OPERA II - OPERA OLE <u>Comparators:</u> ARR, DCP-3, CDP-6, All cause discontinuation, NMA (RRMS) - NMA (HA RRMS) - NMA (RES RRMS) <u>Natural History:</u> RRMS transitions from the British Columbia Multiple Sclerosis registry, ⁶⁷ HA RRMS transitions from the AFFIRM trial. Converting from RRMS to SPMS from the London, Ontario MS database. ⁶⁸ ARR by EDSS. ⁶⁸ Relative risk of relapse from the AFFIRM trial. Relative risk of death applied to EDSS states ¹⁰¹
TA312 (2014, update 2020) Alemtuzumab (Lemtrada, Sanofi) ³⁶	Multi- state Markov Cohort Model	Lifetime 50 years (annual cycles)	3.5 %	RRMS <u>Subgroups:</u> HA RRMS RES RRMS	<u>RRMS</u> • Beta interferons, • Glatiramer acetate, <u>HA RRMS</u> • Fingolimod <u>RES RRMS</u> • Natalizumab	<u>Intervention & Comparators relative treatment effects:</u> ARR, SAD-3, SAD-6, relapse free patients, discontinuation due to AEs from NMAs per group / sub-group (RRMS, HA RRMS and RES RRMS) <u>Intervention:</u> AEs, SAEs, EQ-5D from CAMMS223, CARE-MS I & II <u>Natural History:</u> RRMS transitions EDSS (1-9) and converting from RRMS to SPMS were sourced from the London Ontario MS database. ⁶⁸ RRMS-EDSS 0 from the placebo arms of TOWER & TEMSO trials ARR by EDSS ⁶⁸ Relative risk of death applied to EDSS states ¹⁰¹

TA (year) Intervention	Model type	Time horizon	Discount Rate	Population	Comparators	Outcomes and sources of data
TA254 (2012) Fingolimod (Gilenya, Novartis) ³⁷	Markov Cohort Model	Lifetime 50 years (annual cycles)	3.5 %	<u>Main analysis:</u> 1b)HA RRMS <u>In DP not in CE analysis:</u> 1a)HA RRMS 2)RES RRMS	<u>1b)HA RRMS</u> • beta interferon-1a (Avonex) • Rebif-22 • Rebif-44 • Betaferon • Extavia	<u>Intervention</u> ARR, SAD-3, SAD-6 from the TRANSFORMS & FREEDOMS trials. <u>Comparators:</u> ARR, SAD-3, SAD-6 from NMAs (HA RRMS) <u>Natural History:</u> RRMS transitions EDSS (1-9) and converting from RRMS to SPMS from the London, Ontario MS database . ⁷⁶ ARR by EDSS ⁶⁸ Relative risk of death applied to EDSS states. ¹⁰¹
TA127 (2007) (Tysabri, Biogen Inc) ¹	Multi- state Markov Cohort Model	Lifetime 20 years (annual cycles)	3.5 %	RES RRMS SOT RRMS	• Beta interferons, • Glatiramer acetate.	<u>Intervention</u> ARR, SAD-3, SAD-6 from AFFIRM. <u>Comparators:</u> ARR, SAD-3, SAD-6 from pairwise meta-analyses <u>Natural History:</u> RRMS transitions EDSS (1-9) and converting from RRMS to SPMS from the London, Ontario MS database . ⁷⁶ } HA RRMS transitions from the AFFIRM trial. ARR by EDSS ⁶⁸ Relative risk of death applied to EDSS states ¹⁰¹

Table 5 (continued) Summary of economic evaluations of Highly Active Relapse Remitting Multiple Sclerosis technologies with marketing authorisation in the UK

TA, year	Health states	Utilities & Costs	EAG key Criticism	Results
TA767 (2022) Ponesimod (Ponvory, Janssen) ³⁹	20 in total: • 10 EDSS RRMS • 9 EDSS SPMS • Death	• RRMS EQ-5D EDSS 0-9, • SPMS Utility decrement • Caregiver disutilities • Relapse HS disutilities • AE utility decrements • Drug acquisition, administration and monitoring costs • HS Costs EDSS 0-9, • AE Costs	Treatment switching or sequencing – The EAG acknowledged the availability of data a limitation on modelling this aspect of clinical practice, leading to an oversimplified model. Implausible no. of patients in high EDSS states – Contrary to the expert opinion of clinical advisors a higher proportion of patients than would be observed in practice progressed to EDSS 8 and 9 where they accumulated negative QALYs. The EAG was critical of this aspect of the model, despite it being broadly in line with other appraisals. The committee concluded that this model, as with other multiple sclerosis models, was limited in its ability to accurately reflect the course of the condition. More appropriate data on mortality - Clinical experts considered the mortality data was outdated and that managing acute infection and nursing has fundamentally reduced mortality with MS. That new standardised mortality rates by EDSS state had been recently published. The committee concluded that in future appraisals in MS, it would like to see more appropriate sources of mortality data in a model with plausible distributions of people in EDSS states.	The committee concluded that overall, the cost-effectiveness results were acceptable and the most likely estimates were below what NICE considers an acceptable use of NHS resources

TA, year	Health states	Utilities & Costs	EAG key Criticism	Results
TA699 (2021) Ofatumumab (Kesimpta, Novartis) ³⁸	21 in total: • 10 EDSS RRMS • 10 EDSS SPMS • Death	• RRMS EQ-5D EDSS 0-9, • SPMS Utility decrement • Caregiver disutilities • Relapse HS disutilities • AE utility decrements • Drug acquisition, administration and monitoring costs • HS Costs EDSS 0-9, • AE Costs	loss of treatment effectiveness – The committee referred to TA533 (Ocrelizumab) which had accepted treatment discontinuation as proxy for loss of effectiveness over time, despite lack of evidence on waning from the key trials. Implausible relapse rates in higher EDSS states – Contrary to clinical advice the company modelled increasing relapse rates at the higher EDSS SPMS states. The EAG went with values that were decreasing as severity increased, reported in TA 527. Conflicting approaches to converting from RRMS to SPMS – the company used transition matrices from the British Columbia longitudinal multiple sclerosis dataset (TA254). The EAG preferred to use transition matrices from the London Ontario multiple sclerosis dataset (TA624) Both data sources had been accepted previously by NICE technology appraisal committees and were found to have minimal impact on the ICERs.	The committee referred to the appraisal guidelines stating that, above a most plausible ICER of £20,000 per quality-adjusted life year (QALY) gained, judgements about the acceptability of a technology as an effective use of NHS resources will take into account the degree of certainty around the ICER. The committee noted that, with the exception of waning of treatment effect, changes to each assumption had a minor impact on the base-case ICER. The committee concluded that it could recommend ofatumumab as an additional treatment option for relapsing–remitting multiple sclerosis.
TA616 (2019) Cladribine tablets (Mavenclad, Merck Serono) ³⁵	21 in total: • 10 EDSS RRMS • 10 EDSS SPMS • Death	• RRMS EQ-5D EDSS 0-9, • SPMS Utility decrement • Caregiver disutilities • Relapse HS disutilities	Inaccurate RES RRMS & SOT RRMS natural history - The company calculating different rates of disability progression in the subgroups. The clinical experts and the EAG explained that, although assuming different rates of disease progression for each subgroup was reasonable, the company's approach was simplistic and potentially inaccurate. The committee appreciated that there was no clear alternative data source or method, and was	Cladribine dominated all other treatments in both RES RRMS and SOT RRMS groups. Cladribine was more effective and cheaper than fingolimod and natalizumab. It was less effective and cheaper than alemtuzumab. The ICERs vs. alemtuzumab were: • £219,549 gained per QALY lost (RES RRMS)

TA, year	Health states	Utilities & Costs	EAG key Criticism	Results
		• AE utility decrements • Drug acquisition, administration and monitoring costs • HS Costs EDSS 0-9, • AE Costs	aware that such adjustment had not been used in previous technology appraisals. loss of treatment effectiveness – The company used treatment switching analysis to support their assumption; treatment waning for Cladribine to begin 2 years later than comparators. The committee noted that there was no statistically significant evidence to support different waning effects and that patient numbers used for the analysis in the subgroups were very small. It concluded that the company's evidence was insufficient to justify using a different treatment waning assumption for cladribine. Treatment stopping rates are not constant - The EAG explained that people are more likely to stop treatment during the first year of treatment than in a subsequent year. Therefore, the company's approach of applying trial-based discontinuation rates to subsequent years would overestimate the number of people stopping treatment.	• £372,802 gained per QALY lost SOT (RRMS) The committee concluded that cladribine was a cost-effective use of NHS resources for rapidly evolving severe relapsing–remitting multiple sclerosis and sub optimally treated relapsing–remitting multiple sclerosis.
TA533 (2018) Ocrelizumab (Ocrevus, Roche) ³²	31 in total: • 20 EDSS RRMS • 10 EDSS SPMS • Death	• RRMS EQ-5D EDSS 0-9, • SPMS Utility decrement • Caregiver disutilities • Relapse HS disutilities	loss of treatment effectiveness – In clinical practice, when a drug is no longer effective, patients switch on to alternative treatments. Treatment switching was not included in the model. The EAG accepted treatment discontinuation as proxy for loss of effectiveness over time, despite lack of evidence on waning from the key trials.	The most plausible ICERs were below £30,000 per QALY gained in the relapsing–remitting multiple sclerosis population compared with all relevant comparators, apart from alemtuzumab, which dominated all comparisons.

TA, year	Health states	Utilities & Costs	EAG key Criticism	Results
		• AE utility decrements • Drug acquisition, administration and monitoring costs • HS Costs EDSS 0-9, • AE Costs		In the highly active subgroup, the most plausible ICER for ocrelizumab compared with fingolimod was below £20,000 per QALY gained. In the rapidly evolving severe subgroup, ocrelizumab was cheaper and less effective than natalizumab. The most plausible ICER for ocrelizumab compared with natalizumab was In the range of £350,000 to £125,000 saved per QALY lost .
TA312 (2014, update 2020) Alemtuzumab (Lemtrada, Sanofi) ³⁶	20 in total: • 10 EDSS RRMS • 9 EDSS SPMS • Death	• RRMS EQ-5D EDSS 0-9, • SPMS Utility decrement • Caregiver disutilities • Relapse HS disutilities • AE utility decrements • Drug acquisition, administration and monitoring costs • HS Costs EDSS 0-9, • AE Costs	loss of treatment effectiveness – The company assumed treatment with Alemtuzumab would persist indefinitely. The clinical specialists also stated that people who experience a relapse soon after treatment with alemtuzumab will probably be offered alternative treatment. The Committee stated that, for some people, alemtuzumab might not provide long-term enduring effect and other treatments might be required. The Committee concluded that because of the uncertainty about the long-term treatment effects it was appropriate to incorporate waning effects into the model.	The most plausible ICER for alemtuzumab compared with glatiramer acetate for people with active relapsing-remitting multiple sclerosis is likely to lie between £13,600 and £24,500 per QALY gained active relapsing–remitting multiple sclerosis. The most plausible ICER for patients with highly active relapsing-remitting multiple sclerosis despite beta interferon treatment was £8900 per QALY gained for alemtuzumab compared with fingolimod. Alemtuzumab dominated natalizumab (that is, less expensive and more effective) for patients with rapidly evolving severe relapsing-remitting multiple sclerosis.

TA, year	Health states	Utilities & Costs	EAG key Criticism	Results
TA254 (2012) Fingolimod (Gilenya, Novartis) ¹⁰⁴	21 in total: • 10 EDSS RRMS • 10 EDSS SPMS • Death	• RRMS EQ-5D EDSS 0-9, • SPMS Utility decrement • Caregiver disutilities • Relapse HS disutilities • AE utility decrements • Drug acquisition, administration and monitoring costs • HS Costs EDSS 0-9, • AE Costs	Uncertainty in the analysis on the population of interest - analysis of population 1b that excluded people who also met the criteria for population 2 (that is, a population in which people with rapidly evolving severe disease were excluded) was provided. The Committee noted that this analysis generated lower ICERs than those for the whole of population 1b, but was aware of reservations expressed by the manufacturer and the EAG about the small samples on which the subgroup analysis was based Uncertainty around the improvements in quality of life - There weren't statistically significant changes from baseline for EQ-5D measures observed for people with relapsing–remitting multiple sclerosis treated with fingolimod or placebo in the FREEDOMS trial. A slight, non-statistically significant improvement in the PRIMUS-QoL scale was observed for people treated with fingolimod or Avonex in the TRANSFORMS trial.	The Committee acknowledged that there was variation in current practice and therefore concluded that fingolimod should be compared with a weighted average of the comparators used in UK clinical practice of RRMS. That the most plausible ICER for fingolimod compared with the weighted average of the comparators was likely to be in the range of £25,000 to £35,000 per QALY gained from the main analysis on population 1b. In supplementary analyses For population 1b, excluding those who also met the criteria for population 2, the EAG concluded that the incremental analysis shows that in both populations Avonex is either dominated or extendedly dominated. The EAG therefore advised that the cost effectiveness of fingolimod should be derived from incremental analysis.

TA, year	Health states	Utilities & Costs	EAG key Criticism	Results
			Loss of treatment effectiveness – The Committee preferred a 50% waning of treatment effect after 5 years be included in the base-case analysis. Unrealistic disability progression – The Committee noted the concerns of the clinical specialists that the model may not reflect the natural history of multiple sclerosis, because it does not allow for improvement in EDSS scores. Call for an economic model that reflects clinical practice in UK - The Committee emphasised that it is important that a new model for multiple sclerosis is developed for any future appraisals of treatments for multiple sclerosis. The new model should ideally be based on UK patient cohorts, should use the best available evidence (including experience to date from the risk-sharing scheme) and should include all currently available treatments for multiple sclerosis, so that future appraisals of treatments for multiple sclerosis are directly relevant to UK clinical practice.	
TA127 (2007) (Tysabri, Biogen Inc.) ¹	21 in total: • 10 EDSS RRMS • 10 EDSS SPMS	• RRMS EQ-5D EDSS 0-9, • SPMS Utility decrement	Uncertainty in the analysis on the population of interest - The EAG was critical that the data for the comparators derived from people with RRMS rather than HA RRMS . The company excluded the SENTINEL trial SOT RRMS subgroup data from the	The Committee noted that the base case ICERs estimated by the manufacturer for the suboptimal therapy group were £43,400 per QALY gained or higher. It therefore concluded

TA, year	Health states	Utilities & Costs	EAG key Criticism	Results
	• Death	• Caregiver disutilities • Relapse HS disutilities • AE utility decrements • Drug acquisition, administration and monitoring costs • HS Costs EDSS 0-9, • AE Costs	model, especially that these was relied on for the marketing authorisation. Loss of treatment effectiveness – The EAG expressed concern about the extrapolation of 2-year data from the AFFIRM study to a 20-year time horizon. Unrealistic disability progression – the EAG expressed concern that, although the transition probabilities in the manufacturer’s model were based on data from AFFIRM, the model appeared to predict a higher rate of sustained disability progression at 2 years than reported in AFFIRM. Treatment effects on progression from RRMS to SPMS – There wasn’t evidence to support the assumption that Natalizumab reduces progression from RRMS to SPMS	that natalizumab would not be a cost-effective use of NHS resources in this group of people. The Committee concluded that the ICER of £32,000 per QALY for natalizumab compared with beta interferon presented by the manufacturer was more likely to be an overestimate. They concluded natalizumab for the treatment of RES RRMS patients was a cost-effective use of NHS resources.

Abbreviations: **AE**: Adverse Events, **ARR**: Annualised Relapse Rate, **CDP**: Confirmed Disability Progression, **EDSS**: Expanded Disability Scale Status, **EQ-5D**: EuroQol five dimensions quality of life index, **GBP £**: Great Britain Pound, **HA RRMS**: Highly Active Relapse Remitting Multiple Sclerosis, **HDA RRMS**: High Disease Activity Relapse Remitting Multiple Sclerosis, **HS**: Health State, **ICER**: Incremental Cost-Effectiveness Ratio, **NHS**: National Health Service, **NMA**: Network Meta-Analysis, **QALY**: Quality Adjusted Life, **RES RRMS**: Rapidly Evolving Severe Relapse Remitting Multiple Sclerosis, **RRMS**: Relapse Remitting Multiple Sclerosis, **SAD**: Sustained Accumulation of Disability, **SOT RRMS**: Sub-Optimally Treated Relapse Remitting Multiple Sclerosis, **SPMS**: Secondary Progressive Multiple Sclerosis,