MS SOCIETY

Developing a Case for Investment in MS Services: A Feasibility Scoping Study

Final Report

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Executive Summary

The Multiple Sclerosis (MS) Society commissioned YHEC to undertake a structured feasibility scoping study to identify economic evidence and make the case for investment in two selected elements of the MS treatment pathway: symptom management services and disease modifying treatment (DMT) prescribing.

The project assessed the ‘*Evidence Weight’* (quantity x quality) available from various evidence sources and the potential for development of additional evidence resources, such as new guidelines, where evidence gaps were identified.

Formal evidence searches of electronic databases were undertaken, supplemented by pragmatic searches of UK health technology assessments, guideline publications and grey literature.

Evidence was considered in terms of the following three ‘baskets’ of evidence:

1. Currently available and appropriate quality for full review and reporting (in phase 2).
2. Deliverable in shorter term (4 to 8 months) research and data analysis consultancy projects combining (analysis/modelling) current evidence resources (potentially in phase 2).
3. Deliverable through longer term research strategies.

**Symptom Management Services**

Four UK cost-effectiveness studies (Das Nair, 2019; Jukes, 2019; Mosweu, 2017; Turner-Stokes, 2020) and three systematic reviews (SRs) of clinical effectiveness (Amatya, 2019a; Gutkin, 2020; Nair, 2017) evidence of high or moderate quality were selected.

Das Nair (2019), Jukes (2019) and Mosweu (2017) were allocated to Basket 1 (appropriate quality for reporting). Turner-Stokes (2020) and Amatya (2019a) were allocated to Basket 2. The remaining two SRs were not found to be of appropriate quality and design for allocation to a basket.

Amatya (2019a) provided strong evidence for inpatient multidisciplinary rehabilitation, but limited evidence for outpatient multidisciplinary rehabilitation. Given the quality and design of the study, it would merit consideration as a base for the development of a health economic model. The model could be also be potentially informed by the economics data from the Turner-Stokes (2020) study.

We note that NICE excluded rehabilitation from the scope of its recent MS guideline and additional work may contribute to filling this gap in health economics evidence.

***Basket 3: Longer-term Research***

In line with findings from the NICE guidelines, there was a lack of high-quality studies showing the effectiveness of services other than rehabilitation for people with MS. Accordingly, there are no health economics studies evaluating other MS services.

More health economic studies, with robust methodologies, are needed to understand the costs and benefits of many MS interventions. According to wider sources reviewed through the course of our scoping study, potential priorities appear to include the following topics:

* Management of symptoms giving rise to non-elective hospitalisation, including bladder management, bladder infections and constipation.
* Improving psychological support for people with secondary progressive MS (SPMS) as identified by Wilmington Healthcare (2020).
* Provision of information.
* Interventions to improve mood and emotional outcomes for people with MS.
* Adoption of formalised multidisciplinary teams across specialist teams.

In addition to prioritising research topics for clinical effectiveness, health services and health economic studies, the MS Society could also consider strengthening its strategic research capacity in these methodologies. This might include the following:

* Forming research coalitions with other MS organisations.
* Ensuring MS Society funded service development & pilots are rigorously evaluated.
* Applying for external research funding from national bodies such as National Institute for Health Research (NIHR) & Wellcome.
* Funding academic research capacity via grants & training fellowships.

**DMT Evidence**

Two publications and four NICE technology appraisals were selected on the use of beta interferon and/or glatiramer acetate in the NHS (Giovannoni, 2019; Melendez-Torres, 2017; NICE, 2018), siponimod(NICE, 2020), dimethyl fumarate (DF)(NICE, 2014a)and natalizumab(NICE, 2007) (see Table 4.2).

The only publicly available efficacy data were from the UK Multiple Sclerosis Risk Sharing Scheme (RSS) [as reported by Giovannoni(2020), Melendez-Torres(2017)].

**DMT Prescribing**

Thirteen Scottish health boards and the Northern Irish Board responded to a freedom of information (FOI) request. These responses, together with data reported by Blueteq for NHS England, provide the evidence base for the current levels of prescribing in the UK.

The MS Survey seems to provide the most accurate data on take-up of DMTs. However, there is no complete or reliable evidence at a population level on the proportion of people with MS in England who are managed on a DMT.

Prevalence data on the number of people with MS and by sub-category of MS were also not available in Northern Ireland or England. These are material data gaps, partially filled by the MS Survey data.

***Baskets 1 & 2***

No DMT evidence sources can be allocated to Basket 1.

In Basket 2, whilst the potential exists to develop a model/practical calculator to estimate the net economic benefits of individual DMTs compared with best supportive care (BSC), the lack of fully transparent evidence sources due to redaction of key data means that considerable further work would be required to deliver this, confirm the availability of all required data, and assure validity and confidence in its findings.

Consequently, the MS Society will need to undertake a careful assessment of the likely benefits a model would bring to its strategic goals, alongside the likely costs and challenges for its development.

***Basket 3: Longer-term Research***

Current data sources, such as the MS Register (2021) could be expanded to gather additional data to allow outcomes and economic analyses, by adding collection of data such as:

* Diagnosis.
* Start and end date for DMT.
* Start and end values of EDSS, EQ-5D and clinical quality of life measures.
* Number of relapses during the period.
* Change in symptoms during the period.
* NHS resources used.

Acknowledgements

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Abbreviations

ADL Activities of Daily Living

AE adverse event

AFO Ankle foot orthosis

AG Assessment Group

BI Beta interferon

BNF British National Formulary

BSC Best supportive care

CAMBS Cambridge Multiple Sclerosis Basic Score

CDSR Cochrane Database of Systematic Reviews

CBT Cognitive behavioural therapy

CCA cost consequences analysis

CEA Cost-effectiveness analysis

CENTRAL Cochrane Central Register of Controlled Trials

CI Confidence intervals

CIS Clinically isolated syndrome

CRD Centre for Reviews and Dissemination

CUA Cost utility analysis

DARE Database of Abstracts of Reviews of Effects

DF Dimethyl fumarate

DMT Disease-modifying therapy

EADL Extended Activities of Daily Living

EDSS Expanded Disability Status Scale

EQ-5D Euroqol-Five Dimensions

ERG Evidence Review Group

FAM Functional Assessment Measure

FAMS Functional Assessment of Multiple Sclerosis

FES Functional electrical stimulation

FIM Functional Independence Measure

FND Functional neurological disorder

FOI Freedom of information

FSS Fatigue Severity Scale

GA Glatiramer acetate

GBP British Pound Sterling

GHQ-12 General Health Questionnaire-12

GP General practitioner

HR Hazard ratio

HES Hospital episodes statistics

HRQoL Health-related quality of life

HSCT Haematopoietic stem cell transplantation

HTA Health Technology Assessment

IAPT Improving Access to Psychological Therapies

ICER Incremental cost-effectiveness ratio

IFB Interferon β-1b

IFN Interferon

LYG Life years gained

MA Meta-analysis

m/s Meters per second

MHRA Medicines and Healthcare products Regulatory Agency

MS Multiple sclerosis

MSFC Multiple Sclerosis Functional Composite

MSIS Multiple Sclerosis Impact Scale

MSNQ Multiple Sclerosis Neuropsychological Screening Questionnaire

ND Neurodegenerative

NFI National Fatigue Index

NHS National Health Service

NHS EED NHS Economic Evaluation Database

NICE National Institute for Health and Care Excellence

NIHR National Institute for Health Research

NPDCNA Northwick Park Dependency Care Needs Assessment

NPDS Northwick Park Dependency Score

NR Not reported

NS Not stated

OP Outpatient

PAS Patient Access Scheme

PDT Psychodynamic therapy

PPMS Primary progressive multiple sclerosis

PSA Probabilistic sensitivity analyses

PSS Personal Social Services

PSSRU Personal Social Services Research Unit

QALY Quality-adjusted life-year

QoL Quality of life

RCT Randomised controlled trial

Rehab Rehabilitation

RES Rapidly evolving severe relapsing-remitting multiple sclerosis

ROC Rehabilitation Outcomes Collaborative

RRMS Relapsing-remitting multiple sclerosis

RSS Risk Sharing Scheme

SD Standard deviation

SF-36 36-Item Short Form Survey

SL Supportive listening

SNRS Scripps Neurological Rating Scale

SPMS Secondary progressive multiple sclerosis

SR Systematic review

TA Technology appraisal

VAS Visual anologue scale

WTP Willingness-to-pay

YHEC York Health Economics Consortium

# Introduction

## Multiple Sclerosis

Over 130,000 people in the UK have multiple sclerosis (MS). It’s unpredictable and different for everyone. It’s often painful and exhausting, and can cause problems with how people walk, move, see, think and feel.

MS is a highly heterogeneous disease but three broad patterns of disease have been identified, classified by the pattern and frequency of relapses and the rate of progression of the disease: relapsing-remitting MS (RRMS); secondary progressive MS (SPMS); and primary progressive MS (PPMS) (MS Trust, 2020). The disease courses of MS can be seen as a continuum. At the point of diagnosis, the majority of people (around 85%) exhibit a relapsing-remitting pattern, with periods of relapse where symptoms flare up aggressively followed by periods of remission. The majority of people with RRMS will eventually experience a change in their MS, with fewer or no relapses, but increasing disability and decline in neurological function, reflecting a secondary progressive pattern.

## Management of Symptoms

Two key publications by The National Institute for Health and Care Excellence (NICE) inform the expectations for the treatment of MS.

First, a clinical guideline provides the evidence and recommendations on diagnosis, symptom management, comprehensive reviews and effective relapse treatment (NICE, 2014b). However, some symptoms and problems associated with MS are addressed in other NICE guidance, for example urinary symptoms and swallowing. The guideline also does not address the interventions used in a rehabilitation (rehab) setting to alleviate symptoms nor the secondary complications of immobility. [NICE notes many of these problems are complex and need individual assessment and management strategies](https://www.nice.org.uk/guidance/cg186/chapter/Context). Hence, the guideline was aimed primarily at services provided in primary and secondary care.

Second, a number of NICE technology appraisal reports separately address the use of disease modifying therapies (DMTs) and are summarised in a treatment pathway (NICE, 2021).

Most DMTs are prescribed and monitored in specialised tertiary services, and an NHS England treatment algorithm sets out the commissioning policy for DMT prescribing. For example, this specifies that DMTs are discontinued for patients with expanded disability status scale (EDSS) scores of ≥7 (NHS England, 2019).

This report follows the approach of NICE by addressing DMT prescribing and treatment services separately.

## Aims and Objectives

The MS Society commissioned YHEC to undertake a feasibility scoping study to identify economic evidence which could be used to make the case for investment in MS services.

The aim of the study was to examine the feasibility of demonstrating how selected interventions on the care pathway improve the quality of life for people with MS and affect costs to the NHS and social care. This scoping study is a precursor to inform a potential second study. The latter would use the evidence from this study to inform its scope methodology and outputs, with a view to the future design and delivery of a comprehensive later project and document to inform decision-makers. Building on this, the study’s research question was to examine:

How can the health economic case be made for key elements of the MS pathway?

1. What level of analysis can be achieved for each selected element/intervention in the pathway?
2. In areas of the pathway that may not be currently be feasible, what further research may be required to unlock feasibility?

This report sets out the findings from the feasibility study which will inform potential further phases of work.

This report sets out the methodologies used (Section 2), results for papers on services (Section 3), papers on DMTs (Section 4) and provides real world prescribing information (Section 5), and concludes with a discussion and consideration of potential ways forward (Section 6). Seven appendices provide more details of the searches and findings.

# Methods

## Overview

The project was conceived as a scoping study and delivered using desk-based research methods, working iteratively in close collaboration with MS Society staff and nominated experts including people with MS.

The conceptual framework for the project sought to assess the following dimensions.

**Evidence Weight** - Assessment of current evidence sources & potential evidence resources for further analysis (quantity & quality).

1. Quantity assessment – metric of studies, publications, data bases etc.
2. Quality assessment – against recognised standards for quality of health economics studies.

**Evidence Gaps** - Identify gaps in current health economics evidence and requirements for future analyses/models.

**Findings** - Outline the following ‘baskets’ of evidence:

1. Currently available for full review & reporting (in phase 2).
2. Deliverable in shorter-term (4-8 months) research & data analysis consultancy projects combining (analysis/modelling) current evidence resources (potentially in phase 2).
3. Deliverable through longer-term research strategies.

The project was delivered through an iterative process with regular disussions and sharing of interim outputs with the MS Society.

**Project Scoping**

An initial outline scope for the project was agreed based on early evidence searches and consultation with MS Society staff and advisors.

An iterative approach resulted in a final topic scope being agreed, which included:

* DMTs for relapsing remitting MS, including prescribing data for the DMTs across the UK.
* Symptom management services, including mental health services.

## Evidence Searches, Review and Summary Reporting

### Protocol Development

Following agreement of the scope, we developed two protocols, one which addressed the search proposed for all symptom management services (that is combining physical and mental health services) and one addressing searches for DMTs. Each protocol included:

* A defined a research question specific to the search.
* The inclusion and exclusion criteria for the population, interventions, comparators, outcomes, setting and study types.
* The proposed criteria for the search (e.g start dates and language limitations).
* The proposed databases to be searched.

Drafts were shared with members of the MS Society and thence with people with MS to get user feedback. Such feedback informed further iterations of the protocols.

The final protocol for symptom management included people with non-specific neurological disorders except those with strokes, headaches, infections, seizures, spinal cord disordersand sudden brain injury. This search was for observational studies, randomised controlled trials (RCT), economic/cost/budgets studies and systematic reviews. The DMT protocol was limited to people with MS (People with MS) and for economic/cost/budgets studies and systematic reviews.[[1]](#footnote-2)

In addition to formal literature searches, more pragmatic searches were identified in the protocols including searching:

* UK health technology assessments published by the National Institute of Health Research and NICE.
* Reference lists of included studies and relevant systematic reviews.

The MS Society also provided details of any additional relevant studies that they were aware of.

### Literature Searches and Deduplication

Each protocol informed a detailed search strategy. These are provided in Appendix A and Appendix B for symptom management services and DMTs respectively. Once the searches had been run, the records were de-duplicated to give the number of unique records. In addition, the studies provided by the MS Society and identified from NICE and other sources were added to provide a list of the total records identified from the searches.

### Inclusion and Exclusion Criteria

Following discussion of draft criteria with the MS Society, the agreed inclusion and exclusion criteria for the symptom management and mental health support services are provided in Table 2.1 and Table 2.2 respectively, with Table 2.3 and Table 2.4 providing the criteria for DMTs.

Table 2.1**: Inclusion Criteria for Searches on the Provision of, and Access to, MS Symptom Management and Mental Health Support Services**

| Inclusion criteria | |
| --- | --- |
| Population | Adults who have a diagnosis of MS or a non-specific neurological disorder |
| Interventions | * Multi-disciplinary teams * Continence service * Physiotherapy service * Occupational therapy service * Dietician service * Speech & language therapy service * MS nurse service * Neuro-rehabilitation * Re-enablement * Functional electrical stimulation * Rehabilitation spasticity clinic * Rehabilitation * Non-specific mental health support services (including online mental health support) * Peer support (including online) * Neuropsychology service (including online) * Psychologist service (including online) * Counselling (including online) * IAPT * Memory loss clinics (including online) * CBT (including online) |
| Comparators | Standard care |
| Outcomes | **Health-related Quality of Life**   * E.g EQ-5D, SF-36, Leeds MS quality of life scale, MS Impact Scale * Patient-reported outcomes, for example symptoms, activities * Impact on carers * Functional scales that quantify level of disability, such as the EDSS, the MSFC, the CAMBS, the FAMS or the NFI * Mobility, for example the MS walking scale * Cognitive functions, such as memory and concentration, and physical symptoms including fatigue, spasticity, spasms, assessed by validated and disease-specific scales, questionnaires or similar instruments, for instance the SNRS or the Krupp FSS * Psychological symptoms assessed by validated and disease-specific scales, questionnaire or similar instruments * Adverse effects of treatment * Mortality   **Costs**   * NHS and social care costs   **Access**   * Referral rates * Barriers to providing services from an organisational perspective * Barriers to providing services from a clinical perspective * Barriers to providing services from a patient or carer perspective |
| Setting | * Any setting that provides primary and secondary NHS care, rehabilitation or social care * Western Europe[[2]](#footnote-3), Australia, USA and Canada |
| Study types | * Cost-effectiveness analysis, cost utility analysis, cost minimisation, cost of disease, budget impact and systematic reviews and meta analyses * Effectiveness studies (prospective and retrospective comparative cohort studies/RCTs/SRs, observational[[3]](#footnote-4)) * English language only |

Key: CAMBS – Cambridge Multiple Sclerosis Basic Score; CBT – cognitive behavioural therapy; EQ-5D – Euroqol-Five Dimensions; EDSS – Expanded Disability Status Scale; FAMS – Functional Assessment of Multiple Sclerosis; FSS – Fatigue Severity Scale; IAPT – Improving Access to Psychological Therapies; MS – multiple sclerosis; MSFC – Multiple Sclerosis Functional Composite; NFI – National Fatigue Index; NHS – National Health Service; RCT – randomised controlled trial; SF-36 – 36-Item Short Form Survey; SNRS – Scripps Neurological Rating Scale; SR – systematic review

Table 2.2 **Exclusion criteria for searches on the provision of, and access to, MS symptom management and mental health support services**

|  |  |
| --- | --- |
| Exclusion criteria | |
| Population | * Children and young people under the age of 18 years * Adults who have a diagnosis of possible MS or are being investigated for MS * People with specific neurological disorders which will not generalise to people with MS. This includes those with strokes, headaches, infections, seizures, sudden brain injury, and spinal cord disorders |
| Interventions | * Self-management * All medication * Telecare, telehealth, all devices for use in the home |
| Comparators | Placebo |
| Setting | Settings that will not generalise to UK and countries outside Western Europe, Australia, USA and Canada[[4]](#footnote-5) |
| Study type | All qualitative studies, quality of life studies and surveys. Non-English language |

Key: MS – multiple sclerosis

Table 2.3**: Inclusion criteria to inform searches for studies of net economic benefit of DMTs evidence**

|  |  |
| --- | --- |
| Inclusion criteria | |
| Population | Adults who have a diagnosis of MS |
| Interventions | **All DMTS being:**   * Alemtuzumab (Lemtrada) * Avonex (interferon beta-1a) * Betaferon (interferon beta-1b) * Cladribine (Mavenclad) * Dimethyl fumarate (Tecfidera) * Extavia (beta interferon-1b) * Fingolimod (Gilenya) * Glatiramer acetate (Copaxone) * HSCT * Natalizumab (Tysabri) * Ocrelizumab (Ocrevus) * Ozanimod * Plegridy (peginterferon beta 1a) * Rebif (beta interferon-1a) * Siponimod (Mayzent) * Teriflunomide (Aubagio) |
| Comparators | Other DMTs, placebo and no treatment |
| Outcomes | **Health-related Quality of Life**   * E.g EQ-5D, SF-36, Leeds MS quality of life scale, MS Impact Scale * Patient-reported outcomes, for example symptoms, activities * Impact on carers * Functional scales that quantify level of disability, such as the EDSS, the MSFC, the CAMBS, the FAMS or the NFI * Mobility, for example the MS walking scale * Cognitive functions, such as memory and concentration, and physical symptoms including fatigue, spasticity, spasms, assessed by validated and disease-specific scales, questionnaires or similar instruments, for instance the SNRS or the Krupp FSS * Psychological symptoms assessed by validated and disease-specific scales, questionnaire or similar instruments * Adverse effects of treatment * Mortality   **Costs**   * NHS and social care costs |
| Setting | * Any setting that provides primary and secondary NHS care, rehabilitation or social care * Western Europe[[5]](#footnote-6), Australia, USA and Canada[[6]](#footnote-7) |
| Study types | * Cost-effectiveness analysis, cost utility analysis, cost minimisation, cost of disease, budget impact and systematic reviews and meta-analyses * English language only |

Key: CAMBS – Cambridge Multiple Sclerosis Basic Score; DMT – disease-modifying therapy; EQ-5D – Euroqol-Five Dimensions; EDSS – Expanded Disability Status Scale; FAMS – Functional Assessment of Multiple Sclerosis; FSS – Fatigue Severity Scale; HSCT - haematopoietic stem cell transplantation; MS – multiple sclerosis; MSFC – Multiple Sclerosis Functional Composite; NFI – National Fatigue Index; NHS – National Health Service; SF-36 – 36-Item Short Form Survey; SNRS – Scripps Neurological Rating Scale

Table 2.4**: Exclusion criteria to inform searches for studies of net economic benefit of DMTs evidence**

|  |  |
| --- | --- |
| Exclusion criteria | |
| Population | * Children and young people under the age of 18 years who have a diagnosis of MS or possible MS, or are being investigated for MS * Adults who have a diagnosis of possible MS or are being investigated for MS |
| Interventions | * All pharmacological interventions other than those identified by MS Society as DMTs (MS Society, 2021), (e.g those to manage fatigue with amantadine, B12 injections and selective serotonin reuptake inhibitors or spasticity using baclofen, tizanidine, gabapentin, dantrolene, benzodiazepines, botulinum toxin, pregabalin and sativex or mobility with fampridine or visual problems including nystagmus or ataxia and tremor) * Vitamins, steroids and omega 3 or 6 |
| Comparators | Nil |
| Setting | Settings that will not generalise to UK and countries outside Western Europe, Australia, USA and Canada |
| Study type | All clinical, qualitative, quality of life studies and surveys, abstracts, conference proceedings, editorials, non-English language |

Key: DMT – disease-modifying therapy; MS – multiple sclerosis

### Study Selection from Identified Records

Record selection and assessment involved a number of stages:

* A single researcher assessed the search results, using titles and removed the obviously irrelevant records such as those about ineligible diseases or in children.
* The titles and abstracts[[7]](#footnote-8) of remaining records were assessed for relevance against the inclusion and exclusion criteria by a single researcher, with a second reviewer checking 1 in 10 of the records.
* The full text of potentially relevant studies were obtained and these were assessed for relevance against the protocol criteria by a single researcher, with the second reviewer available to discuss any uncertain records.
* An initial summary of the final selection of studies for each research question[[8]](#footnote-9) was provided to the MS Society and we invited comments on any potential gaps in the evidence base.
* Following feedback from the MS Society, these were further refined to inform the final studies to be data extracted. These comprised economic studies and systematic review evidence.

## Data Extraction and Quality Assessment

Evidence tables were developed for the economic studies and the systematic reviews. The economic tables contain information on:

* Study detail (type, design, perspective, time horizon, treatment effect and discount rates).
* Population, interventions and setting.
* Costs reported, cost base year, unit cost value and source.
* Health outcomes including health related quality of life (HRQoL), utilities for health states and quality adjusted life years (QALYs).
* Cost effectiveness measure and sensitivity analysis, further analysis recommended and conclusion.

The systematic review tables contain similar information on:

* Study details.
* Population, interventions, setting and included studies.
* Results.
* Comments on strengths and weaknesses, further analysis recommended and conclusion.

Quality assessment was undertaken using the tools recommended by NICE being a 35 question checklist developed by Drummond (1996) and the AMSTAR checklist for systematic reviews (AMSTAR team, 2015).

## Reporting and Interpretation

Sections 3 and 4 of this report provide the findings at each stage in this process for symptom management services and DMTs respectively. Section 6 provides a narrative synthesis of this evidence, its strengths and limitations and suggested next steps.

## Prescribing of DMTs

Staff at the MS Society advise that a move to devolve the budget for DMTs threatens to reduce the total budget available for DMTs. Hence, the Society is keen to get evidence on the current level of prescribing across the four nations. One possible use for this evidence is to test if it can support an argument that prescribing DMTs saves the NHS money through reducing the need for management and care services by reducing the rate of progression.

Hence, YHEC set out to answer the research question:

*What are the prescribing rates for DMTs for People with MS in the UK?*

We also wanted to identify the market share of different DMTs in each nation. Where possible further analysis was undertaken, such as looking at yearly trends.

### Methods

In England, all DMTs are commissioned centrally by NHS England. The scheme is managed by a company, Blueteq, which approves requests for prescribing new High cost drugs (NHS England, 2021) or switching between such drugs, using criteria based on NICE guidance. Blueteq does not record price information, only relevant prescribing data. The MS Society has access to a dataset set recording all approvals made by Blueteq. It was able to get clearance for YHEC to use the Blueteq data.

The MS Society agreed that YHEC should make a Freedom of Information (FOI) request to each Scottish health board and the Northern Ireland Health and Social Care Board. The Society advised it was not an appropriate time to ask for this information from NHS Wales because of COVID requirements on clinical staff time.

The FOI request was agreed with the MS Society (see Appendix G). The FOI request has three sections. The first section asked what the first and second line treatments are for RRMS, PPMS & SPMS. The second section asked the responder to complete a table requesting the number of people being treated with each DMT and the total cost of the drug. The final section asked for the number of people diagnosed with each type of MS.

Responses from the Scottish and Northern Irish health boards on use of each DMT and prevalence were tabulated and compared with the data from Blueteq. The DMTs with the highest market shares across the three nations were identified. The Scottish responses also enabled us to calculate the prescribing rate of DMTs as a percentage of the RRMS prevalent population and the total MS population. The Blueteq data were provided for three years, 2018 to 2020, enabling trend analyses to be undertaken. All analyses, together with Information on first and second line treatments are provided in Section 5 and Appendix G.

# Symptom Management Services

This section presents information on the papers relating to symptom management services. It sets out the number of papers meeting the inclusion criteria for these services, those selected for data extraction and quality assurance, and services potentially suitable for economic modelling. The same information is presented for DMTs in Section 4.

## Results of Literature Searches for Symptom Management

### Database Searches

Table 3.1 provides the number of records identified by database searching and other sources relating to symptom management studies. In total 2,526 studies were identified from the databases, with 55% of these from MEDLINE. A further 16 relevant studies were provided by the MS Society and one NICE guideline (NICE, 2014b). Once duplicate records were removed there were 2,111 unique records.

Table 3.1**: Literature search results for symptom management studies**

|  |  |
| --- | --- |
| **Resource** | **Number of records identified** |
| **Databases** |  |
| MEDLINE ALL | 1,396 |
| Cochrane Database of Systematic Reviews | 30 |
| Cochrane Central Register of Controlled Trials | 707 |
| Epistemonikos | 246 |
| HTA Database | 51 |
| Econlit | 18 |
| Social Care Online | 78 |
| **Total records identified through database searching** | **2,526** |
| **Other sources** |  |
| Check of NICE guidelines | 1 |
| Check of health technology assessments published by the National Institute of Health Research | 0 |
| Checking of reference lists of included studies and relevant systematic reviews | 0 |
| Consultation with MS Society for other relevant studies (both published literature and 'grey literature') and business cases | 16 |
| **Total additional records identified through other sources** | **17** |
| **Total number of records retrieved** | **2,543** |
| **Total number of records after deduplication** | **2,111** |

These records were sifted using the abstracts and the agreed inclusion and exclusion criteria, with 54 unique papers meeting these criteria. Full details of the search are at Appendix A and an analysis of each included paper, sorted by type of service, is provided at Appendix C.

Three services account for about 80% of the papers:

* Rehabilitation services (x 16 papers, 30% of total).
* CBT (x 15 papers, 28%).
* Functional electrical stimulation service (FES) (x 11 papers, 20%).

The other services are: multi-disciplinary teams (x4); continence service (x1); physiotherapy service (x2); occupational therapy (x1); neuro-rehabilitation (x2); memory loss (x1); and a functional neurological disorders clinic (x1).

An analysis by study type showed:

* Most study were reviews (25, 46%).
* Followed by RCTs (14, 26%).
* Others [e.g surveys, registry data, retrospective case studies] (9, 17%).
* Economic evaluations (4, 7%).
* Comparative clinical studies (2, 4%).

Of the economic evaluations, two are of rehab services and one each of a FES intervention and a CBT programme.

Following discussion with the MS Society, we presented more information on each of the reviews and the economic evaluations, leading to a decision to data extract the four economic evaluations and one systematic review for each of rehab, CBT and FES (see Sections 3.2.1 and 3.2.2).

### Grey Literature from MS Society

Sixteen of the papers provided by the MS Society were identified as having some measure of cost and/or benefit. These are listed at Appendix D. None of the papers met the formal inclusion criteria, failing to meet the study type criterion but are potentially useful to inform the parameters in an economic model.

However, the following studies included content relevant to the wider context of our findings and conclusions.

The NHS RightCare: Progressive Neurological Conditions Toolkit (NHS Rightcare, 2019) was developed by a group of experts, following consultation with stakeholders and drawing on evidence-based recommendations from NICE. This toolkit prioritised four MS specific system improvements being:

* Formalised MDTs across specialised teams.
* Better use of data and technology.
* Improved DMT administration.
* Comprehensive access to holistic support (particularly for advanced MS patients).

Various publications used national datasets to prompt service improvement. For example, in 2016, NHS RightCare produced a ‘Commissioning for Value Focus Pack’, which used Hospital Episodes Statistics (HES) data to produce a benchmarking tool for Clinical Commissioning Groups. The tool reporting metrics for MS **and** Inflammatory Disorders for:

* Elective and non-elective admissions length of stays.
* Rate of day case admissions per 100,000.
* Elective and non-elective spend per 1,000.

‘Measuring the burden of hospitalisation in multiple sclerosis’ by Wilmington Healthcare reported findings from a detailed analysis of HES data to understand why people with MS were being admitted to hospital. The main reasons for non-elective admissions were bladder management related and MS relapse. These findings led to improved patient pathways, services, education and training.

However, no examples were found of studies which analysed clinical outcomes – data were limited to hospital admissions and the cost thereof.

A social return on investment tool for the Spanish NHS was reported by Moral Torres (2020). Nine experts estimated the costs and benefits associated with 18 areas of perceived unmet need, as advised by people with MS. They estimated that investing in all 18 elements gave a return on investment of £2 for every £1 invested.

Wilmington Healthcare (2020) also reported on the needs of people with SPMS. Major priorities included agreeing the outcomes which services for people with SPMS should focus on and undertaking national clinical audits to identify and address variations in care. The top-level message was the need to use data better to better understand patient need.

## Data Extraction and Quality Assurance

Data extraction tables are provided at Appendix D for the four economic evaluations and Appendix E for the three systematic reviews.

### Economic Evaluations of MS Symptom Management Services

Two of the four economic evaluations addressed rehab, with one appraising cognitive rehab in an outpatient setting (Das Nair, 2019) and one appraised specialist inpatient rehabilitation (Turner-Stokes, 2020). Das Nair (2019) was quality assessed as high and Turner-Stokes(2020) as moderate.

Das Nair (2019)undertook a cost utility analysis(CUA) which accompanied an RCT. This was set in five NHS sites in England and enrolled 204 people in standard care and 245 people in the intervention arm. Inclusion criteria included having cognitive deficits of > 1 standard deviation from the mean of healthy people. The intervention consisted of providing 10 sessions, each of 1.5 hours, in cognitive rehabilitation, provided by a clinical psychologist in addition to usual care. Cognitive rehabilitation is a structured set of therapeutic activities designed to retrain an individual’s cognitive functions and to teach strategies to cope with these problems in daily life.

Use of NHS services were measured at 6 and 12 months and costed using valid datasets. The NICE preferred QoL measure, EQ-5D was used to measure utilities. Secondary outcomes included improvements in participants’ attention and memory abilities, self-reported cognitive problems in daily life, mood and fatigue. The intervention was cost saving at 12 months (saving £575 per participant for an intervention costing £209 per participant) and improved memory and mood. No change in quality-adjusted life-years was detected. The intervention dominated standard care, having lower total costs and the same quality-adjusted life-years. The analysis was judged by us as conservative as it assumed no benefits after the RCT ended at 12 months.

Turner-Stokes(2020)estimated the time it would take for savings fromreduced rehab costs to offset the cost of multidisciplinary specialist inpatient rehabilitation. The clinical data came from a before and after multicentre cohort study from level 1 and level 2 rehab services centres in England. The cohort comprised of 149 people with low dependency needs, 349 with medium dependency and 509 with high dependency needs. Savings were estimated from recorded changes in each patient’s levels of disability and costs were measured by change in inpatient length of stay. All benefits at discharge were assumed to be maintained, with no waning effect. The study found investing in services for people with high dependency broke-even at 13 months, 29 months for people with medium dependency and 77 months for those with low dependency. It concluded such rehab was not cost efficient for people with low dependency needs at entry. There were several potential sources of bias in the data which makes the results subject to material uncertainty.

Juckes(2019)undertook a CUA comparing FES (n = 82) with management using an ankle foot orthosis (n = 44). The clinical data were recorded at The National Hospital for Neurology and Neurosurgery Outpatient therapy service. The cost of the FES was almost £3,400 higher per patient than standard care. This study also used the EQ-5D measure to estimate changes in utilities. The incremental cost-effectiveness ratio (ICER) for the intervention compared with the orthosis was £6,137. The authors assumed maintained benefit from the end of follow-up at 6 months to 5 years. The study was judged as high quality.

The final study was by Mosweu (2017) which compared CBT delivered by trained nursesover eightone-to-one sessions (two face-to-face and six telephone calls) with supportive listening. The interventions were conducted in MS Centres in southern England, with about 48 people with MS in each arm. The incremental costs and QALYs, measured using EQ-5D over 12 months, were used to calculate an ICER of over £300,000.

Of the four studies, the Das Nair (2019) study is the most robust and has the highest certainty that the intervention, cognitive rehab delivered by a psychologist in addition to usual care, is cost-saving compared with usual care in an NHS setting. No difference was found in quality of life at one year but those receiving the rehabilitation intervention had fewer memory problems and reported better mood than those who received only usual care. These findings are summarised in Table 3.2.

Table 3.2**: Summary of Four Economic Studies of Symptom Management Services**

| Study Reference | Das Nair (2019) | Mosweu (2017) | Turner-Stokes(2020) | Juckes(2019) |
| --- | --- | --- | --- | --- |
| Patients | Adults with cognitive problems (n = 449) | Patients with MS attending National Hospital for Neurology and Neurosurgery Outpatient therapy service with dropped foot (n = 126) | Adults with MS admitted to multidisciplinary specialist inpatient rehabilitation between 2010-2018 (n = 1,007) | Patients with MS attending MS centres in London and Hampshire (n = 94) |
| Intervention | Cognitive rehabilitation provided by a clinical psychologist plus usual care | Nurse-delivered CBT | Multidisciplinary specialist inpatient rehabilitation | Odstock Dropped Foot Stimulator |
| Comparator | Usual care | Supportive listening | Notionally costs pre admission | Standard care |
| Outcomes | Costs and QALYs using EQ-5D | Costs and QALYs using EQ-5D | Estimated savings in NHS and social care costs using a needs assessment tool and cost of the intervention | Costs and QALYs using EQ-5D |
| Results | Intervention dominant – cost saving and higher QALYs | ICER > £300,000 per QALY | It is not cost efficient to provide inpatient rehab to people with low levels of care dependency | ICER £6,137 per QALY |
| Limitations | Possibly recall bias and only within RCT analysis (12 months) | Possibly recall bias | No waning effect- benefits at discharge are maintained over time. No costs were collected so all were derived from outside sources and these could not be validated. No generic QoL measure or MS specific outcome measures were reported. Also costs likely to be understated because of recording issues with database | Benefit at 6 months assumed to last for 5 years |
| Quality assessment | High | Moderate | Moderate | High |

Key: CBT – cognitive behavioural therapy; EQ-5D – Euroqol-Five Dimensions; ICER – incremental cost-effectiveness ratio; MS – multiple sclerosis; NHS – National Health Service; QALY – quality-adjusted life-year; QoL – quality of life; RCT – randomised controlled trial

### Systematic Reviews of Effectiveness of MS Symptom Management Services

Evidence tables were prepared for three systematic reviews on the effectiveness of multidisciplinary rehabilitation programmes (Amatya, 2019a), CBT and psychodynamic therapy (PDT) (Gutkin, 2020) and FES (Nair, 2017).

Only Amatya (2019a), which was a review of published Cochrane reviews was rated as high quality. This review of reviews included over 10,000 people. One multidisciplinary rehabilitation review (Khan, 2007) reported strong evidence from three RCTs (N = 217) that inpatient rehabilitation could improve disability, mobility and symptoms. Khan (2017) also included four RCTs from an outpatient setting. These reported limited evidence for improved EDSS scores and short-term benefits in activity level. Amatya (2019a) also found moderate evidence from 54 RCTs (one with strong evidence) on physical therapy and 10 RCTs on information provision. Hence, the best evidence was on the use of specialist inpatient rehab programmes. There was no evidence of cost effectiveness.

Gutkin (2020)found robust RCT evidence to support use of CBT in people with functional neurological disorders, with better evidence required to support using PDT. This review was conducted by one reviewer and is thus subject to potential bias.

Nair (2017)found RCT evidence that FES improved speed of walking and reduced falls compared with standard care. However, the authors noted the comparators were not against standard care and were conducted in labs. Hence, findings cannot be generalised to the NHS.

Overall, there is systematic review evidence from a high-quality review supporting use of specialist inpatient rehab (Amatya, 2019a) and evidence supporting CBT from a weaker review (Gutkin, 2020), see Table 3.3.

Table 3.3**: Summary of Three Systematic Reviews of Symptom Management Services**

| Study Reference | Amatya (2019a) | Gutkin (2020) | Nair(2017) |
| --- | --- | --- | --- |
| Patients | People with MS attending rehab programmes (n = 10,396) | Adults with functional neurological disorder (n = 994). The majority presented with psychogenic non-epileptic seizures | People with MS attending centres with foot drop (n = 183) |
| Intervention | Inpatient and outpatient multidisciplinary rehabilitation | CBT or PDT delivered in outpatients | FES |
| Comparator | Standard care | Standard care | Standard care |
| Evidence | 3 RCTs for inpatients and 4 for outpatients | 8 RCTs, others 11 (before and after) | 1 review, 3 RCTs (all same centre), others 10 |
| Outcomes | Function eg mobility, activities of daily living; symptoms or impairments, eg pain; and spasticity; restriction in participation eg quality of life | Seizure frequency, seizure freedom, psychosocial functioning, self-rated and clinician global change and physical symptoms | Speed of walking, activities of daily living, energy expenditure for walking, gait analysis and patient reported outcomes |
| Results | Strong evidence for inpatients, limited evidence for outpatients | Supports use of CBT, with more limited evidence to support PDT. Authors conclude efficacy of PDT needs to be confirmed by an RCT | Comparative evidence that FES improves speed of walking and reduces falls |
| Limitations | This is a review of reviews and may be more recent evidence from that included in original review | Limitations include the lack of good quality RCTs for PDT and the heterogeneity of published studies. Also this review was conducted by a single reviewer and thus subject to potential bias | Need adequately powered RCT of FES vs relevant comparator – these are mainly lab-based studies so may not reflect people’s experience in the community |
| Quality | High | Medium | Low |

Key: CBT – cognitive behavioural therapy; FES - functional electrical stimulation; MS – multiple sclerosis; PDT – psychodynamic therapy; RCT – randomised controlled trial

Section 6 considers the implications of these findings.

### NICE Recommendations that might be Possible to Model

We also identified which non-DMT recommendations within the NICE MS management guideline (NICE,2014b) might have sufficient clinical evidence to inform an economic evaluation, and extracted the Guideline Group’s assessment of the clinical evidence (studies were graded high, moderate, low and very low quality).

There were seven such recommendations (see Table 3.4). Only three of the recommendations were supported by an economic evaluation (see shaded rows). These all addressed the management of MS-related fatigue.

These studies were included in a report presented to the MS Society during earlier stages of the project which summarised findings from an early literature review. Its purpose was to inform the selection of studies for data extraction. The MS Society did not prioritise this intervention or these studies for further review and hence they were not taken forward.

Table 3.4**: NICE Recommendations that might be possible to model**

|  |  |
| --- | --- |
| Recommendation | Evidence base |
| Explain that MS-related fatigue may be precipitated by heat overexertion and stress or may be related to the time of day | 3 RCTs on electromagnetic field therapy (1 very low, 1 moderate, 1 high quality) and 2 economic evaluations (2013 and 2014) |
| Consider mindfulness-based training, CBT or fatigue management for treating MS-related fatigue | 1 RCT (low quality) and 1 economic evaluation (2013) |
| Advise people that aerobic, balance and stretching exercises including yoga may be helpful in treating MS-related fatigue | 3 RCTs on yoga and other interventions (all low or very low quality) and 1 economic evaluation (2014) |
| Consider supervised exercise programmes involving moderate progressive resistance training and aerobic exercise to treat people with MS who have mobility problems and/or fatigue | 1 moderate quality RCT and other low or very low clinical studies and a QoL study |
| Consider a comprehensive programme of aerobic and moderate progressive resistance activity combined with cognitive behavioural techniques for fatigue in people with MS with moderately impaired mobility | 1 moderate quality RCT and other low or very low clinical studies and a QoL study |
| Ensure people with MS & mobility problems have access to an assessment to establish individual goals and discuss ways in which to achieve them. This would usually involve rehabilitation specialists and physiotherapists with expertise in MS | 1 poorly conducted cost consequences analysis with no QoL and a second with QoL which recommended supervised resistance training vs. home based training |
| Structured assessment(s) vs. non-structured assessment(s) | 1 moderate quality RCT and no economic evaluations |

Key: CBT – cognitive behavioural therapy; MS – multiple sclerosis; QoL – quality of life; RCT- randomised controlled trial

# DMTs

This section presents findings on the health economics evidence and data sources relating to DMTs. It sets out the number of papers meeting the inclusion criteria for these drugs and findings from the data extraction tables.

## Results of Literature Searches for DMTs

### Database Searches

Table 4.1 provides the number of records identified by database searching and other sources relating to DMTs. Thus, 677 studies were identified from the databases, with 64% of these from MEDLINE. A further 17 relevant studies were provided by the MS Society and 11 NICE technology appraisals (TA). Once duplicate records were removed, there were 573 unique records.

Table 4.1**: Literature search results for DMTs**

|  |  |
| --- | --- |
| **Resource** | **Number of records identified** |
| **Databases** | |
| MEDLINE ALL | 435 |
| Cochrane Database of Systematic Reviews (CDSR) | 73 |
| HTA Database | 25 |
| Econlit | 13 |
| Epistemonikos | 131 |
| **Total records identified through database searching** | **677** |
| **Other sources** | |
| Check of manufacturer submissions to NICE | 11 |
| Check of UK health technology assessments published by the National Institute of Health Research | 0 |
| Checking of reference lists of included studies and relevant systematic reviews | 0 |
| Consultation with MS Society for details of any other relevant studies | 17 |
| **Total additional records identified through other sources** | 28 |
| **Total number of records retrieved** | **705** |
| **Total number of records after deduplication** | **573** |

The literature databases searches identified 52 economic evaluations of DMTs. Of these, eight were set in the UK. Only two compared the DMT to BSC, thereby providing directly relevant evidence of the full benefits of treatment. One of these presented the final results of the long-term efficacy of glatiramer acetate (GA) as reported by the UK Risk Sharing Scheme (RSS) (Giovannoni, 2019). The second provided a systematic review and economic evaluation comparing beta interferon (IFN) with GA in England (Melendez-Torres, 2017). This also used the results from the RSS.

There was one recent cost-effectiveness systematic review (Navarro, 2020), which included nine studies. The authors noted there were high levels of methodological variability, with many trials having sponsorship bias and some reached contradictory results. As a result, they concluded it is not possible to determine which DMT was most cost-effective to manage RRMS.

### Evidence from NICE Appraisals

NICE has conducted 11 appraisals of DMTs. A 2018 appraisal of several alpha and beta interferons and GA compared with BSC (NICE, 2018) used four network analyses created from the RSS data and RCT evidence. This appraisal was more comprehensive than the papers by Giovannoni (2019) or Melendez-Torres(2017). Hence, these papers are not considered further.

Appendix F provides an overview of each of the NICE appraisals. For the majority of these, the manufacturers submitted patient access schemes. Hence, actual prices and ICERs were not stated, being commercial in confidence. Rather NICE simply indicated whether the drug was expected to be cost effective against comparators.

Information on the market shares of the various DMTS (presented in Section 5) informed the four DMTs selected for data extraction. These are:

* Beta interferon and glatiramer acetate.
* Dimethyl fumarate.
* Natalizumab.
* Siponimod.

Siponimod was only approved in November 2020 and thus has not gained market share. It was included because it is the only approved DMT to manage people with SPMS.

#### Other relevant literature

Seventeen other relevant background papers were identified mainly from the grey literature provided by the MS Society, structured Google scholar searches on DMTs used in UK and the YHEC literature search. These may inform the background and any future modelling projects. The papers are listed in Appendix F.

A paper by the Nuffield Trust (Castle-Clarke, 2018) noted that mechanisms other than Blueteq are required to collect treatment outcome data. It suggested an enhanced UK MS Register and audits could fill this gap (MS Register, 2021).

A MS Trust report on the provision of DMTs (Mynors, 2016). Improving the efficiency of DMT provision Nov 2016) noted the absence of information systems is holding back the planning and delivery of efficient DMT coordination and prescribing.

Currently, the UK MS Register (MS Register, 2021) holds data from almost 20,000 people with MS. It was launched in September 2011 and is maintained by Swansea University. The register holds a series of questionnaires which are completed every six months on:

* Demographics.
* Employment, education and family details.
* Diagnosis, symptoms and relapses.
* EDSS state, EQ-5D and clinical quality of life measures.

Participants can consent to have their medical records linked to the Register, thereby adding data on, for example DMT dose, administration and side effects. In Wales links are also made to General Practice and patient episode databases. The MS Society is exploring links to similar databases, including HES, for England.

## Evidence Tables for Four NICE TAs of DMTs

Evidence tables for the four selected NICE TAs of DMTs are presented at Appendix F and summarised in Table 4.2 below.

Table 4.2**: Overview of four NICE TAs on DMTs**

| Study Reference | NICE(2018) | NICE(2020) | NICE(2014a) | NICE(2007) |
| --- | --- | --- | --- | --- |
| Patients | RRMS | SPMS | RRMS | Rapidly evolving RRMS |
| Intervention | Beta interferon and glatiramer acetate | Siponimod | Dimethyl fumarate | Natalizumab |
| Comparator | Standard care | Other DMTs | Other DMTs | Other DMTs and BSC |
| Outcomes | Costs (drug costs, management costs for each EDSS state and cost of relapse) and QALYS (utility values by EDSS state) | Costs (drug costs and management costs for each EDSS state and cost of relapse) and QALYS (utility values by EDSS state but only for Orme as a sensitivity analysis; base case was utilities from RCT but these were redacted) | Costs (list price cost of drugs, administration costs by drug, management costs for each EDSS state, cost of each adverse event, and cost of relapse) and QALYS (utility values by EDSS state) | No detail of costs or QALYs are reported |
| Results | Pooled ICER £27,200 per incremental QALY | All results and sensitivity analysis were redacted | Pooled ICER £27,700 per incremental QALY | Base case ICERs were reported but all baseline incremental costs and QALYs and sensitivity analysis were redacted |
| Limitations | High risk of bias in clinical evidence and need longer term follow-up | RCT was vs BSC so uncertainty from the indirect network analysis. Also most information on clinical parameters, utilities and drug costs were redacted | Clinical evidence, results and sensitivity analysis virtually all redacted | Unusable due to limited reporting. |

Key: BSC – best supportive care; DMT – disease-modifying therapy; EDSS – Expanded Disability Status Scale; ICER – incremental cost-effectiveness ratio; QALY – quality-adjusted life-year; RCT – randomised controlled trial; RRMS – relapsing remitting multiple sclerosis; SPMS – secondary progressive multiple sclerosis

One report by Norman (2013) is also helpful in that it lists the values used in the dimethyl fumarate submission and all earlier ones for various cost parameters such cost of administration, EDSS states and relapse. As that report shows the TAs adopt widely differing costs. For example, two of the four TAs report costs by EDSS state. For state 9, the range is £22,648 (NICE, 2018) to £52,679 (NICE, 2020), with NICE seemingly accepting both values. Two TAs also provided utility values for each EDSS state and these were reasonably consistent.

Overall, the reporting in these TAs was highly incomplete due to being heavily redacted. Key missing data include:

* The transitional probabilities relating to movements between health states as a result of being prescribed a DMT compared with best supportive care.
* The results of indirect network analyses or meta-analyses undertaken to inform these probabilities.
* The absolute risk of relapse in each health state.
* Discounts from the published prices, as agreed within the Patient Access Schemes were also redacted.
* Base case ICERs and sensitivity analyses.

In all cases, the DMT was cost incurring compared with the chosen comparators. Moreover, the results were often contradictory with biases evident in favour of the DMT under review. This is consistent with findings from the systematic review by Navarro (2020).

No checklist was used to quality assure the NICE TAs. These are commissioned by NICE from external groups. The groups must ensure their analyses and reporting complies with the NICE reference case and use a NICE template. These requirements are in place to ensure the TAs provide the information required by a high quality health economics evaluation. Thus, the NICE process ensure only high quality economic evaluations are produced by the external groups.

Section 6 considers the implications of these findings.

# DMT Prescribing Trends

## Response to FOIs

The Northern Irish Board and 13 of the 14 Scottish health boards have responded to the FOI request. The missing board is NHS Fife, which delivers services to about 7% of the Scottish population. Responses varied greatly in their level of completeness, with only NHS Lothian providing cost information for most DMTs, although the Northern Irish Board did advise the total spend on DMTs. NHS Highland and NHS Lanarkshire were unable to provide data on people treated with each DMT and only seven provided prevalence data.

The data from Scotland and N Ireland are based on total People with MS receiving a DMT within a year, whilst the English data are from records of People with MS starting new DMTs or switching from one DMT to another. Thus, the values are not directly comparable.

## Absolute Level of DMTs by Country

### England

Table 5.1 provides the number of prescriptions recorded each year in Blueteq and as a percentage of the estimated population in England with MS. The estimated population and incidence rates were made by Public Health England for 2018 (Multiple Sclerosis News Today, 2020). In total, the number of prescriptions increased by over 24% for 2019 over 2018 but then dipped slightly in 2020. This may be because the Covid pandemic has inhibited prescribers switching people with MS from one DMT to a second. An analysis of the market shares by DMT is provided at Section 5.3.

The low rates of prescribing, just 20% of People with MS, arise because of data inadequacies. Many people with MS will have been maintained on their existing DMT in each year; these people are not recorded by Blueteq. Moreover, not all patients consent to their data being shared with Blueteq but the extent of this is unknown.

This method of data collection also has implications for data collection. The Nuffield Trust (Castle-Clarke, 2018) advised that the clinician form used to request a DMT asks for a measure of disability which is often not routinely collected which means some of the data are incomplete and inaccurate.

The decline in alemtuzumab is because of updated restrictions and strengthened monitoring requirements imposed by the MHRA in February 2020,following a review of serious cardiovascular and immune-mediated reactions.

Table 5.1**: DMT prescriptions in England and as % of people with MS**

|  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- |
| DMT | 2018 | 2019 | 2020 | % Change  (2018-2019) | % Change  (2018-2020) |
| Alemtuzumab | 1,468 | 777 | 201 | -47.1% | -86.3% |
| Cladribine | 497 | 823 | 738 | 65.6% | 48.5% |
| Dimethyl Fumarate | 5,563 | 6,542 | 6,793 | 17.6% | 22.1% |
| Fingolimod | 2,616 | 2,779 | 2,565 | 6.2% | -1.9% |
| Glatiramer acetate | 2,523 | 3,505 | 3,337 | 38.9% | 32.3% |
| Interferon beta | 3,527 | 3,782 | 3,732 | 7.2% | 5.8% |
| Natalizumab | 2,249 | 2,642 | 2,823 | 17.5% | 25.5% |
| Ocrelizumab | 161 | 2,177 | 2,569 | 1252.2% | 1495.7% |
| Teriflunomide | 1,006 | 1,342 | 1,312 | 33.4% | 30.4% |
| **Total** | **19,610** | **24,369** | **24,070** | **24.3%** | **22.7%** |
| **People with MS** | **105,450** | **110,817** | **116,185** | **5.1%** | **10.2%** |
| **DMTs as % people with MS** | **19%** | **22%** | **21%** |  |  |

Key: DMT – disease-modifying therapy; MS – multiple sclerosis

### Scotland and Northern Ireland

Data by Scottish health board are detailed in Table G.1 at Appendix G, with the Scottish-wide and Northern Irish totals provided in Table 5.2. We have compared these data to the results of the My MS My Needs Survey (see Section 5.6). Assuming only people with RRMS are prescribed DMTs gives similar take-up rates across the two datasets. No further external validation has been possible and thus we cannot vouch for their quality.

The average prescribing rate of 35% could be calculated for seven Scottish board. There was a large disparity across boards with Orkney, Shetland and the Westerns Isles only managing 14%, 18% and 21% of People with MS on DMTs, compared with 55% at NHS Grampian and 46% at NHS Tayside. If one assumes DMTs were only being prescribed to those with RRMS, these data show 62% of people with RRMS in Scotland in 2020 received a DMT.

Table 5.2 also presents data from the Northern Irish Board. Using the estimated number of people with MS from Public Health England for 2018 (Multiple Sclerosis News Today, 2020), increased for 2 years growth in incidence cases, suggests about 5,325 people there may have MS, giving a prescribing rate of 48%.

Table 5.2**: People with MS prescribed DMTs by Health Board 2020**

|  |  |  |
| --- | --- | --- |
| DMT | 11 Scottish health boards | Northern Ireland Board |
| Alemtuzumab | 62 |  |
| Interferon beta 1-a | 394 | 213 |
| Interferon alpha | 2 |  |
| Interferon beta | 46 | 27 |
| Cladribine | 298 | 28 |
| Daclizumb | 9(a) |  |
| Dimethyl fumarate | 1460 | 810 |
| Extavia (beta interferon-1b) | 120 | 9 |
| Fingolimod | 429 | 122 |
| Glatiramer acetate | 561 | 271 |
| Natalizumab | 780 | 163 |
| Ocrelizumab | 228 | 118 |
| Peginterferon alpha | 17 |  |
| Peginterferon beta 1a | 304 | 81 |
| Beta interferon -1a | 97 | 191 |
| Teriflunomide | 13 | 308 |
| Other drugs | 2 |  |
| **Total** | **4,822** | **2,341** |
| **DMTs as % people with MS** | **35%** | **48%** |

Key: DMT – disease-modifying therapy; MS – multiple sclerosis

## Market Shares by DMT

Table 5.3 presents the market share of each DMT for the three countries. Dimethyl fumarate had the highest market share across the three being around 30% in each. Glatiramer acetate consistently had the third highest market share but the second most prescribed DMT differed being an interferon in England, natalizumab in Scotland and teriflunomide in Northern Ireland.

The data for each Scottish board were reasonably consistent with the national pattern with the main outliers being:

* Natalizumab in NHS Lothian which has a 48% total market share.
* Interferon beta 1-a which has an 11% and 24% market share in NHS Greater Glasgow & Clyde and NHS Grampian respectively.

Table 5.3**: Market share by DMT by country 2020**

|  |  |  |  |
| --- | --- | --- | --- |
| DMT | Scotland | N Ireland | England |
| Alemtuzumab | 1% | 0% | 1% |
| Interferon beta 1-a | 8% | 9% | 16% |
| Interferon alpha | 0% | 0% |
| Interferon beta | 1% | 1% |
| Cladribine | 6% | 1% | 3% |
| Dimethyl fumarate | 30% | 35% | 28% |
| Beta interferon-1b | 2% | 0% |  |
| Fingolimod | 9% | 5% | 11% |
| Glatiramer acetate | 12% | 12% | 14% |
| Natalizumab | 16% | 7% | 12% |
| Ocrelizumab | 5% | 5% | 11% |
| Peginterferon beta 1a | 6% | 3% |  |
| Beta interferon -1a | 2% | 8% |  |
| Teriflunomide | 0% | 13% | 5% |
| **Total** | **100%** | **100%** | **100%** |

Key: DMT – disease-modifying therapy

Legend: Blue is highest market share, green second highest and orange third highest.

## Treatment Costs

Table 5.4 reports the cost per person with MS treated by DMT, with cost per person ranging from £624,420 for fingolimod to around £2,000 per person for alemtuzumab, dimethyl fumarate and natalizumab, with a mean cost of £5,360. No cost data were provided on the interferons or GA due to commercial agreements.

The only other cost data is from Northern Ireland which held a budget of £18.5m for DMTs in 2020. If this was all spent on the 2,341 People with MS receiving a DMT then the mean cost per person was about £7,900. This is almost 50% higher than the mean spend at NHS Lothian. Unfortunately, we cannot advise which, if any, of these costs generalise to other Scottish NHS boards or elsewhere in the UK.

Table 5.4**: Cost of Prescribed DMTs for NHS Lothian**

|  |  |  |  |
| --- | --- | --- | --- |
| **DMT** | **No of people with MS treated in 2020** | **Total cost of treatment** | **Cost per person with MS** |
| Alemtuzumab | 35 | £50,724 | £1,449 |
| Interferon beta-1a | 15 | N/A |  |
| interferon beta | 2 | £137,990 | £68,995 |
| Cladribine | 54 | £460,937 | £8,536 |
| Daclizumab - withdrawn | 9 | N/A |  |
| Dimethyl fumarate | 113 | £227,274 | £2,011 |
| Beta interferon-1b | 47 | N/A |  |
| Fingolimod (a) | 2 | £1,248,839 | £624,420 |
| Glatiramer acetate | 3 | £139,446 | £46,482 |
| Natalizumab | 381 | £793,260 | £2,082 |
| Ocrelizumab | 79 | £463,603 | £5,868 |
| Peginterferon alpha | 10 | N/A |  |
| Peginterferon beta 1a | 49 | £327,000 | £6,673 |
| Beta interferon-1a | 27 | N/A |  |

Key: DMT – disease-modifying therapy; MS – multiple sclerosis; N/A – not applicable

* + - * 1. Data being checked

## First & Second Line DMTs for MS

In Northern Ireland, GA and interferons are first line treatments for RRMS, whilst the Scottish boards advised they use these plus dimethyl fumarates, teriflunomide and ocrelizumab. All boards responding agreed ocrelizumab was the DMT of choice to manage people with PPMS and siponimod for people with SPMS. More information is provided in Appendix G.

Section 6 considers the strengths and weaknesses of these findings.

## My MS My Needs

The MS Society advises that the results of the My MS My Needs 2019 survey (MS Society, 2019) provided data on the prescribing of DMTs to 8,281 people with MS. Eighty-two percentage of respondents were from England, 8% from Scotland, 5% from Wales, 4% from Northern Ireland and for 1% their location was unknown. The respondents reported that in England 60% were taking a DMT compared with 61% in Scotland, 81% in Northern Ireland and 52% in Wales. These rates are similar to the take-up rates in Scotland of 62% assuming only people with RRMS are prescribed DMTs, suggesting the FOI data have reasonable external validity.

## Summary

Thirteen Scottish health boards and the Northern Irish Board responded to a FOI request. These responses, together with data reported by Blueteq for NHS England, provide the evidence base for the current levels of prescribing in the UK.

The data for England are incomplete, with Blueteq only recording changes in prescriptions or initial prescriptions for DMTs. Thus, people who are maintained on an existing DMT are not recorded. This is a material gap. Consequently, there is no good quality evidence at a population level on the proportion of people with MS in England who are managed on a DMT. Rather the MS Survey seems to provide the most accurate data on take-up of DMTs.

There are also data gaps in Scotland, notably NHS Fife who did not respond to the FOI request. Two other boards, NHS Highland and NHS Lanarkshire, did not report the total number of people with MS treated with a DMT. These boards, together with four others (NHS Glasgow & Clyde, NHS Ayrshire & Arran, NHS Dumfries & Galloway and NHS Borders) and the Northern Irish Board did not provide prevalence data. Only NHS Lothian provided any information on the cost of certain DMTs, but not for interferons or GA. These material limitations, together with the questionable validity of the data reported, impact on the generalisability of the findings.

Prevalence data on the number of people with MS and by sub-category of MS were also not available in Northern Ireland or England. These are material data gaps, partially filled by the MS Survey data.

Despite these limitations, key findings from the available data include that:

* About 62% of People with MS in Scotland are receiving a DMT.
* There is a wide disparity in prescribing rates across the Scottish boards.
* Dimethyl fumarate had the highest market share across the three countries being around 30% in each.
* Glatiramer acetate consistently had the third highest market share.
* The second most prescribed DMT differed by nation, being an interferon in England, natalizumab in Scotland and teriflunomide in Northern Ireland.
* Northern Ireland and the Scottish boards had similar approaches to the use of DMTs as first and second line for RRMS and for managing people with PPMs and SPMS.

# Conclusions & Ways Forward

## Background

This feasibility study has adopted a structured and participative approach to assess the availability of health economics evidence for two selected elements of the MS treatment pathway (symptom management services & DMT prescribing), and to consider how evidence gaps might be filled by assessing sources which may be candidates for economic modelling. The steps included a systematic literature search, combined with reviewing NICE guidance evidence sources, and grey literature from the MS Society. Interim findings were shared with the MS Society to inform the selection of topics and specific studies for data extraction.

The strength of this approach is that it has been systematic in seeking to identify economic evaluations, clinical trials, effectiveness studies and systematic reviews which provide evidence regarding the clinical and/or cost effectiveness of specific interventions to improve patient outcomes in the UK and similar countries. All studies considered at the later stages have been quality graded to ensure findings are not based on biased or low grade studies.

However, also, as a scoping study, the approach has the inherent limitation of considering a limited range, or sample, of prioritised interventions for people with MS; and restrictions on the number of evidence sources reviewed in detail. To mitigate this, the researchers worked in close consultation with the MS Society to make informed collective judgements on the focus of evidence review work and data collection (FOI requests).

Beyond the scope of this work, it is important to remember that in addition to those focussing on specific interventions documented here, other health economic study methods, such as cost of illness and social return on investment (Moral Torres, 2020), quantifying the overall net costs and benefts of MS and MS services are also available for consideration.

The following sections set out our conclusions on the evidence sources that were fully assessed and the implications for the MS Society in their consideration of future ways forward in health economics evidence development work.

Conclusions are drawn in light of the following ‘baskets’ of evidence:

1. Currently available & of appropriate quality for full review & reporting (in Phase 2).

2. Deliverable in shorter-term (4-8 months) research & data analysis consultancy projects combining (analysis/modelling) current evidence resources (potentially in Phase 2).

3. Deliverable through longer-term research strategies.

## Symptom Management Services

A literature search was conducted to identify evidence on a wide range of services for people with MS or neurological disorders except those with strokes, headaches, infections, seizures, sudden brain injury, and spinal cord disorders.

Of the 2,100 retrieved records, grey literature and NICE references, four economic papers and three systematic reviews which covered the chosen interventions (rehabilitation, CBT, FES), were selected for full consideration. Their content and the basis for their inclusion in the evidence baskets is discussed in the following sections.

### Health Economics Studies

The following considerations were made in allocating health economics studies to the baskets:

* 1. Study quality.
  2. Validity & confidence of findings & conclusions.

Table 6.1 shows the allocation of the health economics studies to evidence baskets. All four studies were of appropriate quality for inclusion in the evidence baskets.

Table 6.1**: Allocation of health economics evaluation to baskets**

| Das Nair (2019) | Mosweu (2017) | Turner-Stokes (2020) | Juckes (2019) |
| --- | --- | --- | --- |
| Basket 1 | Basket 1 | Basket 2 | Basket 1 |

The Das Nair (2019) study compared cognitive rehabilitation plus usual care to usual care alone. The economic evaluation accompanied a well-conducted RCT. The main result was that the intervention was cheaper (saving £575 per participant), improved mood and memory but not increased quality-adjusted life-years. Sensitivity analysis showed a high probability that cognitive rehabilitation was cost effective at all credible willingness to pay thresholds. This study is suitable for Basket 1.

The study by Mosweu (2017) compared CBT with supportive listening in people with MS (n = 94). The economic evaluation was nested within a well-conducted RCT. The results reported that, at 12 months, CBT was about 46% more expensive per participant (£7,331 versus £5,026). Whilst it was associated with an increase in quality-adjusted life-years, these were insufficient to make it cost-effective (ICER £303,774). Sensitivity analysis confirmed this intervention was unlikely to be cost-effective. The evaluation was judged to be of moderate quality. This study is suitable for Basket 1.

The Juckes (2019) economic evaluation compared using the Odstock Dropped Foot Stimulator with standard care. It reported an ICER of £6,163, but no sensitivity analyses were presented. The study was judged to be high quality, though sensitivity analysis was lacking and uncertainty remains over the confidence of the stated ICER. The evaluation assumed the benefits recorded by patients at their final six-month appointment for FES were maintained over five years, with no waning effect and no impact from progression of the disease. This assumption is considered as valid by the MS Society’s clinical experts, and the study is suitable for Basket 1.

The study by Turner-Stokes (2020) compared specialist inpatient rehabilitation with usual care. Clinical data were collected from a national clinical dataset for people with MS (n = 1,007). No resource or cost information were available from this dataset. These were derived from an algorithm which estimated care hours by level of dependence (low, medium, high). The cost of the intervention was estimated based on mean length of stay for each dependency level. The results were expressed as time to offset the costs of rehabilitation. The conclusion was the intervention was not cost-effective for people with low dependency needs.

The issues with this evaluation relate to the need to validate:

* The estimated cost of the intervention and related savings.
* The assumption that the clinical benefit measured at discharge is maintained over subsequent years.

However, given our conclusion on the Amatya (2019a) systematic review on inpatient rehabilitation (see next section), we judge this is suitable for potential development in Basket 2.

### Systematic Reviews

The following considerations were made in allocating systematic reviews to the baskets:

1. Study quality.
2. Validity & confidence of findings & conclusions.
3. Relevance of clinical endpoints.

Table 6.2 shows the allocation of the systematic reviews to evidence baskets.

Table 6.2**: Allocation of systematic reviews to baskets**

|  |  |  |
| --- | --- | --- |
| Amatya(2019a) | Gutkin(2020) | Nair(2017) |
| Basket 2 | Not allocated | Not allocated |

The Cochrane Review by Amatya (2019a) was high quality and provided relevant outcomes (see Table 3.3). Strong evidence was found for inpatient multidisciplinary rehabilitation (three RCTs, n = 217, two were set in England), with limited evidence for outpatient multidisciplinary rehabilitation. No evidence was found on the cost-effectiveness of these interventions. Following review of the endpoints reported in the RCTs, we judge there is sufficient clinical evidence to consider modelling inpatient multidisciplinary rehabilitation and hence put this review into Basket 2. The health economics study by Turner-Stokes (2020) could also inform such a model. We also note that NICE excluded rehabilitation from the scope of its recent MS guideline. There is thus an evidence gap in the patient pathway.

The review by Gutkin (2020) had several weaknesses, many arising because only one reviewer did everything e.g study selection, data extraction and reporting, with no information provided on excluded studies. It is thus potentially subject to the bias of this reviewer. The population was wider than people with MS, being primarily those with psychogenic non-epileptic seizures, and endpoints related to number and frequency of seizures. The population and endpoints are thus not directly relevant to people with MS. Given the risk of bias and concerns about generalisability, we do not think this should be taken into phase 2.

The review by Nair (2017) on FES was judged low quality (see Table E.3) and thus was not allocated to a basket.

### Developing Evidence from Baskets 1 & 2

**Das Nair (2019)**

Going forward we consider there may be material benefit and impact from developing the Das Nair study into a report for commissioners and others. The main result is that providing cognitive rehabilitation can reduce future health care costs in the short to medium term (up to one year), whilst improving memory and mood.

**Mosweu (2017)**

We see little benefit from taking forward Mosweu’s findings that CBT is not cost effective compared with supportive listening delivered by nurses. The major weakness with this evaluation is the comparator is not usual care. The result is thus not relevant to the NHS setting and highlighting it risks commissioners and others interpreting the results to imply CBT is not cost-effective.

**Juckes (2019)**

We see benefit from taking forward the economic evaluation by Juckes on FES. In 2016, NICE published a Medtech Innovation Briefing on the technology but in the absence of a cost-effectiveness analysis it was unable to recommend it. However, if there is clinical consensus on assumptions in Juckes on extrapolating the clinical evidence from the end of the trial to 5 years then this could be develop into a report for commissioners and others.

**Amatya (2019a)**

The Amatya paper found that three RCTs examining multidisciplinary inpatient rehabilitation were judged by the authors to provide ‘strong evidence’ to support this intervention clinically but there was no economic evidence. The strength of the clinical evidence gives us confidence in proposing undertaking an economic evaluation.

This would seek to answer a research question such as: W*hat is the clinical and cost-effectiveness of multidisciplinary inpatient rehabilitation compared with usual care in people with MS*?

The steps involved could include:

1. Working with the MS Society, people with MS and clinicians to define the scope of the appraisal (for example, population, intervention, comparators, health outcome and cost measures and time horizon).
2. Systematic searching for evidence related to each element within the scope.
3. Analysing the included evidence transparently, using robust methods which minimise bias.
4. Developing a protocol to inform a de novo model. This would be consistent with the methods defined in the NICE reference case (NICE, 2013), see Table 6.3.
5. Creating a quality assured de novo mode and undertaking sensitivity analysis.
6. Writing a manuscript for a high-impact, peer-reviewed journal and disseminating the findings through other channels.

All of the clinical evidence and quality of life data would come from studies identified by the literature search. These will include the three RCTs reported by Amatya (2019a). Resource use may also be identified from papers, including that by Turner-Stokes (2020), with gaps filled by working with experts. Unit costs would be taken from national datasets. Understanding the relationship between dependency and care needs would also benefit from the input of people with MS, their families and carers.

Table 6.3**: Parameters to inform an economic model**

| Elements of the modelling | Reference case |
| --- | --- |
| Defining the population, intervention and comparators | From the scope developed with the MS Society and stakeholders |
| Perspective on outcomes | All direct health effects, whether for patients or, when relevant, carers |
| Perspective on costs | NHS and social services |
| Type of economic evaluation | Cost utility analysis and possibly cost consequences analysis |
| Time horizon | Long enough to reflect all important differences in costs or outcomes between the technologies being compared |
| Synthesis of evidence on clinical effects and quality of life | Based on findings from the systematic review |
| Measuring and valuing health effects | Use quality-adjusted life-years measured by EQ-5D tool and reported by patients and/or carers |
| Evidence on resource use and costs | Based on literature searches and expert opinion to establish resource use and valued using national unit cost datasets where possible |
| Discounting | Currently a discount rate of 3.5% is applied to costs and benefits |

Key: EQ-5D – EuroQol-Five Dimensions; MS – multiple sclerosis; NHS – National Health Service

Results would be presented in tables reporting incremental costs and benefits and the ICER. Sensitivity analysis would be undertaken to characterise the uncertainty in input parameters. Clear conclusions would be made based on the base case ICER and sensitivity analysis.

### Basket 3: Longer-Term Research

The main limitation with the current evidence base is the lack of high-quality studies exploring the effectiveness of services other than rehabilitation for people with MS. This in turn means health economics studies built on these are also lacking.

This is consistent with the findings from the NICE guideline on MS Services(NICE, 2019), which found only a handful of high quality RCTs on services. Indeed, this may be why NICE did not take forward its own economic modelling.

Hence, we concur with the conclusions made by the authors of each of the systematic reviews that more studies, with robust methodologies, are needed to justify the use of many of these interventions.

According to wider sources reviewed through the course of our scoping study, potential priorities appear to include the following topics:

* Management of symptoms giving rise to non-elective hospitalisation, such as bladder management, bladder infections and constipation (MS Trust and Wilmington Healthcare).
* Improving psychological support for people with SPMS as identified by Wilmington Healthcare, 2020).
* Provision of information - This need was identified from recent MS Society (2020) research. We note Amatya’s (2019a) review found 10 RCTs which included interventions giving MS-specific information and these were rated as providing moderate evidence (See Figure E.1).
* Interventions to improve mood and emotional outcomes for people with MS. This need was identified from MY MS My Needs 2019 (MS Society, 2019) and was the largest area of unmet need. The Amatya (2019a) review did look for evidence on effective interventions to manage these aspects but found none.
* Adoption of formalised multidisciplinary teams across specialist teams (NHS Rightcare, 2019).

In addition to prioritising research topics for clinical effectiveness, health services and health economic studies, the MS Society could also consider strengthening its strategic research capacity in these methodologies. This might include the following:

* Forming research coalitions with other MS organisations.
* Ensuring MS Society funded service development & pilots are rigorously evaluated.
* Apply for external research funding from national bodies such as NIHR & Wellcome.
* Fund academic research capacity via grants & training fellowships.

## DMT Prescribing

The feasibility study has considered the evidence and data available to assess the net economic benefit (i.e. net total of costs & benefits) of current DMT prescribing to the NHS and social care system in the UK, and what impact would result from increased DMT prescribing.

A literature search was undertaken to identify evidence on the cost-effectiveness of each DMT and as a class. From the 573 records retrieved plus the grey literature provided, we found two papers related to the use of beta interferon and/or glatiramer acetate in the NHS (Giovannoni, 2019; Melendez-Torres, 2017). These studies were overtaken by the NICE TA on these DMTs (NICE, 2018). This is one of 11 NICE TAs published on DMTs.

We data extracted the NICE TAs for these drugs, siponimod(NICE, 2020), dimethyl fumarate (NICE, 2014a)and natalizumab(NICE, 2007) (see Table 4.2). Due to the extensive use of redaction (for example of the values used to inform the modelled clinical effectiveness parameters, cost to the NHS of the drugs, and the results), the data available for extraction are limited. However, we were able to extract data on the NHS and social services costs and quality of life associated with each EDSS state and the administration and monitoring costs for each DMT.

Also, the findings of our FOI requests provide ‘real world’ evidence on the level of prescribing of DMT, and the NHS Lothian reply details prescribing costs of the newer DMTs.

The FOI responses show variation in prescribing levels and usage of each DMT across the four nations and within Scottish health boards. Taken in the round, they suggest that prescribers regard the efficacy of the newer DMTs for RRMS to be similar, with the majority using dimethyl fumarate (DF) as their DMT of choice. Unfortunately, the Biogen submission for DF redacted all information on variables such as relapse rates, EDSS changes and discontinuation rates. These were obtained from a mixed treatment comparison of DF against the other DMTs and placebo. This level of redacting is common across all the newer DMTs. Indeed, the only publicly available efficacy data are from the UK Multiple Sclerosis Risk Sharing Scheme (RSS) [for example as reported by Giovannoni(2019) and Melendez-Torres(2017)].

In England, the absence of patient-based prescribing data is a major concern, especially at a time of potential change to budgets (see Section 2.6). It means there is no baseline to measure change against, or consider equity of access to DMTs in the population.

### Consideration & Development of Evidence Baskets 1 & 2

The lack of unbiased evidence from published literature plus the heavy redaction of the NICE TAs means that the available evidence is incomplete and no evidence sources can be allocated to Basket 1.

Consequently, we explore the feasibility of opportunities to develop the available evidence and data sources for Basket 2 below.

We consider it potentially feasible to develop a model/practical calculator to answer questions on the net economic benefits of individual DMTs, compared with BSC, such that all the inputs are user defined, with default values available if the user wants to adopt them. The starting point would be to develop a scope and protocol, working with stakeholders to ensure these adequately capture the decision problem.

The model structure could be based on EDSS health states (0 to 9) and death. Each state would be associated with costs and quality of life values. It would capture disease progression and relapses over time, using transitional probabilities to move people across states over time. Other key inputs include duration of treatment and waning effect.

Key available data include:

* Disease progression and relapses, rates from:
  + Published evaluations of beta-interferons and GA and values from a natural history disease register for the standard care arm.
  + A high quality systematic review and meta-analysis.
* Mortality risk from published literature.
* A choice of assumptions on waning effect and duration of treatments.
* Costs for each state extracted from the NICE TAs.
* Quality of life utilities from the NICE TAs.
* Prices for DMTs using list price and a range of discounts.

The model would output the following results:

* The cost consequences to the NHS and social care services from prescribing more DMTs.
* The value of the associated improvement in quality of life.

However, the model would be complex to design, build and populate; and as a result would be relatively expensive (over £50,000). Early stages of the work would need to determine the precise availability of all data sources necessary. Consequently, the MS Society would need to consider the added value the model could bring to its strategic objectives on the health economics of DMT prescribing.

Also, to be considered adequately rigorous and valid by users and commissioner audiences, such a model would need to provide confidence in relation to transparency of methods, external validity of assumptions, developer or user bias in input values selected, and acceptable levels of uncertainty in findings.

The lack of fully transparent evidence sources due to redaction of key data means that adequately mitigating these concerns would currently be difficult.

Furthermore, output calculations may conflict with existing health economics findings published by NICE and manufacturers, and cause confusion amongst decision makers.

### Basket 3: Longer-Term Research

The limitations of the current evidence base on the effectiveness and economics of DMTs are set out above. Opportunity exists for the MS Society to work with national research organisations and manufacturers to seek to broker more comprehensive access to existing evidence and to develop future evidence generation initiatives.

As pointed out by numerous earlier studies and observers (including the Nuffield Trust (Castle-Clarke, 2018) & Mynors for MS Trust (Mynors, 2016), this includes the collection of long-term real world outcome data in clinical trials and/or monitoring databases.

Potentially, current data sources, such as the MS Register (2021) could be expanded to gather additional data to allow outcomes and economic analyses, by adding collection of data such as:

* Diagnosis.
* Start and end date for DMT.
* Start and end values of EDSS, EQ-5D and clinical quality of life measures.
* Number of relapses during the period.
* Change in symptoms during the period.
* NHS resources used.
* DMT preceding and post the DMT of interest.

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Appendix A: Literature Search Methods for Symptom Management Services

The search methods (including search strategy and selection of search resources) reflected the pragmatic review context. The methods were designed to enable searches and study assessment to be completed within project resources and timelines. The pragmatic search approach was discussed and agreed within the research team and with the MS Society.

**SEARCH STRATEGY**

A MEDLINE (OvidSP) search strategy was designed to identify economic evaluations, systematic reviews, RCTs and observational studies on the eligible interventions in:

* Patients with MS.
* Patients included in studies where the database record referred to non-specific neurological disorders.

The final MEDLINE strategy is presented in Figure A1.

The strategy comprised seven concepts:

* MS (search lines 1 to 5).
* Non-specific neurological disorders (search lines 6 to 9).
* Eligible interventions (search lines 11 to 91).
* Economic evaluations (search lines 94 to 110).
* Systematic reviews (search lines 111 to 180).
* RCTs (search lines 181 to 189).
* Observational studies (including comparative cohort studies) (search lines 190 to 202).

The concepts were combined as follows: (MS OR non-specific neurological disorders) AND eligible interventions AND (economic evaluations OR systematic reviews OR RCTS OR observational studies).

The strategy was devised using a combination of subject indexing terms and free text search terms in the Title, Abstract and Keyword Heading Word fields.

The search terms for the economic evaluations concept (search lines 94 to 110) were based on the filter developed by the University of York Centre for Reviews and Dissemination (CRD) to identify economic evaluations to include in NHS Economic Evaluation Database (NHS EED)[[9]](#footnote-10).

The search terms for the SR concept (search lines 111 to 180) were based on the filter developed by the University of York CRD to identify systematic reviews to include in the Database of Abstracts of Reviews of Effects (DARE)[[10]](#footnote-11).

The search terms for the RCTs concept (search lines 181 to 189) were based on the Cochrane Highly Sensitive Search Strategy for identifying randomized trials in MEDLINE (sensitivity-maximizing version (2008 revision), Ovid format)[[11]](#footnote-12).

The search terms for the observational studies concept (search lines 190 to 202) were based on the Observational Studies MEDLINE search filter developed by the Scottish Intercollegiate Guidelines Network (SIGN)[[12]](#footnote-13).

The search strategy reflected the pragmatic review context and the selection of terms was intentionally limited. The strategy was designed to retrieve records that explicitly referred to the interventions of interest using a limited range of terms based on the specific terms used for the interventions in the eligibility criteria.

The search terms for the service interventions were designed to retrieve records that explicitly referred to terms for the service intervention itself, or to a limited selection of terms that might indicate a service intervention context. The strategy was not designed to retrieve records for studies on specific, named interventions delivered *by* these services – unless the record also referred to the service. For example, where the eligible intervention was 'dietician service' the strategy was designed to retrieve records that explicitly referred to a 'dietician service', or to a limited range of terms that might indicate a dietician service context (for example 'dietician', 'diet therapy', 'diet support'). It was *not* designed to retrieve records for studies on specific, named interventions that might be delivered by dietician services.

The MS Society requested that the search be designed to retrieve records that referred to MS or non-specific neurological disorders. The strategy was not designed to retrieve records that only referred to specific, named neurological disorders (other than MS). To reduce the number of retrieved records, the search terms for the non-specific neurological disorders concept were highly pragmatic. Pragmatic approaches for the non-specific neurological disorder terms included:

* The subject heading used in MEDLINE for neurological disorders (*Nervous System Diseases*) was searched as a major descriptor only (search line 6).
* The strategy was designed to retrieve records that referred to textword terms in the title field, the author keyword field (search line 7), or *at least twice* in the abstract field (search line 8). It was not designed to retrieve records that referred just once to the textword terms in the abstract field.
* The strategy included a *limited range of terms* for neurological disorders i.e. neurologic or neurologic conditions / diseases / disorders only. The strategy was not designed to retrieve records that only refer to variant textword descriptions – for example: neurological complaints / syndromes; nervous system conditions / diseases / disorders / complaints / syndromes.

The strategy excluded animal studies from MEDLINE using a standard algorithm (search line 204). The strategy also excluded some publication types which were unlikely to yield relevant study reports (news items, comments, editorials, letters and case reports) and records with the phrase 'case report' in the title (search lines 205 to 206).

The strategy was restricted to studies published in English language from 2015 to date. The date and language restrictions reflected the eligibility criteria.

The final Ovid MEDLINE strategy was peer-reviewed by a second Information Specialist for errors in spelling, syntax and line combinations.

**Figure A.1: Search strategy for MEDLINE ALL**

1 exp Multiple Sclerosis/ (60223)

2 multiple scleros$.ti,ab,kf. (78920)

3 (disseminated scleros$ or sclerosis multiplex or insular scleros$ or encephalomyelitis disseminata or chariot disease).ti,ab,kf. (769)

4 ms.ti,kf. or (rms or rrms or prms or ppms or cpms or spms or rspms).ti,ab,kf. (80234)

5 or/1-4 (158537)

6 \*Nervous System Diseases/ (30648)

7 ((neurological or neurologic) adj3 (condition$1 or disease$1 or disorder$1)).ti,kf. (12431)

8 ((neurological or neurologic) adj3 (condition$1 or disease$1 or disorder$1)).ab. /freq=2 (11669)

9 6 or 7 or 8 (45727)

10 5 or 9 (201174)

11 Patient Care Team/ (66412)

12 (multi-disciplin$ or multidisciplin$).ti,ab,kf. (98446)

13 (inter-disciplin$ or interdisciplin$).ti,ab,kf. (40330)

14 exp Urinary Incontinence/nu [Nursing] (1814)

15 Fecal Incontinence/nu [Nursing] (603)

16 ((continence or incontinence) adj3 (centre or centres or center or centers or clinic or clinics or service$ or team$ or nurs$ or advisor$)).ti,ab,kf. (1237)

17 ((continence or incontinence) adj3 (therap$ or treatment$ or support$)).ti,ab,kf. (4404)

18 Physical Therapy Modalities/ (37404)

19 Physical Therapy Specialty/ (2888)

20 Physical Therapists/ (2047)

21 (physiotherap$ or physio-therap$ or neurophysiotherap$ or neurophysio-therap$).ti,ab,kf. (27875)

22 (physical therap$ or neurophysical therap$).ti,ab,kf. (26888)

23 (physical treatment$ or neurophysical treatment$).ti,ab,kf. (1420)

24 Occupational Therapy/ (13470)

25 Occupational Therapists/ (358)

26 (occupational adj3 therap$).ti,ab,kf. (16177)

27 exp Dietary Services/ (7035)

28 Nutritionists/ (1285)

29 ((diet$ or nutrition$) adj3 (centre or centres or center or centers or clinic or clinics or service$ or team$)).ti,ab,kf. (4407)

30 ((diet$ or nutrition$) adj3 (therap$ or treatment$ or support$)).ti,ab,kf. (52199)

31 (dietician$ or nutritionist$).ti,ab,kf. (4845)

32 "rehabilitation of speech and language disorders"/ (0)

33 Speech Therapy/ (6446)

34 Language Therapy/ (1896)

35 Speech-Language Pathology/ (3170)

36 ((speech$ or language$) adj3 (centre or centres or center or centers or clinic or clinics or service$ or team$)).ti,ab,kf. (1915)

37 ((speech$ or language$) adj3 (therap$ or treatment$ or support$ or training or education)).ti,ab,kf. (11637)

38 (slt or slts).ti,ab,kf. (2225)

39 exp Nursing Services/ (49811)

40 ((nurse$ or nursing) adj3 (centre or centres or center or centers or clinic or clinics or service$ or team$)).ti,ab,kf. (19703)

41 Rehabilitation/ (18404)

42 Hospitals, Rehabilitation/ (75)

43 Rehabilitation Centers/ (8295)

44 Rehabilitation Nursing/ (1419)

45 (rehab$ adj3 (centre or centres or center or centers or clinic or clinics or service$ or team$ or nurs$)).ti,ab,kf. (18318)

46 (rehab$ adj3 (therap$ or treatment$ or support$)).ti,ab,kf. (17772)

47 Neurological Rehabilitation/ (1021)

48 (neuro$ adj rehab$).ti,ab,kf. (2162)

49 neurorehab$.ti,ab,kf. (3409)

50 (rehab$ adj6 spasticit$).ti,ab,kf. (328)

51 (reenabl$ or re-enabl$).ti,ab,kf. (57)

52 (reabl$ or re-abl$).ti,ab,kf. (369)

53 Electric Stimulation Therapy/ (20750)

54 electric$ stimulation$.ti,ab,kf. (52083)

55 (electrostimulation$ or electro-stimulation$).ti,ab,kf. (3447)

56 (fes or fet or fest).ti,ab,kf. (9469)

57 nmes.ti,ab,kf. (1255)

58 or/11-57 (544176)

59 10 and 58 (5246)

60 exp Multiple Sclerosis/nu (519)

61 ((multiple sclerosis or ms) adj3 nurs$).ti,ab,kf. (430)

62 ((multiple sclerosis or ms) adj3 champion$).ti,ab,kf. (3)

63 or/60-62 (862)

64 59 or 63 (5972)

65 mental health services/ or community mental health services/ (52817)

66 (mental health$ adj5 (centre or centres or center or centers or clinic or clinics or service$ or team$ or nurs$)).ti,ab,kf. (37704)

67 (mental health$ adj5 (therap$ or treatment$ or support$)).ti,ab,kf. (19674)

68 Peer Group/ and Social Support/ (2841)

69 ((peer or peers) adj5 (support$ or assist$ or help$ or connect$)).ti,ab,kf. (9927)

70 "peer-to-peer".ti,ab,kf. (1539)

71 Neuropsychology/ (2440)

72 ((neuropsycholog$ or neuro-psycholog$) adj3 (centre or centres or center or centers or clinic or clinics or service$ or team$)).ti,ab,kf. (325)

73 ((neuropsycholog$ or neuro-psycholog$) adj3 (therap$ or treatment$ or support$)).ti,ab,kf. (948)

74 neuropsychologist$.ti,ab,kf. (1345)

75 Psychology/ (23558)

76 Psychology, Clinical/ (3175)

77 (psycholog$ adj3 (centre or centres or center or centers or clinic or clinics or service$ or team$)).ti,ab,kf. (3238)

78 (psycholog$ adj3 (therap$ or treatment$ or support$)).ti,ab,kf. (19130)

79 psychologist$.ti,ab,kf. (16251)

80 exp Counseling/ (44857)

81 (counselling or counseling).ti,ab,kf. (99452)

82 (counselor$ or counsellor$).ti,ab,kf. (9688)

83 (IAPT or IAPTs).ti,ab,kf. (213)

84 Memory Disorders/ and (centre or centres or center or centers or clinic or clinics or service$ or team$ or support$).ti,ab,kf. (3084)

85 ((memory or memories) adj5 (centre or centres or center or centers or clinic or clinics or service$ or team$)).ti,ab,kf. (3465)

86 ((memory or memories) adj5 (therap$ or treatment$ or support$)).ti,ab,kf. (9461)

87 Cognitive Behavioral Therapy/ (26272)

88 psychotherap$)).ti,ab,kf. (21164)

89 ((cognitive or cognition) adj3 (therap$ or treatment$ or psychotherap$)).ti,ab,kf. (32710)

90 (cbt or cbts).ti,ab,kf. (11940)

91 or/65-90 (332389)

92 10 and 91 (1859)

93 64 or 92 (7475)

94 Economics/ (27284)

95 exp "costs and cost analysis"/ (242099)

96 Economics, Dental/ (1915)

97 exp economics, hospital/ (24921)

98 Economics, Medical/ (9117)

99 Economics, Nursing/ (4002)

100 Economics, Pharmaceutical/ (2969)

101 (economic$ or cost or costs or costly or costing or price or prices or pricing or pharmacoeconomic$).ti,ab. (843136)

102 (expenditure$ not energy).ti,ab. (31262)

103 value for money.ti,ab. (1805)

104 budget$.ti,ab. (30660)

105 or/94-104 (997806)

106 ((energy or oxygen) adj cost).ti,ab. (4223)

107 (metabolic adj cost).ti,ab. (1479)

108 ((energy or oxygen) adj expenditure).ti,ab. (25907)

109 or/106-108 (30614)

110 105 not 109 (990781)

111 systematic$ review$.ti,ab. (199782)

112 meta-analysis as topic/ (18917)

113 meta-analytic$.ti,ab. (7753)

114 meta-analysis.ti,ab,pt. (193854)

115 metanalysis.ti,ab. (291)

116 metaanalysis.ti,ab. (1670)

117 meta analysis.ti,ab. (166007)

118 meta-synthesis.ti,ab. (976)

119 metasynthesis.ti,ab. (355)

120 meta synthesis.ti,ab. (976)

121 meta-regression.ti,ab. (8840)

122 metaregression.ti,ab. (740)

123 meta regression.ti,ab. (8840)

124 (synthes$ adj3 literature).ti,ab. (4006)

125 (synthes$ adj3 evidence).ti,ab. (12090)

126 integrative review.ti,ab. (3423)

127 data synthesis.ti,ab. (11931)

128 (research synthesis or narrative synthesis).ti,ab. (3961)

129 (systematic study or systematic studies).ti,ab. (12766)

130 (systematic comparison$ or systematic overview$).ti,ab. (3621)

131 evidence based review.ti,ab. (2123)

132 comprehensive review.ti,ab. (17081)

133 critical review.ti,ab. (16565)

134 quantitative review.ti,ab. (708)

135 structured review.ti,ab. (879)

136 realist review.ti,ab. (364)

137 realist synthesis.ti,ab. (244)

138 or/111-137 (386027)

139 review.pt. (2758995)

140 medline.ab. (126662)

141 pubmed.ab. (134907)

142 cochrane.ab. (93618)

143 embase.ab. (104018)

144 cinahl.ab. (30915)

145 psyc?lit.ab. (915)

146 psyc?info.ab. (40232)

147 (literature adj3 search$).ab. (67443)

148 (database$ adj3 search$).ab. (68426)

149 (bibliographic adj3 search$).ab. (2879)

150 (electronic adj3 search$).ab. (24671)

151 (electronic adj3 database$).ab. (33410)

152 (computeri?ed adj3 search$).ab. (3645)

153 (internet adj3 search$).ab. (3523)

154 included studies.ab. (27972)

155 (inclusion adj3 studies).ab. (18427)

156 inclusion criteria.ab. (95677)

157 selection criteria.ab. (31557)

158 predefined criteria.ab. (2095)

159 predetermined criteria.ab. (1105)

160 (assess$ adj3 (quality or validity)).ab. (87346)

161 (select$ adj3 (study or studies)).ab. (72224)

162 (data adj3 extract$).ab. (70946)

163 extracted data.ab. (15939)

164 (data adj2 abstracted).ab. (5623)

165 (data adj3 abstraction).ab. (1863)

166 published intervention$.ab. (195)

167 ((study or studies) adj2 evaluat$).ab. (200526)

168 (intervention$ adj2 evaluat$).ab. (12336)

169 confidence interval$.ab. (447994)

170 heterogeneity.ab. (180379)

171 pooled.ab. (98438)

172 pooling.ab. (13263)

173 odds ratio$.ab. (291799)

174 (Jadad or coding).ab. (196892)

175 or/140-174 (1578823)

176 139 and 175 (259960)

177 review.ti. (517993)

178 177 and 175 (171799)

179 (review$ adj4 (papers or trials or studies or evidence or intervention$ or evaluation$)).ti,ab. (202936)

180 138 or 176 or 178 or 179 (632718)

181 randomized controlled trial.pt. (521951)

182 controlled clinical trial.pt. (94049)

183 randomized.ab. (510387)

184 placebo.ab. (215580)

185 drug therapy.fs. (2274478)

186 randomly.ab. (351559)

187 trial.ab. (541682)

188 groups.ab. (2157361)

189 or/181-188 (4916506)

190 Epidemiologic studies/ (8545)

191 exp case control studies/ (1138918)

192 exp cohort studies/ (2084575)

193 Case control.tw. (131322)

194 (cohort adj (study or studies)).tw. (227029)

195 Cohort analy$.tw. (8770)

196 (Follow up adj (study or studies)).tw. (50590)

197 (observational adj (study or studies)).tw. (117351)

198 Longitudinal.tw. (260478)

199 Retrospective.tw. (572223)

200 Cross sectional.tw. (382783)

201 Cross-sectional studies/ (351920)

202 or/190-201 (3163261)

203 93 and (110 or 180 or 189 or 202) (3290)

204 exp animals/ not humans/ (4782806)

205 (news or comment or editorial or letter or case reports).pt. (4054155)

206 case report.ti. (251546)

207 203 not (204 or 205 or 206) (3112)

208 limit 207 to english language (2849)

209 limit 208 to yr="2015 -Current" (1396)

Key to Ovid symbols and commands

$ Unlimited right-hand truncation symbol

? Wildcard symbol

ti,ab,kf Searches are restricted to the Title (ti), Abstract (ab) and Keyword Heading Word (kf) fields

adj Retrieves records that contain terms next to each other (in the shown order)

adjN Retrieves records that contain terms (in any order) within a specified number (N) of words of each other

/ Searches are restricted to the Subject Heading field

exp The subject heading is exploded

pt. Search is restricted to the publication type field

or/1-4 Combines sets 1 to 4 using OR

**RESOURCES SEARCHED**

We conducted the literature search in the databases and information resources shown in Table A1. The selection of search resources reflected the pragmatic review context.

**Table A.1: Databases and information sources searched**

|  |  |
| --- | --- |
| Resource | Interface / URL |
| MEDLINE ALL | OvidSP |
| Cochrane Database of Systematic Reviews | Cochrane Library / Wiley |
| Cochrane Central Register of Controlled Trials | Cochrane Library / Wiley |
| Epistemonikos | https://www.epistemonikos.org/ |
| HTA Database | https://database.inahta.org/ |
| Econlit | OvidSP |
| Social Care Online | https://www.scie-socialcareonline.org.uk/ |

The Epistemonikos search was restricted by category to systematic reviews.

In addition to searching the above resources, the following supplementary searches were conducted to identify additional eligible studies:

* Relevant NICE guidelines were checked for economic studies.
* Relevant health technology assessments published by the National Institute of Health Research were checked.
* Reference lists of included studies and relevant systematic reviews were checked.
* The MS Society was asked to provide details of any relevant studies (both published literature and 'grey literature') or business cases that they were aware of.

**RUNNING THE SEARCH STRATEGIES AND DOWNLOADING RESULTS**

We conducted searches using each database or resource listed above, translating the agreed Ovid MEDLINE strategy appropriately. Translation included consideration of differences in database interfaces and functionality, in addition to variation in indexing languages and thesauri. Translation reflected the pragmatic review context. Annex A1 contains the full strategies (including search dates) for all sources searched.

Where possible, we downloaded the results of searches in a tagged format and loaded them into bibliographic software (EndNote). The results were deduplicated using several algorithms and the duplicate references held in a separate EndNote database for checking if required. Results from resources that did not allow export in a format compatible with EndNote were saved in Word or Excel documents as appropriate and manually deduplicated.

**Literature Search Results**

The database searches were conducted between 04/02/2021 and 05/02/2021. The searches identified 2,543 records (Table A.2). Following deduplication, 2,111 records were assessed for relevance.

**Table A.2: Literature search results**

|  |  |
| --- | --- |
| **Resource** | **Number of records identified** |
| **Databases** | |
| MEDLINE ALL | 1396 |
| Cochrane Database of Systematic Reviews | 30 |
| Cochrane Central Register of Controlled Trials | 707 |
| Epistemonikas | 246 |
| HTA Database | 51 |
| Econlit | 18 |
| Social Care Online | 78 |
| **Total records identified through database searching** | 2526 |
| **Other sources** | |
| Check of NICE guidelines | 1 |
| Check of health technology assessments published by the National Institute of Health Research | 0 |
| Checking of reference lists of included studies and relevant systematic reviews | 0 |
| Consultation with MS Society for other relevant studies (both published literature and 'grey literature') and business cases | 16 |
| **Total additional records identified through other sources** | 17 |
| **Total number of records retrieved** | **2543** |
| **Total number of records after deduplication** | **2111** |

**Annex A1**

**Search strategies**

1. **Source: MEDLINE ALL**

Interface / URL: OvidSP

Database coverage dates: 1946 to February 01, 2021

Search date: 04/02/2021

Retrieved records: 1396

Search strategy:

1 exp Multiple Sclerosis/ (60223)

2 multiple scleros$.ti,ab,kf. (78920)

3 (disseminated scleros$ or sclerosis multiplex or insular scleros$ or encephalomyelitis disseminata or chariot disease).ti,ab,kf. (769)

4 ms.ti,kf. or (rms or rrms or prms or ppms or cpms or spms or rspms).ti,ab,kf. (80234)

5 or/1-4 (158537)

6 \*Nervous System Diseases/ (30648)

7 ((neurological or neurologic) adj3 (condition$1 or disease$1 or disorder$1)).ti,kf. (12431)

8 ((neurological or neurologic) adj3 (condition$1 or disease$1 or disorder$1)).ab. /freq=2 (11669)

9 6 or 7 or 8 (45727)

10 5 or 9 (201174)

11 Patient Care Team/ (66412)

12 (multi-disciplin$ or multidisciplin$).ti,ab,kf. (98446)

13 (inter-disciplin$ or interdisciplin$).ti,ab,kf. (40330)

14 exp Urinary Incontinence/nu [Nursing] (1814)

15 Fecal Incontinence/nu [Nursing] (603)

16 ((continence or incontinence) adj3 (centre or centres or center or centers or clinic or clinics or service$ or team$ or nurs$ or advisor$)).ti,ab,kf. (1237)

17 ((continence or incontinence) adj3 (therap$ or treatment$ or support$)).ti,ab,kf. (4404)

18 Physical Therapy Modalities/ (37404)

19 Physical Therapy Specialty/ (2888)

20 Physical Therapists/ (2047)

21 (physiotherap$ or physio-therap$ or neurophysiotherap$ or neurophysio-therap$).ti,ab,kf. (27875)

22 (physical therap$ or neurophysical therap$).ti,ab,kf. (26888)

23 (physical treatment$ or neurophysical treatment$).ti,ab,kf. (1420)

24 Occupational Therapy/ (13470)

25 Occupational Therapists/ (358)

26 (occupational adj3 therap$).ti,ab,kf. (16177)

27 exp Dietary Services/ (7035)

28 Nutritionists/ (1285)

29 ((diet$ or nutrition$) adj3 (centre or centres or center or centers or clinic or clinics or service$ or team$)).ti,ab,kf. (4407)

30 ((diet$ or nutrition$) adj3 (therap$ or treatment$ or support$)).ti,ab,kf. (52199)

31 (dietician$ or nutritionist$).ti,ab,kf. (4845)

32 "rehabilitation of speech and language disorders"/ (0)

33 Speech Therapy/ (6446)

34 Language Therapy/ (1896)

35 Speech-Language Pathology/ (3170)

36 ((speech$ or language$) adj3 (centre or centres or center or centers or clinic or clinics or service$ or team$)).ti,ab,kf. (1915)

37 ((speech$ or language$) adj3 (therap$ or treatment$ or support$ or training or education)).ti,ab,kf. (11637)

38 (slt or slts).ti,ab,kf. (2225)

39 exp Nursing Services/ (49811)

40 ((nurse$ or nursing) adj3 (centre or centres or center or centers or clinic or clinics or service$ or team$)).ti,ab,kf. (19703)

41 Rehabilitation/ (18404)

42 Hospitals, Rehabilitation/ (75)

43 Rehabilitation Centers/ (8295)

44 Rehabilitation Nursing/ (1419)

45 (rehab$ adj3 (centre or centres or center or centers or clinic or clinics or service$ or team$ or nurs$)).ti,ab,kf. (18318)

46 (rehab$ adj3 (therap$ or treatment$ or support$)).ti,ab,kf. (17772)

47 Neurological Rehabilitation/ (1021)

48 (neuro$ adj rehab$).ti,ab,kf. (2162)

49 neurorehab$.ti,ab,kf. (3409)

50 (rehab$ adj6 spasticit$).ti,ab,kf. (328)

51 (reenabl$ or re-enabl$).ti,ab,kf. (57)

52 (reabl$ or re-abl$).ti,ab,kf. (369)

53 Electric Stimulation Therapy/ (20750)

54 electric$ stimulation$.ti,ab,kf. (52083)

55 (electrostimulation$ or electro-stimulation$).ti,ab,kf. (3447)

56 (fes or fet or fest).ti,ab,kf. (9469)

57 nmes.ti,ab,kf. (1255)

58 or/11-57 (544176)

59 10 and 58 (5246)

60 exp Multiple Sclerosis/nu (519)

61 ((multiple sclerosis or ms) adj3 nurs$).ti,ab,kf. (430)

62 ((multiple sclerosis or ms) adj3 champion$).ti,ab,kf. (3)

63 or/60-62 (862)

64 59 or 63 (5972)

65 mental health services/ or community mental health services/ (52817)

66 (mental health$ adj5 (centre or centres or center or centers or clinic or clinics or service$ or team$ or nurs$)).ti,ab,kf. (37704)

67 (mental health$ adj5 (therap$ or treatment$ or support$)).ti,ab,kf. (19674)

68 Peer Group/ and Social Support/ (2841)

69 ((peer or peers) adj5 (support$ or assist$ or help$ or connect$)).ti,ab,kf. (9927)

70 "peer-to-peer".ti,ab,kf. (1539)

71 Neuropsychology/ (2440)

72 ((neuropsycholog$ or neuro-psycholog$) adj3 (centre or centres or center or centers or clinic or clinics or service$ or team$)).ti,ab,kf. (325)

73 ((neuropsycholog$ or neuro-psycholog$) adj3 (therap$ or treatment$ or support$)).ti,ab,kf. (948)

74 neuropsychologist$.ti,ab,kf. (1345)

75 Psychology/ (23558)

76 Psychology, Clinical/ (3175)

77 (psycholog$ adj3 (centre or centres or center or centers or clinic or clinics or service$ or team$)).ti,ab,kf. (3238)

78 (psycholog$ adj3 (therap$ or treatment$ or support$)).ti,ab,kf. (19130)

79 psychologist$.ti,ab,kf. (16251)

80 exp Counseling/ (44857)

81 (counselling or counseling).ti,ab,kf. (99452)

82 (counselor$ or counsellor$).ti,ab,kf. (9688)

83 (IAPT or IAPTs).ti,ab,kf. (213)

84 Memory Disorders/ and (centre or centres or center or centers or clinic or clinics or service$ or team$ or support$).ti,ab,kf. (3084)

85 ((memory or memories) adj5 (centre or centres or center or centers or clinic or clinics or service$ or team$)).ti,ab,kf. (3465)

86 ((memory or memories) adj5 (therap$ or treatment$ or support$)).ti,ab,kf. (9461)

87 Cognitive Behavioral Therapy/ (26272)

88 ((cognitive behavior$ or cognitive behaviour$) adj3 (therap$ or treatment$ or psychotherap$)).ti,ab,kf. (21164)

89 ((cognitive or cognition) adj3 (therap$ or treatment$ or psychotherap$)).ti,ab,kf. (32710)

90 (cbt or cbts).ti,ab,kf. (11940)

91 or/65-90 (332389)

92 10 and 91 (1859)

93 64 or 92 (7475)

94 Economics/ (27284)

95 exp "costs and cost analysis"/ (242099)

96 Economics, Dental/ (1915)

97 exp economics, hospital/ (24921)

98 Economics, Medical/ (9117)

99 Economics, Nursing/ (4002)

100 Economics, Pharmaceutical/ (2969)

101 (economic$ or cost or costs or costly or costing or price or prices or pricing or pharmacoeconomic$).ti,ab. (843136)

102 (expenditure$ not energy).ti,ab. (31262)

103 value for money.ti,ab. (1805)

104 budget$.ti,ab. (30660)

105 or/94-104 (997806)

106 ((energy or oxygen) adj cost).ti,ab. (4223)

107 (metabolic adj cost).ti,ab. (1479)

108 ((energy or oxygen) adj expenditure).ti,ab. (25907)

109 or/106-108 (30614)

110 105 not 109 (990781)

111 systematic$ review$.ti,ab. (199782)

112 meta-analysis as topic/ (18917)

113 meta-analytic$.ti,ab. (7753)

114 meta-analysis.ti,ab,pt. (193854)

115 metanalysis.ti,ab. (291)

116 metaanalysis.ti,ab. (1670)

117 meta analysis.ti,ab. (166007)

118 meta-synthesis.ti,ab. (976)

119 metasynthesis.ti,ab. (355)

120 meta synthesis.ti,ab. (976)

121 meta-regression.ti,ab. (8840)

122 metaregression.ti,ab. (740)

123 meta regression.ti,ab. (8840)

124 (synthes$ adj3 literature).ti,ab. (4006)

125 (synthes$ adj3 evidence).ti,ab. (12090)

126 integrative review.ti,ab. (3423)

127 data synthesis.ti,ab. (11931)

128 (research synthesis or narrative synthesis).ti,ab. (3961)

129 (systematic study or systematic studies).ti,ab. (12766)

130 (systematic comparison$ or systematic overview$).ti,ab. (3621)

131 evidence based review.ti,ab. (2123)

132 comprehensive review.ti,ab. (17081)

133 critical review.ti,ab. (16565)

134 quantitative review.ti,ab. (708)

135 structured review.ti,ab. (879)

136 realist review.ti,ab. (364)

137 realist synthesis.ti,ab. (244)

138 or/111-137 (386027)

139 review.pt. (2758995)

140 medline.ab. (126662)

141 pubmed.ab. (134907)

142 cochrane.ab. (93618)

143 embase.ab. (104018)

144 cinahl.ab. (30915)

145 psyc?lit.ab. (915)

146 psyc?info.ab. (40232)

147 (literature adj3 search$).ab. (67443)

148 (database$ adj3 search$).ab. (68426)

149 (bibliographic adj3 search$).ab. (2879)

150 (electronic adj3 search$).ab. (24671)

151 (electronic adj3 database$).ab. (33410)

152 (computeri?ed adj3 search$).ab. (3645)

153 (internet adj3 search$).ab. (3523)

154 included studies.ab. (27972)

155 (inclusion adj3 studies).ab. (18427)

156 inclusion criteria.ab. (95677)

157 selection criteria.ab. (31557)

158 predefined criteria.ab. (2095)

159 predetermined criteria.ab. (1105)

160 (assess$ adj3 (quality or validity)).ab. (87346)

161 (select$ adj3 (study or studies)).ab. (72224)

162 (data adj3 extract$).ab. (70946)

163 extracted data.ab. (15939)

164 (data adj2 abstracted).ab. (5623)

165 (data adj3 abstraction).ab. (1863)

166 published intervention$.ab. (195)

167 ((study or studies) adj2 evaluat$).ab. (200526)

168 (intervention$ adj2 evaluat$).ab. (12336)

169 confidence interval$.ab. (447994)

170 heterogeneity.ab. (180379)

171 pooled.ab. (98438)

172 pooling.ab. (13263)

173 odds ratio$.ab. (291799)

174 (Jadad or coding).ab. (196892)

175 or/140-174 (1578823)

176 139 and 175 (259960)

177 review.ti. (517993)

178 177 and 175 (171799)

179 (review$ adj4 (papers or trials or studies or evidence or intervention$ or evaluation$)).ti,ab. (202936)

180 138 or 176 or 178 or 179 (632718)

181 randomized controlled trial.pt. (521951)

182 controlled clinical trial.pt. (94049)

183 randomized.ab. (510387)

184 placebo.ab. (215580)

185 drug therapy.fs. (2274478)

186 randomly.ab. (351559)

187 trial.ab. (541682)

188 groups.ab. (2157361)

189 or/181-188 (4916506)

190 Epidemiologic studies/ (8545)

191 exp case control studies/ (1138918)

192 exp cohort studies/ (2084575)

193 Case control.tw. (131322)

194 (cohort adj (study or studies)).tw. (227029)

195 Cohort analy$.tw. (8770)

196 (Follow up adj (study or studies)).tw. (50590)

197 (observational adj (study or studies)).tw. (117351)

198 Longitudinal.tw. (260478)

199 Retrospective.tw. (572223)

200 Cross sectional.tw. (382783)

201 Cross-sectional studies/ (351920)

202 or/190-201 (3163261)

203 93 and (110 or 180 or 189 or 202) (3290)

204 exp animals/ not humans/ (4782806)

205 (news or comment or editorial or letter or case reports).pt. (4054155)

206 case report.ti. (251546)

207 203 not (204 or 205 or 206) (3112)

208 limit 207 to english language (2849)

209 limit 208 to yr="2015 -Current" (1396)

1. **Source: Cochrane Database of Systematic Reviews (CDSR)**

Interface / URL: Cochrane Library / Wiley

Database coverage dates: Information not found. Issue searched: Issue 2 of 12, February 2021

Search date: 04/02/2021

Retrieved records: 30

Search strategy:

#1 [mh "Multiple Sclerosis"] 3501

#2 (multiple next scleros\*):ti,ab 9598

#3 ((disseminated next scleros\*) or "sclerosis multiplex" or (insular next scleros\*) or "encephalomyelitis disseminata" or "chariot disease"):ti,ab 10

#4 ms:ti or (rms or rrms or prms or ppms or cpms or spms or rspms):ti,ab 4674

#5 #1 OR #2 OR #3 OR #4 11774

#6 [mh ^"Nervous System Diseases"] 728

#7 ((neurological or neurologic) near/3 (condition\* or disease\* or disorder\*)):ti 247

#8 #6 OR #7 942

#9 #5 OR #8 12657

#10 [mh ^"Patient Care Team"] 1700

#11 (multi next disciplin\* or multidisciplin\*):ti,ab 6253

#12 (inter next disciplin\* or interdisciplin\*):ti,ab 1817

#13 MeSH descriptor: [Urinary Incontinence] explode all trees and with qualifier(s): [nursing - NU] 65

#14 MeSH descriptor: [Fecal Incontinence] this term only and with qualifier(s): [nursing - NU] 26

#15 ((continence or incontinence) near/3 (centre or centres or center or centers or clinic or clinics or service\* or team\* or nurs\* or advisor\*)):ti,ab 225

#16 ((continence or incontinence) near/3 (therap\* or treatment\* or support\*)):ti,ab 998

#17 [mh ^"Physical Therapy Modalities"] 3745

#18 [mh ^"Physical Therapy Specialty"] 120

#19 [mh ^"Physical Therapists"] 117

#20 (physiotherap\* or physio next therap\* or neurophysiotherap\* or neurophysio next therap\*):ti,ab 12426

#21 (physical next therap\* or neurophysical next therap\*):ti,ab 7473

#22 (physical next treatment\* or neurophysical next treatment\*):ti,ab 225

#23 [mh ^"Occupational Therapy"] 775

#24 [mh ^"Occupational Therapists"] 7

#25 (occupational near/3 therap\*):ti,ab 2826

#26 [mh "Dietary Services"] 95

#27 [mh ^Nutritionists] 44

#28 ((diet\* or nutrition\*) near/3 (centre or centres or center or centers or clinic or clinics or service\* or team\*)):ti,ab 822

#29 ((diet\* or nutrition\*) near/3 (therap\* or treatment\* or support\*)):ti,ab 8679

#30 (dietician\* or nutritionist\*):ti,ab 1428

#31 [mh ^"rehabilitation of speech and language disorders"] 0

#32 [mh ^"Speech Therapy"] 268

#33 [mh ^"Language Therapy"] 220

#34 [mh ^"Speech-Language Pathology"] 67

#35 ((speech\* or language\*) near/3 (centre or centres or center or centers or clinic or clinics or service\* or team\*)):ti,ab 190

#36 ((speech\* or language\*) near/3 (therap\* or treatment\* or support\* or training or education)):ti,ab 2640

#37 (slt or slts):ti,ab 405

#38 [mh "Nursing Services"] 1879

#39 ((nurse\* or nursing) near/3 (centre or centres or center or centers or clinic or clinics or service\* or team\*)):ti,ab 2027

#40 [mh ^Rehabilitation] 316

#41 [mh ^"Hospitals, Rehabilitation"] 3

#42 [mh ^"Rehabilitation Centers"] 313

#43 [mh ^"Rehabilitation Nursing"] 55

#44 (rehab\* near/3 (centre or centres or center or centers or clinic or clinics or service\* or team\* or nurs\*)):ti,ab 3232

#45 (rehab\* near/3 (therap\* or treatment\* or support\*)):ti,ab 4457

#46 [mh ^"Neurological Rehabilitation"] 109

#47 (neuro\* next rehab\*):ti,ab 484

#48 neurorehab\*:ti,ab 730

#49 (rehab\* near/6 spasticit\*):ti,ab 95

#50 (reenabl\* or re next enabl\*):ti,ab 1

#51 (reabl\* or re next abl\*):ti,ab 100

#52 [mh ^"Electric Stimulation Therapy"] 1894

#53 (electric\* next stimulation\*):ti,ab 5870

#54 (electrostimulation\* or electro next stimulation\*):ti,ab 594

#55 (fes or fet or fest):ti,ab 1661

#56 (nmes) 715

#57 #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 OR #28 OR #29 OR #30 OR #31 OR #32 OR #33 OR #34 OR #35 OR #36 OR #37 OR #38 OR #39 OR #40 OR #41 OR #42 OR #43 OR #44 OR #45 OR #46 OR #47 OR #48 OR #49 OR #50 OR #51 OR #52 OR #53 OR #54 OR #55 OR #56 62166

#58 #9 and #57 919

#59 MeSH descriptor: [Multiple Sclerosis] explode all trees and with qualifier(s): [nursing - NU] 11

#60 ((multiple sclerosis or ms) near/3 nurs\*):ti,ab 101

#61 ((multiple sclerosis or ms) near/3 champion\*):ti,ab 1

#62 #59 or #60 or #61 110

#63 #58 or #62 1008

#64 [mh ^"mental health services"] or [mh ^"community mental health services"] 1377

#65 ((mental next health\*) near/5 (centre or centres or center or centers or clinic or clinics or service\* or team\* or nurs\*)):ti,ab 3472

#66 ((mental next health\*) near/5 (therap\* or treatment\* or support\*)):ti,ab 2305

#67 [mh ^"Peer Group"] and [mh ^"Social Support"] 245

#68 ((peer or peers) near/5 (support\* or assist\* or help\* or connect\*)):ti,ab 2056

#69 "peer-to-peer":ti,ab 162

#70 [mh ^Neuropsychology] 22

#71 ((neuropsycholog\* or neuro next psycholog\*) near/3 (centre or centres or center or centers or clinic or clinics or service\* or team\*)):ti,ab 31

#72 ((neuropsycholog\* or neuro next psycholog\*) near/3 (therap\* or treatment\* or support\*)):ti,ab 306

#73 neuropsychologist\*:ti,ab 172

#74 [mh ^Psychology] 276

#75 [mh ^"Psychology, Clinical"] 29

#76 (psycholog\* near/3 (centre or centres or center or centers or clinic or clinics or service\* or team\*)):ti,ab 497

#77 (psycholog\* near/3 (therap\* or treatment\* or support\*)):ti,ab 4767

#78 psychologist\*:ti,ab 2728

#79 [mh Counseling] 5479

#80 (counselling or counseling):ti,ab 18792

#81 (counselor\* or counsellor\*):ti,ab 2091

#82 (IAPT or IAPTs) 83

#83 [mh ^"Memory Disorders"] and (centre or centres or center or centers or clinic or clinics or service\* or team\* or support\*):ti,ab 183

#84 ((memory or memories) near/5 (centre or centres or center or centers or clinic or clinics or service\* or team\*)):ti,ab 356

#85 ((memory or memories) near/5 (therap\* or treatment\* or support\*)):ti,ab 1471

#86 [mh ^"Cognitive Behavioral Therapy"] 8234

#87 ((cognitive next behavior\* or cognitive next behaviour\*) near/3 (therap\* or treatment\* or psychotherap\*)):ti,ab 13329

#88 ((cognitive or cognition) near/3 (therap\* or treatment\* or psychotherap\*)):ti,ab 18667

#89 (cbt or cbts):ti,ab 8433

#90 64 OR #65 OR #66 OR #67 OR #68 OR #69 OR #70 OR #71 OR #72 OR #73 OR #74 OR #75 OR #76 OR #77 OR #78 OR #79 OR #80 OR #81 OR #82 OR #83 OR #84 OR #85 OR #86 OR #87 OR #88 OR #89 143515

#91 #9 and #90 1193

#92 #63 or #91 2069

#93 #92 with Cochrane Library publication date Between Jan 2015 and Feb 2021, in Cochrane Reviews, Cochrane Protocols 30

Search notes:

Reflecting the pragmatic review context, a number of pragmatic decisions were made when translating the MEDLINE strategy for use in CDSR. These included:

* Free text searches were restricted to the title and abstract fields – rather than leaving unrestricted, or restricting to the title, abstract and keyword fields.
* The free text search on non-specific neuromuscular disorder terms was further restricted to the title field only.

1. **Source: Cochrane Central Register of Controlled Trials**

Interface / URL: Cochrane Library / Wiley

Database coverage dates: Information not found. Issue searched: Issue 2 of 12, February 2021

Search date: 04/02/2021

Retrieved records: 707

Search strategy:

#1 [mh "Multiple Sclerosis"] 3501

#2 (multiple next scleros\*):ti,ab 9598

#3 ((disseminated next scleros\*) or "sclerosis multiplex" or (insular next scleros\*) or "encephalomyelitis disseminata" or "chariot disease"):ti,ab 10

#4 ms:ti or (rms or rrms or prms or ppms or cpms or spms or rspms):ti,ab 4674

#5 #1 OR #2 OR #3 OR #4 11774

#6 [mh ^"Nervous System Diseases"] 728

#7 ((neurological or neurologic) near/3 (condition\* or disease\* or disorder\*)):ti 247

#8 #6 OR #7 942

#9 #5 OR #8 12657

#10 [mh ^"Patient Care Team"] 1700

#11 (multi next disciplin\* or multidisciplin\*):ti,ab 6253

#12 (inter next disciplin\* or interdisciplin\*):ti,ab 1817

#13 MeSH descriptor: [Urinary Incontinence] explode all trees and with qualifier(s): [nursing - NU] 65

#14 MeSH descriptor: [Fecal Incontinence] this term only and with qualifier(s): [nursing - NU] 26

#15 ((continence or incontinence) near/3 (centre or centres or center or centers or clinic or clinics or service\* or team\* or nurs\* or advisor\*)):ti,ab 225

#16 ((continence or incontinence) near/3 (therap\* or treatment\* or support\*)):ti,ab 998

#17 [mh ^"Physical Therapy Modalities"] 3745

#18 [mh ^"Physical Therapy Specialty"] 120

#19 [mh ^"Physical Therapists"] 117

#20 (physiotherap\* or physio next therap\* or neurophysiotherap\* or neurophysio next therap\*):ti,ab 12426

#21 (physical next therap\* or neurophysical next therap\*):ti,ab 7473

#22 (physical next treatment\* or neurophysical next treatment\*):ti,ab 225

#23 [mh ^"Occupational Therapy"] 775

#24 [mh ^"Occupational Therapists"] 7

#25 (occupational near/3 therap\*):ti,ab 2826

#26 [mh "Dietary Services"] 95

#27 [mh ^Nutritionists] 44

#28 ((diet\* or nutrition\*) near/3 (centre or centres or center or centers or clinic or clinics or service\* or team\*)):ti,ab 822

#29 ((diet\* or nutrition\*) near/3 (therap\* or treatment\* or support\*)):ti,ab 8679

#30 (dietician\* or nutritionist\*):ti,ab 1428

#31 [mh ^"rehabilitation of speech and language disorders"] 0

#32 [mh ^"Speech Therapy"] 268

#33 [mh ^"Language Therapy"] 220

#34 [mh ^"Speech-Language Pathology"] 67

#35 ((speech\* or language\*) near/3 (centre or centres or center or centers or clinic or clinics or service\* or team\*)):ti,ab 190

#36 ((speech\* or language\*) near/3 (therap\* or treatment\* or support\* or training or education)):ti,ab 2640

#37 (slt or slts):ti,ab 405

#38 [mh "Nursing Services"] 1879

#39 ((nurse\* or nursing) near/3 (centre or centres or center or centers or clinic or clinics or service\* or team\*)):ti,ab 2027

#40 [mh ^Rehabilitation] 316

#41 [mh ^"Hospitals, Rehabilitation"] 3

#42 [mh ^"Rehabilitation Centers"] 313

#43 [mh ^"Rehabilitation Nursing"] 55

#44 (rehab\* near/3 (centre or centres or center or centers or clinic or clinics or service\* or team\* or nurs\*)):ti,ab 3232

#45 (rehab\* near/3 (therap\* or treatment\* or support\*)):ti,ab 4457

#46 [mh ^"Neurological Rehabilitation"] 109

#47 (neuro\* next rehab\*):ti,ab 484

#48 neurorehab\*:ti,ab 730

#49 (rehab\* near/6 spasticit\*):ti,ab 95

#50 (reenabl\* or re next enabl\*):ti,ab 1

#51 (reabl\* or re next abl\*):ti,ab 100

#52 [mh ^"Electric Stimulation Therapy"] 1894

#53 (electric\* next stimulation\*):ti,ab 5870

#54 (electrostimulation\* or electro next stimulation\*):ti,ab 594

#55 (fes or fet or fest):ti,ab 1661

#56 (nmes) 715

#57 #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 OR #28 OR #29 OR #30 OR #31 OR #32 OR #33 OR #34 OR #35 OR #36 OR #37 OR #38 OR #39 OR #40 OR #41 OR #42 OR #43 OR #44 OR #45 OR #46 OR #47 OR #48 OR #49 OR #50 OR #51 OR #52 OR #53 OR #54 OR #55 OR #56 62166

#58 #9 and #57 919

#59 MeSH descriptor: [Multiple Sclerosis] explode all trees and with qualifier(s): [nursing - NU] 11

#60 ((multiple sclerosis or ms) near/3 nurs\*):ti,ab 101

#61 ((multiple sclerosis or ms) near/3 champion\*):ti,ab 1

#62 #59 or #60 or #61 110

#63 #58 or #62 1008

#64 [mh ^"mental health services"] or [mh ^"community mental health services"] 1377

#65 ((mental next health\*) near/5 (centre or centres or center or centers or clinic or clinics or service\* or team\* or nurs\*)):ti,ab 3472

#66 ((mental next health\*) near/5 (therap\* or treatment\* or support\*)):ti,ab 2305

#67 [mh ^"Peer Group"] and [mh ^"Social Support"] 245

#68 ((peer or peers) near/5 (support\* or assist\* or help\* or connect\*)):ti,ab 2056

#69 "peer-to-peer":ti,ab 162

#70 [mh ^Neuropsychology] 22

#71 ((neuropsycholog\* or neuro next psycholog\*) near/3 (centre or centres or center or centers or clinic or clinics or service\* or team\*)):ti,ab 31

#72 ((neuropsycholog\* or neuro next psycholog\*) near/3 (therap\* or treatment\* or support\*)):ti,ab 306

#73 neuropsychologist\*:ti,ab 172

#74 [mh ^Psychology] 276

#75 [mh ^"Psychology, Clinical"] 29

#76 (psycholog\* near/3 (centre or centres or center or centers or clinic or clinics or service\* or team\*)):ti,ab 497

#77 (psycholog\* near/3 (therap\* or treatment\* or support\*)):ti,ab 4767

#78 psychologist\*:ti,ab 2728

#79 [mh Counseling] 5479

#80 (counselling or counseling):ti,ab 18792

#81 (counselor\* or counsellor\*):ti,ab 2091

#82 (IAPT or IAPTs) 83

#83 [mh ^"Memory Disorders"] and (centre or centres or center or centers or clinic or clinics or service\* or team\* or support\*):ti,ab 183

#84 ((memory or memories) near/5 (centre or centres or center or centers or clinic or clinics or service\* or team\*)):ti,ab 356

#85 ((memory or memories) near/5 (therap\* or treatment\* or support\*)):ti,ab 1471

#86 [mh ^"Cognitive Behavioral Therapy"] 8234

#87 ((cognitive next behavior\* or cognitive next behaviour\*) near/3 (therap\* or treatment\* or psychotherap\*)):ti,ab 13329

#88 ((cognitive or cognition) near/3 (therap\* or treatment\* or psychotherap\*)):ti,ab 18667

#89 (cbt or cbts):ti,ab 8433

#90 64 OR #65 OR #66 OR #67 OR #68 OR #69 OR #70 OR #71 OR #72 OR #73 OR #74 OR #75 OR #76 OR #77 OR #78 OR #79 OR #80 OR #81 OR #82 OR #83 OR #84 OR #85 OR #86 OR #87 OR #88 OR #89 143515

#91 #9 and #90 1193

#92 #63 or #91 2069

#93 #92 with Publication Year from 2015 to 2021, in Trials 1044

#94 (clinicaltrials or trialsearch):so 353838

#95 #93 not #94 707

Search notes:

Reflecting the pragmatic review context, a number of pragmatic decisions were made when translating the MEDLINE strategy for use in CENTRAL. These included:

* Free text searches were restricted to the title and abstract fields – rather than leaving unrestricted, or restricting to the title, abstract and keyword fields.
* The free text search on non-specific neuromuscular disorder terms was further restricted to the title field only.
* The search was designed to exclude records from trials registers using the syntax NOT (clinicaltrials or trialsearch):so.

1. **Source: Econlit**

Interface / URL: OvidSP

Database coverage dates: 1886 to January 21,2021

Search date: 04/02/2021

Retrieved records: 18

Search strategy:

1 multiple scleros$.af. (53)

2 (disseminated scleros$ or sclerosis multiplex or insular scleros$ or encephalomyelitis disseminata or chariot disease).af. (0)

3 ((neurological or neurologic) adj3 (condition$1 or disease$1 or disorder$1)).af. (26)

4 or/1-3 (77)

5 limit 4 to english (76)

6 limit 5 to yr="2015 -Current" (18)

Search note: reflecting the pragmatic review context, condition abbreviations (for example *ms*) were not included in the EconLit search.

1. **Source: HTA Database**

Interface / URL: <https://database.inahta.org/>

Database coverage dates: Information not found. The former database was produced by the CRD until March 2018, at which time the addition of records was stopped as INAHTA was in the process of rebuilding the new database platform. In July 2019, the database records were exported from the CRD platform and imported into the new platform that was developed by INAHTA. The rebuild of the new platform was launched in June 2020.

Search date: 04/02/2021

Retrieved records: 51

Search strategy:

9 #8 AND #7 51

8 \* FROM 2015 TO 2021 2787

7 #6 OR #5 OR #4 OR #3 OR #2 OR #1 261

6 ((neurological OR neurologic) AND (condition OR conditions OR disease OR diseases OR disorder OR disorders)) 118

5 "Nervous System Diseases"[mh] 26

4 rms OR rrms OR prms OR ppms OR cpms OR spms OR rspms 16

3 "disseminated sclerosis" OR "disseminated scleroses" OR "sclerosis multiplex" OR "insular sclerosis" OR "insular scleroses" OR "encephalomyelitis disseminata" OR "chariot disease" 0

2 "multiple sclerosis" OR "multiple scleroses" 126

1 "Multiple Sclerosis"[mhe] 81

Search note: in the HTA Database it is not possible to search on terms of two characters. The term *ms* was therefore not included in the search.

1. **Source: Epistemonikos**

Interface / URL: <https://www.epistemonikos.org/>

Database coverage dates: Information not found.

Search date: 05/02/2021

Retrieved records: 246

Search strategy:

The following 8 searches were conducted separately. The searches were conducted using the Advanced search interface at <https://www.epistemonikos.org/en/advanced_search>.

For each search the Filter options from the results page were used to limit the results. A custom year range of 2015-2021 was applied for "Publication Year". Results were limited by "Publication type" to systematic review.

7 of the searches retrieved results. The 7 sets of results (323 in total) were downloaded and imported into an empty ENL. Records were deduplicated using EndNote default settings. 77 records were removed as duplicates. The remaining 246 records were retrieved for assessment.

Search 1. The following terms were entered into the field restricted 'Query' search box, with the field restrictions set to 'Title/Abstract'

(("multiple sclerosis" OR "multiple scleroses" OR "disseminated sclerosis" OR "disseminated scleroses" OR "sclerosis multiplex" OR "insular sclerosis" OR "insular scleroses" OR "encephalomyelitis disseminata" OR "chariot disease") AND ("multi-disciplinary" OR "multi-discipline" OR multidisciplin\* OR "inter-disciplinary" "inter-discipline" OR interdisciplin\* OR physiotherap\* OR "physio-therapy" OR "physio-therapies" OR "physio-therapist" OR "physio-therapists" OR neurophysiotherap\* OR "neurophysio-therapy" OR "neurophysio-therapies" OR "neurophysio-therapist" OR "neurophysio-therapists" OR "physical therapy" OR "physical therapies" OR "physical therapist" OR "physical therapists" OR "neurophysical therapy" OR "neurophysical therapies" OR "neurophysical therapist" OR "neurophysical therapists" OR "physical treatment" OR "physical treatments" OR "neurophysical treatment" OR "neurophysical treatments")) = 39

Search 2. The following terms were entered into the field restricted 'Query' search box, with the field restrictions set to 'Title/Abstract'

(("multiple sclerosis" OR "multiple scleroses" OR "disseminated sclerosis" OR "disseminated scleroses" OR "sclerosis multiplex" OR "insular sclerosis" OR "insular scleroses" OR "encephalomyelitis disseminata" OR "chariot disease") AND ("occupational therapy" OR "occupational therapies" OR "occupational therapist" OR "occupational therapists" OR dietician\* OR nutritionist\* OR slt OR slts OR "neuro rehab" OR "neuro rehabilitation" OR "neurological rehab" OR "neurological rehabilitation" OR neurorehab\* OR "rehabilitation spasticity" OR reenabl\* OR "re-enable" OR "re-enables" OR "re-enabled" OR "re-enabling" OR reabl\* OR "re-able" OR "re-ables" OR "re-abled" OR "re-abling" OR "electric stimulation" OR "electric stimulations" OR "electrical stimulation" OR "electrical stimulations" OR electrostimulation\* OR "electro-stimulation" OR "electro-stimulations" OR fes OR fet OR fest OR nmes OR peer OR peers OR neuropsychologist\* OR psychologist\* OR counselling OR counseling OR counselor\* OR counsellor\* OR IAPT OR IAPTs OR "cognitive behavior" OR "cognitive behaviour" OR cbt OR cbts)) = 51

Search 3. The following terms were entered into the field restricted search box, with the field restrictions set to 'Title':

((neurological OR neurologic) AND (condition\* or disease\* or disorder\*))

The above line was combined using the AND option with the following terms, which were entered into the field restricted search box, with the field restrictions set to 'Title/Abstract':

(("multi-disciplinary" OR "multi-discipline" OR multidisciplin\* OR "inter-disciplinary" "inter-discipline" OR interdisciplin\* OR physiotherap\* OR "physio-therapy" OR "physio-therapies" OR "physio-therapist" OR "physio-therapists" OR neurophysiotherap\* OR "neurophysio-therapy" OR "neurophysio-therapies" OR "neurophysio-therapist" OR "neurophysio-therapists" OR "physical therapy" OR "physical therapies" OR "physical therapist" OR "physical therapists" OR "neurophysical therapy" OR "neurophysical therapies" OR "neurophysical therapist" OR "neurophysical therapists" OR "physical treatment" OR "physical treatments" OR "neurophysical treatment" OR "neurophysical treatments" OR "occupational therapy" OR "occupational therapies" OR "occupational therapist" OR "occupational therapists" OR dietician\* OR nutritionist\* OR slt OR slts OR "neuro rehab" OR "neuro rehabilitation" OR "neurological rehab" OR "neurological rehabilitation" OR neurorehab\* OR "rehabilitation spasticity" OR reenabl\* OR "re-enable" OR "re-enables" OR "re-enabled" OR "re-enabling" OR reabl\* OR "re-able" OR "re-ables" OR "re-abled" OR "re-abling" OR "electric stimulation" OR "electric stimulations" OR "electrical stimulation" OR "electrical stimulations" OR electrostimulation\* OR "electro-stimulation" OR "electro-stimulations" OR fes OR fet OR fest OR nmes OR peer OR peers OR neuropsychologist\* OR psychologist\* OR counselling OR counseling OR counselor\* OR counsellor\* OR IAPT OR IAPTs OR "cognitive behavior" OR "cognitive behaviour" OR cbt OR cbts)) = 25

Search 4. The following terms were entered into the field restricted search box, with the field restrictions set to 'Title/Abstract'

(("multiple sclerosis" OR "multiple scleroses" OR "disseminated sclerosis" OR "disseminated scleroses" OR "sclerosis multiplex" OR "insular sclerosis" OR "insular scleroses" OR "encephalomyelitis disseminata" OR "chariot disease") AND (continence OR incontinence OR diet\* OR nutrition\* OR speech\* OR language\* OR rehab\* OR "mental health" OR "mental healthcare" OR neuropsycholog\* OR psycholog\* OR memory OR memories) AND (centre OR centres OR center OR centers OR clinic OR clinics OR service OR services OR team OR teams OR nurs\* OR advisor\* OR therap\* OR treatment\* OR support\* OR training OR education)) = 156

Search 5. The following terms were entered into the field restricted search box, with the field restrictions set to 'Title':

((neurological OR neurologic) AND (condition\* or disease\* or disorder\*))

The above line was combined using the AND option with the following terms, which were entered into the field restricted search box, with the field restrictions set to 'Title/Abstract':

((continence OR incontinence OR diet\* OR nutrition\* OR speech\* OR language\* OR rehab\* OR "mental health" OR "mental healthcare" OR neuropsycholog\* OR psycholog\* OR memory OR memories) AND (centre OR centres OR center OR centers OR clinic OR clinics OR service OR services OR team OR teams OR nurs\* OR advisor\* OR therap\* OR treatment\* OR support\* OR training OR education)) = 46

Search 6. The following terms were entered into the field restricted search box, with the field restrictions set to 'Title/Abstract'

("ms nurse" OR "ms nurses" OR "ms champion" OR "ms champions" OR "multiple sclerosis nurse" OR "multiple sclerosis nurses" OR "multiple sclerosis champion" OR "multiple sclerosis champions") = 0

Search 7. The following terms were entered into the field restricted search box, with the field restrictions set to 'Title/Abstract'

(("multiple sclerosis" OR "multiple scleroses" OR "disseminated sclerosis" OR "disseminated scleroses" OR "sclerosis multiplex" OR "insular sclerosis" OR "insular scleroses" OR "encephalomyelitis disseminata" OR "chariot disease") AND (nurse\* OR nursing) AND (centre OR centres OR center OR centers OR clinic OR clinics OR service\* OR team\*)) = 2

Search 8. The following terms were entered into the field restricted search box, with the field restrictions set to 'Title':

((neurological OR neurologic) AND (condition\* or disease\* or disorder\*))

The above line was combined using the AND option with the following terms, which were entered into the field restricted search box, with the field restrictions set to 'Title/Abstract':

((nurse\* OR nursing) AND (centre OR centres OR center OR centers OR clinic OR clinics OR service\* OR team\*)) = 4

Search notes:

Epistemonikos has relatively limited search functionality. Reflecting the pragmatic review context, the strategy does not attempt to achieve a 'comprehensive' translation of the MEDLINE strategy. A number of pragmatic decisions were made when translating the MEDLINE strategy for use in Epistemonikos. These included:

* Searches were restricted to the title and abstract fields – rather than searching without field restrictions.
* The free text search on non-specific neuromuscular disorder terms was further restricted to the title field only.
* Abbreviations for multiple sclerosis (e.g. *ms*) were not searched on.

The interface was unable to process long search strings – it was not possible to apply filters or export results from searches with long strings. Multiple shorter searches were therefore run.

1. **Source: Social Care Online**

Interface / URL: https://www.scie-socialcareonline.org.uk/

Database coverage dates: Updated daily and contains records from the 1980s onwards

Search date: 05/02/2021

Retrieved records: 78

Search strategy:

The following 2 searches were conducted separately using the Advanced search interface at: <https://www.scie-socialcareonline.org.uk/search/expert>

Search 1. Each of the following terms was entered into a separate search box. For the topic terms, the default 'All fields' search was left selected. The topic terms were combined with Boolean OR using the drop-down Boolean options. Then topic terms were then combined with Boolean AND using the publication year field, restricted to 2015 – 2021.

"multiple sclerosis" OR "multiple scleroses" OR "disseminated sclerosis" OR "disseminated scleroses" OR "sclerosis multiplex" OR "insular sclerosis" OR "insular scleroses" OR "encephalomyelitis disseminata" OR "chariot disease" OR ms OR rms OR rrms OR prms OR ppms OR cpms OR spms OR rspms = 22

Search 2. Each of the following terms was entered into a separate search box. For the topic terms, the default 'All fields' search was left selected. The topic terms were combined with Boolean OR using the drop-down Boolean options. Then topic terms were then combined with Boolean AND using the publication year field, restricted to 2015 – 2021.

neurological OR neurologic = 56

Appendix B: Literature Search Methods for DMTs

The search methods (including search strategy and selection of search resources) reflected the pragmatic review context. The methods were designed to enable searches and study assessment to be completed within project resources and timelines. The pragmatic search approach was discussed and agreed within the research team and with the MS Society.

**SEARCH STRATEGY**

A MEDLINE (OvidSP) search strategy was designed to identify economic evaluations and systematic reviews of the eligible interventions in patients with MS. The final MEDLINE strategy is presented in Figure B1.

The strategy comprised four concepts:

1. MS (search lines 1 to 5).
2. Eligible interventions (search lines 6 to 75).
3. Economic evaluations (search lines 77 to 93).
4. Systematic reviews (search lines 94 to 163).

The concepts were combined as follows: MS AND eligible interventions AND (economic evaluations OR systematic reviews).

The strategy was devised using a combination of subject indexing terms and free text search terms in the Title, Abstract, Keyword Heading Word, Registry Number and Name of Substance fields.

The search terms for the economic evaluations concept (search lines 77 to 93) were based on the filter developed by the University of York Centre for Reviews and Dissemination (CRD) to identify economic evaluations to include in NHS Economic Evaluation Database (NHS EED)[[13]](#footnote-14).

The search terms for the SR concept (search lines 94 to 163) were based on the filter developed by the University of York CRD to identify systematic reviews to include in the Database of Abstracts of Reviews of Effects (DARE)[[14]](#footnote-15).

The strategy excluded animal studies from MEDLINE using a standard algorithm (search line 167). The strategy also excluded some publication types which were unlikely to yield relevant study reports (news items, comments, editorials, letters and case reports) and records with the phrase 'case report' in the title (search lines 168 to 169).

The strategy was restricted to studies published in English language from 2015 to date. The date and language restrictions reflected the eligibility criteria.

The final Ovid MEDLINE strategy was peer-reviewed by a second Information Specialist for errors in spelling, syntax and line combinations.

**Figure B.1: Search strategy for MEDLINE ALL**

1 exp Multiple Sclerosis/ (60183)

2 multiple scleros$.ti,ab,kf. (78842)

3 (disseminated scleros$ or sclerosis multiplex or insular scleros$ or encephalomyelitis disseminata or chariot disease).ti,ab,kf. (768)

4 (ms or rms or rrms or prms or ppms or cpms or spms or rspms).ti,ab,kf. (370552)

5 or/1-4 (413822)

6 Alemtuzumab/ (2018)

7 alemtuzumab$.ti,ab,kf,rn,nm. (3237)

8 (campath$ or cd52 monoclonal antibod$ or ldp 103 or "ldp 03" or ldp103 or ldp03 or lemtrada$2 or mabcampath$2 or monoclonal antibody cd52).ti,ab,kf,rn,nm. (938)

9 (216503-57-0 or 3a189dh42v).ti,ab,kf,rn,nm. (2019)

10 or/6-9 (3609)

11 exp Interferon-beta/ (9654)

12 (interferon$ adj3 beta$).ti,ab,kf,rn,nm. (18764)

13 (actoferon$2 or avonex$2 or beneseron$2 or bene seron$ or betaseron$2 or beta seron$2 or betaferon$2 or beta-feron$2 or betaifn$ or beta-ifn$ or blastoferon$2 or cinnovex$2 or extavia$2 or fibroblast interferon$ or ifnb$ or ifn-beta$ or neoferon$2 or plegridy$2 or rebif$2 or rifn beta$ or sh 579 or sh579 or uribeta$2 or zk 157046 or zk157046).ti,ab,kf,rn,nm. (11985)

14 (145155-23-3 or 145258-61-3 or 90598-63-3 or ttd90r31wz or xro4566q4r or 77238-31-4).ti,ab,kf,rn,nm. (9655)

15 or/11-14 (22987)

16 Cladribine/ (1525)

17 cladribine$.ti,ab,kf,rn,nm. (2117)

18 (2cda$2 or 2clado$2 or 2-clado$2 or ai bo ding$2 or biodribin$2 or cda or chlorodeoxyadenosine or cladribin$2 or cladribina$2 or cladribinum$2 or cldado$2 or hemobine$2 or intocel$2 or leustat$2 or leustatin$2 or leustatine$2 or litak$2 or litax$2 or mavenclad$2 or movectro$2 or mylinax$2 or rwj 26251$2 or rwj26251$2).ti,ab,kf,rn,nm. (4767)

19 (chloro adj3 (deoxyadenosine or deoxy-adenosine or deoxy-beta-adenosine or deoxybetaadenosine or deoxy-betaadenosine)).ti,ab,kf,rn,nm. (330)

20 (deoxy adj3 chloroadenosine).ti,ab,kf,rn,nm. (8)

21 (4291-63-8 or 47m74x9yt5).ti,ab,kf,rn,nm. (1526)

22 or/16-21 (4840)

23 Dimethyl Fumarate/ (731)

24 dimethyl fumarate$.ti,ab,kf,rn,nm. (1305)

25 (azl o 211089 or "bg 00012" or bg 12 or bg00012 or bg12 or dimethyl ester fumaric acid$1 or dimethyl trans-ethylenedicarboxylate$1 or dimethyl transethylenedicarboxylate$1 or dimethylfumarate$1 or dmf or fag 201 or fag201 or fp187 or fp-187 or fumaderm$2 or fumaric acid dimethyl ester$1 or panaclar$2 or tecfidera$2 or trans butenedioic acid dimethyl ester$1).ti,ab,kf,rn,nm. (8834)

26 (dimethyl adj3 butenedioate$1).ti,ab,kf,rn,nm. (4)

27 (210-849-0 or 624-49-7 or fo2303mni2).ti,ab,kf,rn,nm. (732)

28 or/23-27 (9405)

29 Fingolimod Hydrochloride/ (2234)

30 fingolimod$.ti,ab,kf,rn,nm. (3157)

31 (fingolimob$ or fingolimodum$ or fty 720$ or fty720$ or gilenia$2 or gilenya$2).ti,ab,kf,rn,nm. (1850)

32 (162359-55-9 or 162359-56-0 or 3qn8byn5qf or g926ec510t).ti,ab,kf,rn,nm. (2235)

33 or/29-32 (3579)

34 Glatiramer Acetate/ (1369)

35 glatiramer$.ti,ab,kf,rn,nm. (2172)

36 (cop1 or cop-1 or copaxone$2 or copolymer1 or copolymer-1 or copolymeri or copolymer-I or cpx or glatopa$2 or tv5010$2 or tv-5010$2).ti,ab,kf,rn,nm. (2609)

37 (147245-92-9 or 28704-27-0 or 5m691hl4bo).ti,ab,kf,rn,nm. (1506)

38 or/34-37 (4509)

39 Natalizumab/ (1627)

40 natalizumab$.ti,ab,kf,rn,nm. (2695)

41 (an 100226 or an100226 or antegren$2 or anti-alpha4 integrin or anti-vla4 or tysabri$2).ti,ab,kf,rn,nm. (308)

42 (189261-10-7 or 3jb47n2q2p).ti,ab,kf,rn,nm. (1)

43 or/39-42 (2801)

44 antibodies, monoclonal/ or antibodies, monoclonal, humanized/ (211205)

45 ocrelizumab$.ti,ab,kf,rn,nm. (440)

46 (monoclonal antibody 2h7 or pro 70769 or pro70769 or ocrevus$2 or pr070769 or rhumab 2h7).ti,ab,kf,rn,nm. (27)

47 (637334-45-3 or a10sjl62jy).ti,ab,kf,rn,nm. (148)

48 or/44-47 (211440)

49 Polyethylene Glycols/ (55530)

50 (pegylated adj3 interferon$).ti,ab,kf,rn,nm. (6444)

51 (bms-914143 or hanferon$2 or peg ifn$ or pegasys$2 or pegetron$2 or pegifn$ or peg-il-29 or peginterferon$ or peg-interferon$ or pegintron$2 or peg-ril-29 or pegyinterferon$ or ro 25-8310$ or sylatron$2 or victrelis triple$2).ti,ab,kf,rn,nm. (8260)

52 (198153-51-4 or 215647-85-1 or 914617-98-4 or g8rgg88b68 or q46947fe7k or 0t0250n43u).ti,ab,kf,rn,nm. (5453)

53 or/49-52 (60318)

54 siponimod$.ti,ab,kf,rn,nm. (131)

55 (baf312$ or baf-312$ or mayzent$2 or nvpbaf$ or nvp-baf$).ti,ab,kf,rn,nm. (45)

56 (1230487-00-9 or 1230487-85-0 or 1234627-85-0 or rr6p8l282i).ti,ab,kf,rn,nm. (60)

57 or/54-56 (136)

58 Toluidines/ (1910)

59 Crotonates/ (642)

60 teriflunomide$.ti,ab,kf,rn,nm. (582)

61 (a 771726 or a 77-1726 or a77 1726 or a771726 or a77-1726 or aubagio$2 or hmr 1726 or hmr1726 or leflunomide related compound b or leflunomide specified impurity b or rs 61980 or rs61980 or "su 0020" or su0020 or teriflunomida or teriflunomidum).ti,ab,kf,rn,nm. (270)

62 (108605-62-5 or 163451-81-8 or 1c058ikg3b or 282716-73-8).ti,ab,kf,rn,nm. (399)

63 or/58-62 (2824)

64 exp Hematopoietic Stem Cell Transplantation/ (46565)

65 ((stem cell$1 or hsc) adj (transplant$ or graft$ or transfer$ or transfus$ or therap$ or treatment$)).ti,ab,kf. (60967)

66 (hsct or hscts).ti,ab,kf. (13026)

67 (allohsct or allohscts or autohsct or autohscts).ti,ab,kf. (328)

68 or/64-67 (81416)

69 Sphingosine 1 Phosphate Receptor Modulators/ (45)

70 Receptors, Lysosphingolipid/ (1899)

71 ozanimod$.ti,ab,kf,rn,nm. (85)

72 (rpc1063$2 or rpc-1063$2 or zeposia$2).ti,ab,kf,rn,nm. (12)

73 (1306760-87-1 or 1618636-37-5 or 3upr33jaam or 500g9f4fg8 or z80293urpv).ti,ab,kf,rn,nm. (35)

74 or/69-73 (2004)

75 10 or 15 or 22 or 28 or 33 or 38 or 43 or 48 or 53 or 57 or 63 or 68 or 74 (396803)

76 5 and 75 (15033)

77 Economics/ (27282)

78 exp "costs and cost analysis"/ (241945)

79 Economics, Dental/ (1915)

80 exp economics, hospital/ (24914)

81 Economics, Medical/ (9116)

82 Economics, Nursing/ (4002)

83 Economics, Pharmaceutical/ (2969)

84 (economic$ or cost or costs or costly or costing or price or prices or pricing or pharmacoeconomic$).ti,ab. (842413)

85 (expenditure$ not energy).ti,ab. (31262)

86 value for money.ti,ab. (1803)

87 budget$.ti,ab. (30646)

88 or/77-87 (997038)

89 ((energy or oxygen) adj cost).ti,ab. (4219)

90 (metabolic adj cost).ti,ab. (1479)

91 ((energy or oxygen) adj expenditure).ti,ab. (25917)

92 or/89-91 (30620)

93 88 not 92 (990015)

94 systematic$ review$.ti,ab. (199665)

95 meta-analysis as topic/ (18903)

96 meta-analytic$.ti,ab. (7749)

97 meta-analysis.ti,ab,pt. (193817)

98 metanalysis.ti,ab. (289)

99 metaanalysis.ti,ab. (1670)

100 meta analysis.ti,ab. (165989)

101 meta-synthesis.ti,ab. (976)

102 metasynthesis.ti,ab. (354)

103 meta synthesis.ti,ab. (976)

104 meta-regression.ti,ab. (8842)

105 metaregression.ti,ab. (741)

106 meta regression.ti,ab. (8842)

107 (synthes$ adj3 literature).ti,ab. (4002)

108 (synthes$ adj3 evidence).ti,ab. (12086)

109 integrative review.ti,ab. (3421)

110 data synthesis.ti,ab. (11944)

111 (research synthesis or narrative synthesis).ti,ab. (3960)

112 (systematic study or systematic studies).ti,ab. (12763)

113 (systematic comparison$ or systematic overview$).ti,ab. (3611)

114 evidence based review.ti,ab. (2119)

115 comprehensive review.ti,ab. (17059)

116 critical review.ti,ab. (16563)

117 quantitative review.ti,ab. (704)

118 structured review.ti,ab. (881)

119 realist review.ti,ab. (365)

120 realist synthesis.ti,ab. (242)

121 or/94-120 (385834)

122 review.pt. (2757297)

123 medline.ab. (126666)

124 pubmed.ab. (134818)

125 cochrane.ab. (93658)

126 embase.ab. (104055)

127 cinahl.ab. (30905)

128 psyc?lit.ab. (915)

129 psyc?info.ab. (40206)

130 (literature adj3 search$).ab. (67398)

131 (database$ adj3 search$).ab. (68412)

132 (bibliographic adj3 search$).ab. (2876)

133 (electronic adj3 search$).ab. (24652)

134 (electronic adj3 database$).ab. (33398)

135 (computeri?ed adj3 search$).ab. (3645)

136 (internet adj3 search$).ab. (3523)

137 included studies.ab. (27982)

138 (inclusion adj3 studies).ab. (18402)

139 inclusion criteria.ab. (95593)

140 selection criteria.ab. (31595)

141 predefined criteria.ab. (2097)

142 predetermined criteria.ab. (1104)

143 (assess$ adj3 (quality or validity)).ab. (87312)

144 (select$ adj3 (study or studies)).ab. (72210)

145 (data adj3 extract$).ab. (70979)

146 extracted data.ab. (15960)

147 (data adj2 abstracted).ab. (5630)

148 (data adj3 abstraction).ab. (1860)

149 published intervention$.ab. (195)

150 ((study or studies) adj2 evaluat$).ab. (200307)

151 (intervention$ adj2 evaluat$).ab. (12324)

152 confidence interval$.ab. (447949)

153 heterogeneity.ab. (180294)

154 pooled.ab. (98440)

155 pooling.ab. (13263)

156 odds ratio$.ab. (291743)

157 (Jadad or coding).ab. (196712)

158 or/123-157 (1577972)

159 122 and 158 (259854)

160 review.ti. (517630)

161 160 and 158 (171678)

162 (review$ adj4 (papers or trials or studies or evidence or intervention$ or evaluation$)).ti,ab. (202848)

163 121 or 159 or 161 or 162 (632363)

164 76 and 93 (553)

165 76 and 163 (575)

166 164 or 165 (1066)

167 exp animals/ not humans/ (4780931)

168 (news or comment or editorial or letter or case reports).pt. (4053506)

169 case report.ti. (251424)

170 166 not (167 or 168 or 169) (982)

171 limit 170 to english language (935)

172 limit 171 to yr="2015 -Current" (435)

Key to Ovid symbols and commands

$ Unlimited right-hand truncation symbol

$N Limited right-hand truncation - restricts the number of characters following the word to N

? Wildcard symbol

ti,ab,kf,rn,nm Searches are restricted to the Title (ti), Abstract (ab), Keyword Heading Word (kf), Registry Number/Name of Substance (rn) and Name of Substance Word (nm) fields

adj Retrieves records that contain terms next to each other (in the shown order)

adjN Retrieves records that contain terms (in any order) within a specified number (N) of words of each other

/ Searches are restricted to the Subject Heading field

exp The subject heading is exploded

pt. Search is restricted to the publication type field

or/1-4 Combines sets 1 to 4 using OR

**RESOURCES SEARCHED**

We conducted the literature search in the databases and information resources shown in Table B.1. The selection of search resources reflected the pragmatic review context.

**Table B.1: Databases and information sources searched**

| **Database / information source** | **Interface / URL** |
| --- | --- |
| MEDLINE ALL | OvidSP |
| Cochrane Database of Systematic Reviews | Cochrane Library / Wiley |
| Epistemonikos | https://www.epistemonikos.org/ |
| HTA Database | https://database.inahta.org/ |
| Econlit | OvidSP |

The Epistemonikos search was restricted by category to systematic reviews.

In addition to searching the above resources, the following supplementary searches were conducted to identify additional eligible studies:

* Economic evaluations referenced by manufacturers in their submissions to NICE were identified.
* UK health technology assessments published by the National Institute of Health Research were checked.
* Reference lists of included studies and relevant systematic reviews were checked.
* An expert in prescribing DMTs was contacted.
* The MS Society and their topic experts were asked to provide details of any additional known relevant studies that they were aware of.

**RUNNING THE SEARCH STRATEGIES AND DOWNLOADING RESULTS**

We conducted searches using each database or resource listed above, translating the agreed Ovid MEDLINE strategy appropriately. Translation included consideration of differences in database interfaces and functionality, in addition to variation in indexing languages and thesauri. Translation reflected the pragmatic review context. Annex B1 contains the full strategies (including search dates) for all sources searched.

Where possible, we downloaded the results of searches in a tagged format and loaded them into bibliographic software (EndNote). The results were deduplicated using several algorithms and the duplicate references held in a separate EndNote database for checking if required. Results from resources that did not allow export in a format compatible with EndNote were saved in Word or Excel documents as appropriate and manually deduplicated.

**Literature Search Results**

The database searches were conducted on 28/01/21. The searches identified 705 records (Table B.2). Following deduplication, 573 records were assessed for relevance.

**Table B.2: Literature search results**

|  |  |
| --- | --- |
| **Resource** | **Number of records identified** |
| **Databases** | |
| MEDLINE ALL | 435 |
| Cochrane Database of Systematic Reviews (CDSR) | 73 |
| HTA Database | 25 |
| Econlit | 13 |
| Epistemonikos | 131 |
| **Total records identified through database searching** | **677** |
| **Other sources** |  |
| Check of manufacturer submissions to NICE | 11 |
| Check of UK health technology assessments published by the National Institute of Health Research | 0 |
| Checking of reference lists of included studies and relevant systematic reviews | 0 |
| Consultation with MS Society for details of any other relevant studies | 17 |
| **Total additional records identified through other sources** | 28 |
| **Total number of records retrieved** | **705** |
| **Total number of records after deduplication** | **573** |

**Annex B1: Search strategies**

1. **Source: MEDLINE ALL**

Interface / URL: OvidSP

Database coverage dates: 1946 to January 26, 2021

Search date: 28/01/2021

Retrieved records: 435

Search strategy:

1 exp Multiple Sclerosis/ (60183)

2 multiple scleros$.ti,ab,kf. (78842)

3 (disseminated scleros$ or sclerosis multiplex or insular scleros$ or encephalomyelitis disseminata or chariot disease).ti,ab,kf. (768)

4 (ms or rms or rrms or prms or ppms or cpms or spms or rspms).ti,ab,kf. (370552)

5 or/1-4 (413822)

6 Alemtuzumab/ (2018)

7 alemtuzumab$.ti,ab,kf,rn,nm. (3237)

8 (campath$ or cd52 monoclonal antibod$ or ldp 103 or "ldp 03" or ldp103 or ldp03 or lemtrada$2 or mabcampath$2 or monoclonal antibody cd52).ti,ab,kf,rn,nm. (938)

9 (216503-57-0 or 3a189dh42v).ti,ab,kf,rn,nm. (2019)

10 or/6-9 (3609)

11 exp Interferon-beta/ (9654)

12 (interferon$ adj3 beta$).ti,ab,kf,rn,nm. (18764)

13 (actoferon$2 or avonex$2 or beneseron$2 or bene seron$ or betaseron$2 or beta seron$2 or betaferon$2 or beta-feron$2 or betaifn$ or beta-ifn$ or blastoferon$2 or cinnovex$2 or extavia$2 or fibroblast interferon$ or ifnb$ or ifn-beta$ or neoferon$2 or plegridy$2 or rebif$2 or rifn beta$ or sh 579 or sh579 or uribeta$2 or zk 157046 or zk157046).ti,ab,kf,rn,nm. (11985)

14 (145155-23-3 or 145258-61-3 or 90598-63-3 or ttd90r31wz or xro4566q4r or 77238-31-4).ti,ab,kf,rn,nm. (9655)

15 or/11-14 (22987)

16 Cladribine/ (1525)

17 cladribine$.ti,ab,kf,rn,nm. (2117)

18 (2cda$2 or 2clado$2 or 2-clado$2 or ai bo ding$2 or biodribin$2 or cda or chlorodeoxyadenosine or cladribin$2 or cladribina$2 or cladribinum$2 or cldado$2 or hemobine$2 or intocel$2 or leustat$2 or leustatin$2 or leustatine$2 or litak$2 or litax$2 or mavenclad$2 or movectro$2 or mylinax$2 or rwj 26251$2 or rwj26251$2).ti,ab,kf,rn,nm. (4767)

19 (chloro adj3 (deoxyadenosine or deoxy-adenosine or deoxy-beta-adenosine or deoxybetaadenosine or deoxy-betaadenosine)).ti,ab,kf,rn,nm. (330)

20 (deoxy adj3 chloroadenosine).ti,ab,kf,rn,nm. (8)

21 (4291-63-8 or 47m74x9yt5).ti,ab,kf,rn,nm. (1526)

22 or/16-21 (4840)

23 Dimethyl Fumarate/ (731)

24 dimethyl fumarate$.ti,ab,kf,rn,nm. (1305)

25 (azl o 211089 or "bg 00012" or bg 12 or bg00012 or bg12 or dimethyl ester fumaric acid$1 or dimethyl trans-ethylenedicarboxylate$1 or dimethyl transethylenedicarboxylate$1 or dimethylfumarate$1 or dmf or fag 201 or fag201 or fp187 or fp-187 or fumaderm$2 or fumaric acid dimethyl ester$1 or panaclar$2 or tecfidera$2 or trans butenedioic acid dimethyl ester$1).ti,ab,kf,rn,nm. (8834)

26 (dimethyl adj3 butenedioate$1).ti,ab,kf,rn,nm. (4)

27 (210-849-0 or 624-49-7 or fo2303mni2).ti,ab,kf,rn,nm. (732)

28 or/23-27 (9405)

29 Fingolimod Hydrochloride/ (2234)

30 fingolimod$.ti,ab,kf,rn,nm. (3157)

31 (fingolimob$ or fingolimodum$ or fty 720$ or fty720$ or gilenia$2 or gilenya$2).ti,ab,kf,rn,nm. (1850)

32 (162359-55-9 or 162359-56-0 or 3qn8byn5qf or g926ec510t).ti,ab,kf,rn,nm. (2235)

33 or/29-32 (3579)

34 Glatiramer Acetate/ (1369)

35 glatiramer$.ti,ab,kf,rn,nm. (2172)

36 (cop1 or cop-1 or copaxone$2 or copolymer1 or copolymer-1 or copolymeri or copolymer-I or cpx or glatopa$2 or tv5010$2 or tv-5010$2).ti,ab,kf,rn,nm. (2609)

37 (147245-92-9 or 28704-27-0 or 5m691hl4bo).ti,ab,kf,rn,nm. (1506)

38 or/34-37 (4509)

39 Natalizumab/ (1627)

40 natalizumab$.ti,ab,kf,rn,nm. (2695)

41 (an 100226 or an100226 or antegren$2 or anti-alpha4 integrin or anti-vla4 or tysabri$2).ti,ab,kf,rn,nm. (308)

42 (189261-10-7 or 3jb47n2q2p).ti,ab,kf,rn,nm. (1)

43 or/39-42 (2801)

44 antibodies, monoclonal/ or antibodies, monoclonal, humanized/ (211205)

45 ocrelizumab$.ti,ab,kf,rn,nm. (440)

46 (monoclonal antibody 2h7 or pro 70769 or pro70769 or ocrevus$2 or pr070769 or rhumab 2h7).ti,ab,kf,rn,nm. (27)

47 (637334-45-3 or a10sjl62jy).ti,ab,kf,rn,nm. (148)

48 or/44-47 (211440)

49 Polyethylene Glycols/ (55530)

50 (pegylated adj3 interferon$).ti,ab,kf,rn,nm. (6444)

51 (bms-914143 or hanferon$2 or peg ifn$ or pegasys$2 or pegetron$2 or pegifn$ or peg-il-29 or peginterferon$ or peg-interferon$ or pegintron$2 or peg-ril-29 or pegyinterferon$ or ro 25-8310$ or sylatron$2 or victrelis triple$2).ti,ab,kf,rn,nm. (8260)

52 (198153-51-4 or 215647-85-1 or 914617-98-4 or g8rgg88b68 or q46947fe7k or 0t0250n43u).ti,ab,kf,rn,nm. (5453)

53 or/49-52 (60318)

54 siponimod$.ti,ab,kf,rn,nm. (131)

55 (baf312$ or baf-312$ or mayzent$2 or nvpbaf$ or nvp-baf$).ti,ab,kf,rn,nm. (45)

56 (1230487-00-9 or 1230487-85-0 or 1234627-85-0 or rr6p8l282i).ti,ab,kf,rn,nm. (60)

57 or/54-56 (136)

58 Toluidines/ (1910)

59 Crotonates/ (642)

60 teriflunomide$.ti,ab,kf,rn,nm. (582)

61 (a 771726 or a 77-1726 or a77 1726 or a771726 or a77-1726 or aubagio$2 or hmr 1726 or hmr1726 or leflunomide related compound b or leflunomide specified impurity b or rs 61980 or rs61980 or "su 0020" or su0020 or teriflunomida or teriflunomidum).ti,ab,kf,rn,nm. (270)

62 (108605-62-5 or 163451-81-8 or 1c058ikg3b or 282716-73-8).ti,ab,kf,rn,nm. (399)

63 or/58-62 (2824)

64 exp Hematopoietic Stem Cell Transplantation/ (46565)

65 ((stem cell$1 or hsc) adj (transplant$ or graft$ or transfer$ or transfus$ or therap$ or treatment$)).ti,ab,kf. (60967)

66 (hsct or hscts).ti,ab,kf. (13026)

67 (allohsct or allohscts or autohsct or autohscts).ti,ab,kf. (328)

68 or/64-67 (81416)

69 Sphingosine 1 Phosphate Receptor Modulators/ (45)

70 Receptors, Lysosphingolipid/ (1899)

71 ozanimod$.ti,ab,kf,rn,nm. (85)

72 (rpc1063$2 or rpc-1063$2 or zeposia$2).ti,ab,kf,rn,nm. (12)

73 (1306760-87-1 or 1618636-37-5 or 3upr33jaam or 500g9f4fg8 or z80293urpv).ti,ab,kf,rn,nm. (35)

74 or/69-73 (2004)

75 10 or 15 or 22 or 28 or 33 or 38 or 43 or 48 or 53 or 57 or 63 or 68 or 74 (396803)

76 5 and 75 (15033)

77 Economics/ (27282)

78 exp "costs and cost analysis"/ (241945)

79 Economics, Dental/ (1915)

80 exp economics, hospital/ (24914)

81 Economics, Medical/ (9116)

82 Economics, Nursing/ (4002)

83 Economics, Pharmaceutical/ (2969)

84 (economic$ or cost or costs or costly or costing or price or prices or pricing or pharmacoeconomic$).ti,ab. (842413)

85 (expenditure$ not energy).ti,ab. (31262)

86 value for money.ti,ab. (1803)

87 budget$.ti,ab. (30646)

88 or/77-87 (997038)

89 ((energy or oxygen) adj cost).ti,ab. (4219)

90 (metabolic adj cost).ti,ab. (1479)

91 ((energy or oxygen) adj expenditure).ti,ab. (25917)

92 or/89-91 (30620)

93 88 not 92 (990015)

94 systematic$ review$.ti,ab. (199665)

95 meta-analysis as topic/ (18903)

96 meta-analytic$.ti,ab. (7749)

97 meta-analysis.ti,ab,pt. (193817)

98 metanalysis.ti,ab. (289)

99 metaanalysis.ti,ab. (1670)

100 meta analysis.ti,ab. (165989)

101 meta-synthesis.ti,ab. (976)

102 metasynthesis.ti,ab. (354)

103 meta synthesis.ti,ab. (976)

104 meta-regression.ti,ab. (8842)

105 metaregression.ti,ab. (741)

106 meta regression.ti,ab. (8842)

107 (synthes$ adj3 literature).ti,ab. (4002)

108 (synthes$ adj3 evidence).ti,ab. (12086)

109 integrative review.ti,ab. (3421)

110 data synthesis.ti,ab. (11944)

111 (research synthesis or narrative synthesis).ti,ab. (3960)

112 (systematic study or systematic studies).ti,ab. (12763)

113 (systematic comparison$ or systematic overview$).ti,ab. (3611)

114 evidence based review.ti,ab. (2119)

115 comprehensive review.ti,ab. (17059)

116 critical review.ti,ab. (16563)

117 quantitative review.ti,ab. (704)

118 structured review.ti,ab. (881)

119 realist review.ti,ab. (365)

120 realist synthesis.ti,ab. (242)

121 or/94-120 (385834)

122 review.pt. (2757297)

123 medline.ab. (126666)

124 pubmed.ab. (134818)

125 cochrane.ab. (93658)

126 embase.ab. (104055)

127 cinahl.ab. (30905)

128 psyc?lit.ab. (915)

129 psyc?info.ab. (40206)

130 (literature adj3 search$).ab. (67398)

131 (database$ adj3 search$).ab. (68412)

132 (bibliographic adj3 search$).ab. (2876)

133 (electronic adj3 search$).ab. (24652)

134 (electronic adj3 database$).ab. (33398)

135 (computeri?ed adj3 search$).ab. (3645)

136 (internet adj3 search$).ab. (3523)

137 included studies.ab. (27982)

138 (inclusion adj3 studies).ab. (18402)

139 inclusion criteria.ab. (95593)

140 selection criteria.ab. (31595)

141 predefined criteria.ab. (2097)

142 predetermined criteria.ab. (1104)

143 (assess$ adj3 (quality or validity)).ab. (87312)

144 (select$ adj3 (study or studies)).ab. (72210)

145 (data adj3 extract$).ab. (70979)

146 extracted data.ab. (15960)

147 (data adj2 abstracted).ab. (5630)

148 (data adj3 abstraction).ab. (1860)

149 published intervention$.ab. (195)

150 ((study or studies) adj2 evaluat$).ab. (200307)

151 (intervention$ adj2 evaluat$).ab. (12324)

152 confidence interval$.ab. (447949)

153 heterogeneity.ab. (180294)

154 pooled.ab. (98440)

155 pooling.ab. (13263)

156 odds ratio$.ab. (291743)

157 (Jadad or coding).ab. (196712)

158 or/123-157 (1577972)

159 122 and 158 (259854)

160 review.ti. (517630)

161 160 and 158 (171678)

162 (review$ adj4 (papers or trials or studies or evidence or intervention$ or evaluation$)).ti,ab. (202848)

163 121 or 159 or 161 or 162 (632363)

164 76 and 93 (553)

165 76 and 163 (575)

166 164 or 165 (1066)

167 exp animals/ not humans/ (4780931)

168 (news or comment or editorial or letter or case reports).pt. (4053506)

169 case report.ti. (251424)

170 166 not (167 or 168 or 169) (982)

171 limit 170 to english language (935)

172 limit 171 to yr="2015 -Current" (435)

1. **Source: Cochrane Database of Systematic Reviews (CDSR)**

Interface / URL: Cochrane Library/Wiley

Database coverage dates: Information not found. Issue searched: Issue 1 of 12, January 2021

Search date: 28/01/2021

Retrieved records: 73

Search strategy:

ID Search Hits

#1 MeSH descriptor: [Multiple Sclerosis] explode all trees 3486

#2 (multiple next scleros\*):ti,ab,kw 10166

#3 ((disseminated next scleros\*) or "sclerosis multiplex" or (insular next scleros\*) or "encephalomyelitis disseminata" or "chariot disease"):ti,ab,kw 10

#4 (ms or rms or rrms or prms or ppms or cpms or spms or rspms):ti,ab,kw 20201

#5 #1 or #2 or #3 or #4 23631

#6 #5 in Cochrane Reviews, Cochrane Protocols 135

#7 #6 with Cochrane Library publication date Between Jan 2015 and Dec 2021 73

1. **Source: HTA Database**

Interface / URL: <https://database.inahta.org/>

Database coverage dates: Information not found. The former database was produced by the CRD until March 2018, at which time the addition of records was stopped as INAHTA was in the process of rebuilding the new database platform. In July 2019, the database records were exported from the CRD platform and imported into the new platform that was developed by INAHTA. The rebuild of the new platform was launched in June 2020.

Search date: 28/01/2021

Retrieved records: 25

Search strategy:

7 #6 AND #5 25

6 \* FROM 2015 TO 2021 2768

5 #4 OR #3 OR #2 OR #1 133

4 rms OR rrms OR prms OR ppms OR cpms OR spms OR rspms 15

3 "disseminated sclerosis" OR "disseminated scleroses" OR "sclerosis multiplex" OR "insular sclerosis" OR "insular scleroses" OR "encephalomyelitis disseminata" OR "chariot disease" 0

2 "multiple sclerosis" OR "multiple scleroses" 124

1 "Multiple Sclerosis"[mhe] 79

Search note: in the HTA Database it is not possible to search on terms of two characters. The term *ms* was therefore not included in the search.

1. **Source: Econlit**

Interface / URL: OvidSP

Database coverage dates: 1886 to January 21,2021

Search date: 28/01/2021

Retrieved records: 13

Search strategy:

1 multiple scleros$.af. (53)

2 (disseminated scleros$ or sclerosis multiplex or insular scleros$ or encephalomyelitis disseminata or chariot disease).af. (0)

3 1 or 2 (53)

4 limit 3 to yr="2015 -Current" (13)

5 limit 4 to english (13)

Search note: reflecting the pragmatic review context, condition abbreviations (for example *ms*) were not included in the EconLit search.

1. **Source: Epistemonikos**

Interface / URL: <https://www.epistemonikos.org/>

Database coverage dates: Information not found.

Search date: 28/01/2021

Retrieved records: 131

Search strategy:

The strategy below was used with the advanced search screen <https://www.epistemonikos.org/en/advanced_search>. The main search box was used, no search field tags were included.

On the results screen, the Filter options were used to limit the results. A custom year range of 2015-2021 was applied for "Publication Year". Results were also limited by "Publication type": systematic review was selected.

("multiple sclerosis" OR "multiple scleroses" OR "disseminated sclerosis" OR "disseminated scleroses" OR "sclerosis multiplex" OR "insular sclerosis" OR "insular scleroses" OR "encephalomyelitis disseminata" OR "chariot disease" OR ms OR rms OR rrms OR prms OR ppms OR cpms OR spms OR rspms) AND (Alemtuzumab\* OR Lemtrada\* OR Avonex\* OR "interferon beta" OR betaferon\* OR Cladribine\* OR Mavenclad\* OR "Dimethyl fumarate" OR "Dimethyl fumarateR" OR "Dimethyl fumarateTM" OR Tecfidera\* OR Extavia\* OR "beta interferon" OR Fingolimod\* OR Gilenya\* OR "Glatiramer acetate" OR "Glatiramer acetateR" OR "Glatiramer acetateTM" OR Copaxone\* OR "haematopoietic stem cell" OR "hematopoietic stem cell" OR HSCT OR Natalizumab\* OR Tysabri\* OR Ocrelizumab\* OR Ocrevus\* OR Plegridy\* OR "peginterferon beta" OR Rebif\* OR Siponimod\* OR Mayzent\* OR Teriflunomide\* OR Aubagio\* OR Ozanimod\* OR "RPC-1063" OR "RPC-1063R" OR "RPC-1063TM" OR Zeposia\*)

Search note: reflecting the pragmatic review context, the drug terms used for the Epistemonikos search were restricted to the main generic and trade name for each eligible drug, as provided on the following MS Society webpage: <https://www.mssociety.org.uk/about-ms/treatments-and-therapies/disease-modifying-therapies>

Appendix C: Papers on Symptoms Management

The literature search sought to identifying evidence on the following symptom management services:

* Multi-disciplinary teams, continence services, physiotherapy services, occupational therapy service, dietician service, speech & language therapy service, MS nurse service, neuro-rehabilitation, re-enablement, functional electrical stimulation, rehabilitation spasticity clinic and rehabilitation. (Note blue font is a symptom management service.)

We also searched for the following mental health services:

* Non-specific mental health support services (including online mental health support), peer support (including online), neuropsychology service (including online), psychologist service (including online), counselling (including online), IAPT (Improving Access to Psychological Therapies), memory loss clinics (including online), and CBT (including online).

The population included adults who have a diagnosis of MS or a non-specific neurological disorder but excluded people with strokes, headaches, infections, seizures, spinal cord disorders and sudden brain injury. We searched for clinical and economic studies including those reporting barriers to service access. We excluded pilot studies, home-based studies and those outside Western Europe, N America and Australia. One key aspect of the search process was to identify evidence on services, not what services should do. Hence, different forms of e.g. neuropsychological assessment or use of goals in neuropsychological rehabilitation were not included. Fifty-five papers met the criteria and these are described in Table C.1. Those with a grey background were selected for data extraction.

**Table C.1: Papers relevant to specific services**

| **Services**  **(number of studies)** | **Studies** | **Type of study** | **Setting** | **Neuro degenerative (ND) or Type of MS** | **Intervention** | **Comparator** | **Country** |
| --- | --- | --- | --- | --- | --- | --- | --- |
| Multi-disciplinary teams  (4) | Jimenez 2019 | Registry data | Interdisciplinary chronic pain rehabilitation programs | Functional Neurological Disorder | Interdisciplinary chronic pain rehabilitation programs | NS | NS |
| Kraft 2020 | Review | Outpatient | MS | Shared decision making | NS | Germany |
| Papeix 2015 | RCT | NS | MS | Integrated multidisciplinary approach | Usual care | NS |
| Pless 2018 | Comparative case study | 4 hospitals | MS | Different approaches to deliver MD care | | NS |
| Continence service  (1) | Castel-Lacanal 2017 | Before and after service evaluation | NS | SPMS | A neuro-urological activity and a care network | Before service | NS |
| Physiotherapy service  (1) | Campbell 2016 | SR | NS | Progressive MS | 8 interventions: exercise, multidisciplinary rehabilitation, FES, botox, muscle training, therapeutic standing, acupuncture, weights &treadmill | Each has separate comparators | NS |
| Occupational therapy service  (2) | Campbell 2017 | Survey using MS registry | NHS physio services | Progressive MS | Access to clinics & activities delivered | Perceived benefit & access | UK |
| Anon 2015 | Evidence table | Any | ND | Any | Any | Any |
| Neuro-rehabilitation  (2) | Khan 2017a | Review | Neuro Rehabilitation | MS + 3 other conditions | NeuroRehabilitation | NS | NS |
| Congiu 2017 | RCT | Neuro Rehabilitation | MS | Intensive NeuroRehabilitation | NS | NS |
| Functional electrical stimulation (11) | Hammond 2015 | Retrospective n=40 | Rehab | MS | FES | NIL | USA |
| Juckes 2019 | CUA | OP | MS | FES | Standard care | NS |
| Miller 2017  Miller 2019 | SR & MA | NS | MS | FES | NS | NS |
| Nair 2017 | SR | NS | MS | FES | NS | NS |
| Prokopiusova 2020 | RCT | NS | MS | FES + posture correction | Physio | NS |
| Renfrew 2019  Renfrew 2018 | RCT | NS | MS | FES | Ankle-foot orthoses | UK |
| Scally 2020 | SR | NS | MS | FES | NS | NS |
| Springer 2017 | SR | NS | MS | FES | NS | NS |
| Street 2018 | 5 year obs study | NS | MS | FES | NS | NS |
| Rehabilitation (16) | Amatya 2019a  Amatya 2019b | Cochrane review | Reb | MS | Rehab service | NS | NS |
| Barbarulo 2018 | Obs study | NS | MS | integrated cognitive and neuromotor rehabilitation program | Neuromotor rehabilitation only | NS |
| Barker 2017 | Obs study | Community rehab service | Neurological condition | Community rehab service | NS | NS |
| Boesen 2016  Boesen 2018  Boesen 2020 | RCT | Inpatient multidisciplinary rehab | MS | Inpatient multidisciplinary rehab | Waiting list | Denmark |
| Haselkorn 2015 | SR | Reb | MS | Rehab txs | NS | NS |
| Jackson 2019 | SR | Rehab &/or support services | MS | Rehab &/or services | NS | NS |
| Khan 2017b | SR | Rehab | MS | Rehab | NS | NS |
| Pappalardo 2016 | RCT | Inpatient vs OP | MS | Rehab | Wait list | Italy |
| Turner-Strokes 2020 | Economic evaluation | Inpatient | MS | Multidisciplinary rehab | NS | UK |
| Zhang 2019 | Patient records | In skilled nursing facilities | MS | Acute rehab | NS | NS |
| Flachenecker 2020 | RCT | Home after inpatient rehab | MS | Internet physical activity & exercise | NS | NS |
| Dardiotis 2018 | SR | Rehab | MS | Computer-based cognitive rehabilitation | NS | Ns |
| Das Nair 2019 | RCT & CUA | Cognitive rehab | MS | Cognitive rehabilitation courses | Usual care | NS |
| Other: functional neurological disorders clinic (1) | Aybek 2020 | Retrospective | 3 functional neurological disorders clinics (1 UK**)** | Not stated | Attend clinic, 61% offered physiotherapy; referral to neuropsychiatry or psychology differed across centers (32%-100%) | No comparator | UK, Switzerland and Canada |
| Non-specific mental health support services (including online) (1) | Sesel 2018 | SR | NS | MS | Psychosocial therapies includes CBT | NS | NS |
| Memory loss clinics (including online) (1) | Das Nair 2016 | Cochrane review | NS | MS | 'Memory rehabilitation | NS | NS |
| CBT (including online) (15) | Gutkin 2020 | SR | CBT & psychodynamic therapy | FND | NS | NS | NS |
| Lampit 2019 | Review | Computerized cognitive training | MS | Computerized cognitive training | NS | NS |
| Levy 2018 | Review | Respiratory rehabilitation | MS | MS | NS | NS |
| Lidal 2016a  Lidal 2016b | Review | Rehab services in community | Neurological disorder | Rehab services in community | NS | NS |
| Madroñero-Miguel 2020 | SR | Rehab | MS | Rehab | NS | NS |
| Mosweu 2017 | CEA | CBT | MS | Nurse delivery | Supportive listening | NS |
| Olivares Perez 2018 | RCT | CBT | MS | CBT | Wait list | NS |
| Sesel 2018 | SR | NS | MS | Psychosocial therapies includes CBT | NS | NS |
| Van Den Akker 2016a  Van Den Akker 2018  Van Den Akker 2017 | RCT | NS | MS | 12 CBT sessions from psychologist | 3 CBT sessions from nurse | Netherlands |
| Van Den Akker 2016b | SR & MA | NS | MS | CBT | NS | NS |
| Fernie 2015 | SR | NS | Chronic neurological conditions | CBT | NS | NS |
| Chalah 2018 | Review | NS | MS | Cognitive behavioural therapies | NS | NS |

Key: CBT - cognitive behavioural therapy; CEA - cost-effectiveness analysis; CUA – cost utility analysis; FES - functional electrical stimulation; FND - Functional neurological disorder; MA - meta-analysis; MS - multiple sclerosis; ND – neurodegenerative; NHS – National Health Service; NS - not stated; OP - outpatient; RCT – randomised controlled trial; SPMS - secondary progressive multiple sclerosis; SR - systematic review

Appendix D: Evidence and Quality Assurance Tables for Four Economic Evaluations

The evidence tables for the four economic evaluation identified addressing symptom management are presented in Tables D.1 to D.4. Table D.5 presents the completed checklist for these studies.

**Service: Rehabilitation**

**Table D.1: Evidence table Das Nair (2019)**

| Study details | Population & interventions | Costs | Health outcomes per patient | Cost effectiveness |
| --- | --- | --- | --- | --- |
| Economic analysis:  CUA, CEA and CCA  Study design:  Costing of a RCT was undertaken, with health outcomes also measured. A CUA was then undertaken  Approach to analysis:  EQ-5D-5L data were derived from the MSIS-Psy scores reported by all participants in the RCT and used in CUA. The intervention was costed together with all relevant costs in primary and secondary care plus medication costs. Results were evaluated at 6 and 12 months. Appropriate statistical tests were applied to compare mean outcomes.  Perspective:  NHS & Personal Social Services  Time horizon:  12 months  Treatment effect duration:  12 months  Discounting:  Not applied and appropriate | Country:  England  Setting:  5 NHS sites providing neurology services for people with MS  Population:  Adults with MS reporting cognitive problems with a cut-off score >27 on MSNQ. They also had cognitive deficits, of at least one SD below mean of healthy people.  Intervention 1:  Standard NHS pathway, including advice from MS specialist nurses & occupational therapist on how to manage cognitive difficulties. Does not usually include any specific intervention for cognitive problems.    Intervention 2:  Cognitive rehabilitation provided by a clinical psychologist for 10 \*1.5 hour sessions  Cohort size:  Usual care 204 people  Intervention: 245 people  Males: 27%  White: 96%  Mean age: 49 (SD 9.9)  Mean time since diagnosis:  11.7 years  RRMS 132 (65%) vs 159 (65%)  SPMS 48 (24%) vs 64 (26%)  PPMS 24 (12%) vs 22 (9%) | Total mean costs per patient:  Intervention 1:  Assumed £0  Intervention 2:  £209.21 (excluding cognitive rehabilitation assessment)  £333.21 (including cognitive assessment)  Currency & year:  2017 GBP  Components:  NR per patient but intervention costs do include training, implementation and delivery costs.  All health care resource use (primary care, A&E, outpatient, and inpatient) plus social services support were collected in the RCT.  Participants were asked to recall drugs used at 3 monthly intervals.  At 12 months, the intervention group compared with usual care had:  Lower drug costs per patient by £320 (-£929 to £288)  Lower cumulative costs per patient of £575 (-£1,879 to £729) (p = 0.39) | LYG:  NR  QALYs:  QALYs derived through EQ-5D-5L:  6 months 0.57 (standard deviation 0.02) vs 0.60 (0.02)  12 months 0.57 (0.02) vs 0.60 (0.02)  Adjusted QALY gain: 0.00 (-0.01 to 0.02) p = 0.91  QALYs derived through MSIS-8D  6 months 0.51(0.01) vs 0.53 (0.01)  12 months 0.51(0.01) vs 0.53 (0.01)  Adjusted QALY gain 0.01 (-0.1 to 0.03) | ICER:  Cost saving, intervention was dominant  85% probability of cost-effectiveness at WTP threshold of £20,000 per QALY.  Analysis of uncertainty:  Deterministic one-way sensitivity analyses were undertaken to examine the impact of changes in key parameters for ICER. A threshold analyses was also conducted.  Bootstrap resampling was undertaken, with a minimum of 1000 resamples.  Further analysis recommended:  If short-term benefits are maintained in the long term.  Small scale efficacy studies to establish appropriate section criteria so intervention can be given to those who benefit most.  Future study to control for effect of group environment, to see if it is the content of sessions or group orientation that is important.  Conclusion:  Some but limited evidence of health, mood and memory problems improved. There was no increased cost to providing cognitive rehabilitation to usual care, but was in fact slightly cost saving however this was not statistically significant. |
| **Data sources** | | | | |
| **Heath outcomes**  Quality of life weights: EQ-5D-5L was measured at 6 months and 12 months and used to derive QALYs. A separate analysis used the MSIS-8D evaluated at 6 and 12 months to calculate QALYs. The MSIS-8D was derived through the MSIS-29 scale using published methods.  Cost sources: Cost recorded within the RCT. | | | | |
| **Comments**  Source of funds: National Institute for Health Research, Novartis International, Teva Pharmaceuticals, Morphosys, Roche, Sanofi-Pasteur-MSD  Limitations:  Authors: Benefits in daily life and mood may have been due to group orientation and not the content of the sessions. Many costs relied on self-reported use of services and medication used, potential for inaccuracies.  YHEC: One year time horizon may not capture benefits accruing after the end of the RCT. | | | | |

Key: CCA - cost consequences analysis; CEA - cost effectiveness analysis; CUA - cost utility analysis; EQ-5D – Euroqol-Five Dimensions; ICER - incremental cost-effectiveness ratio; GBP – British Pound Sterling; LYG - life years gained; MS – multiple sclerosis; MSIS – Multiple Sclerosis Impact Scale; MSNQ - Multiple Sclerosis Neuropsychological Screening Questionnaire; NHS – National Health Service; NR - not reported; PPMS – primary progressive multiple sclerosis; QALY – quality-adjusted life-year; RCT – randomised controlled trial; RRMS – relapsing-remitting multiple sclerosis; SD - standard deviation; SPMS – secondary progressice multiple sclerosis; WTP – willingness-to-pay; YHEC – York Health Economics Consortium

**Table D.2: Evidence table Turner-Stokes (2020)**

| Study details | Population & interventions | Costs | Health outcomes | Cost effectiveness |
| --- | --- | --- | --- | --- |
| Economic analysis:  Cost efficiency measuring length of time to offset initial cost of rehab by savings in ongoing community care, as estimated by NPDCNA for People with MS  Study design:  Clinical data were from a before & after multicentre cohort observational study  Approach to analysis:  NPDCNA was used to evaluate the dependency/care level of people. The UK Functional Assessment Measure was also used to derive the functional independence of people. A patient’s dependency level was measured before and after the intervention, and mean cost, in relation to their dependency level was applied to see reduction of ongoing costs in these people  Perspective:  Not stated (assumed NHS and social care)  Time horizon:  Inpatient stay  Treatment effect duration:  Maintained over time  Discounting:  Not applied | Country:  England  Setting:  Level 1 (tertiary centres) & level 2 (district) rehabilitation service units (90% of people from level 2)  Population:  Adults with MS admitted to levels 1 &2 rehab units between 2010-2018, with stay between 8-180 days  Intervention:  Multidisciplinary specialist inpatient rehabilitation  Cohort size:  1,007  Dependency groups:  Low n = 149  Medium n= 349  High n =509  Mean starting age: 51.7  Mean time since diagnosis: 11.2 years  Males: 37%  Mean length of stay 53 days  Discharge destination:  Home 82%  Nursing home 7%  Acute hospital 3%  Other 2%  Missing 7% | Total mean costs per patient Intervention £22,898  Currency & year:  GBP and 2019 prices  NPDS is a measure of nursing time (number of helpers and time) to assess needs for care and nursing in rehab settings. Three dependency groups: Low, medium and high.  These Inform the NPDCNA which estimates weekly costs of care in the community based on agency costs.  Mean estimated reduction in care costs was £519/ week for high-dependency group, £148 for medium and £36/week for low-dependency. | LYG:  NR  QALYS:  NR  Other outcome measures:  Mean difference in:   * UK FIM+ FAM (global measure of 30 functions to record disability) * EADL | Results expressed as time to offset cost of rehab. Mean time 16.6 months (95%CI:18.7 to 15.3)  High-dependency: 13 months  Medium: 29 months  Low: 77 months  Analysis of uncertainty:  NR  Further analysis recommended:  NR  Conclusion:  Rehab not cost efficient in people with low dependency needs |
| **Data sources** | | | | |
| **Health outcomes**  Outcomes were extracted from the UK ROC  Cost of care in the community were estimated using NPDCNA. Cost of inpatient stay were estimated using NHS tariff for complexity weighted bed-days | | | | |
| **Comments**  Source of funds: Database UK ROC was funded by NIHR, also funds from a NIHR collaborative, the MS Society and Dunhill medical trust. national clinical database  Limitations: UK ROC captures people who progress to level 3 rehab but not those who do not progress. Hence this is a subgroup of complex people. Also about a third of people were excluded due to incomplete datasets. This may have led to selection bias as longer people were inpatient the greater the likelihood of missing data. No MS specific tools were recorded. Some people may have had multiple admissions but this could not be identified from the data. NPDCNA estimates of continuing care costs are not true assessment so estimates of cost-saving must be treated with caution. Benefit at discharge is assumed to be maintained over time, with no waning effect. This questionable with progressive disease such as MS. Cost savings are across health and social care but costs to the NHS.  YHEC: Neither the intervention costs or the weekly NHS and social care costs can be validated. Outcomes are not NICE reference costs. Perspective not stated- assumed to be NHS and social care. | | | | |

Key: CI - confidence intervals; EADL - Extended Activities of Daily Living; FAM – Functional Assessment Measure; FIM – Functional Independence Measure; GBP – British Pound Sterling; ICER - incremental cost-effectiveness ratio; LYG - life years gained; MS – multiple sclerosis; NHS – National Health Service; NICE – National Institute for Health and Care Excellence; NIHR – National Institute for Health Research; NPDCNA - Northwick Park Dependency Care Needs Assessment; NPDS - Northwick Park Dependency Score; NR - not reported; QALY - quality-adjusted life-year; ROC - Rehabilitation Outcomes Collaborative; YHEC – York Health Economics Consortium

**Service: Functional electrical stimulation (FES)**

**Table D.3: Evidence table Juckes (2019)**

| Study details | Population & interventions | Costs | Health outcomes per patient | Cost effectiveness |
| --- | --- | --- | --- | --- |
| Economic analysis:  CUA  Study design:  Retrospective analysis of routine clinical data  Approach to analysis:  Comparison made of QALYs at baseline and 6 months in FES group. Appropriate statistical tests were applied to compare mean outcomes.  Perspective:  NHS  Time horizon:  5 years  Treatment effect duration:  5 years  Discounting:  Not applied | Country:  UK  Setting:  The National Hospital for Neurology and Neurosurgery Outpatient therapy service  Population:  All people with MS attending with dropped foot who had questionnaires completed at 6 months.  Intervention 1:  Standard care - people were managed by ankle foot orthosis  Intervention 2:  FES using Odstock Dropped  Foot Stimulator; plus physiotherapist review at 6 weeks, 3 and 6 months  Cohort size:  Intervention 1 n = 44  FES n = 82  Starting age: NR  Males: 40%  EDSS 6.0 vs 5.9  RRMS 26 (59%) vs 35 (43%)  SPMS 5 (11%) vs 25 (30%)  PPMS 10 (23%) vs 16 (20%)  Not defined 3 (7%) vs 6 (7%) | Total mean costs per patient:  Intervention 1:  £0  Intervention 2:  £3,393  Currency & year:  £ 2017/18  Components:  NR | LYG:  NR  QALYS:  Baseline 0.45 vs 0.49 (p = 0.82)  6 months 0.60 for FES group  Gain 0.11, p < 0.001  Other outcome measures:  Psychosocial Impact of Assistive Device Scale  FES users 3.31 (no baseline reported).  Walking speed over 10 m  FES users gained 0.8m/s over 6 months | ICER:  £6,137 vs standard care  p values NR  Analysis of uncertainty:  NR  Further analysis recommended:  Longer term studies  Conclusion:  FES is a cost-effective treatment to improve walking speed and QoL in people with MS. |
| **Data sources** | | | | |
| **Heath outcomes**  Quality of life weights  EQ-5D-5L was measured at baseline and 6 months. Baseline values assumed to be QoL with standard care.  Cost sources  NICE MIB56. | | | | |
| **Comments**  Source of funds  No financial support was received.  Limitations  Authors: assumption of maintained benefit from 6 months to 5 years. Assumption supported by earlier studies showing benefit maintained over 5 years. Short duration of 6 months for data collection and costs. Cohort is heterogenous.  Adverse events with FES were excluded as not material. No QoL baseline for control group so baseline used. Valid as groups were well-matched.  YHEC: No discounting applied but effect minor given all costs in first year. | | | | |

Key: CUA - cost utility analysis; EDSS - Expanded Disability Status Scale; EQ-5D – Euroqol-Five Dimensions; FES - functional electrical stimulation; ICER - incremental cost-effectiveness ratio; LYG - life years gained; m/s - meters per second; MS – multiple sclerosis; NHS – National Health Service; NICE – National Institute of Health and Care Excellence; NR - not reported; QALY – quality-adjusted life-year; QoL - quality of life; PPMS – primary progressive multiple sclerosis; RRMS – relapsing-remitting multiple sclerosis; SPMS – secondary progressive multiple sclerosis; YHEC – York Health Economics Consortium

**Service: Cognitive Behavioural Therapy (CBT) vs. supportive listening (SL)**

**Table D.4: Evidence table Mosweu (2017)**

|  |  |  |  |  |
| --- | --- | --- | --- | --- |
| Study details | Population & interventions | Costs | Health outcomes per patient | Cost effectiveness |
| Economic analysis:  CUA  Study design:  Two-arm multi-centre RCT  Approach to analysis:  Comparison of QoL scores and costs at 6 months and 12 months. Cost-effectiveness threshold analysis was undertaken  Perspective:  NHS  Time horizon:  12 months  Treatment effect duration:  15 weeks of treatment, 12 months for final outcome measurements  Discounting:  Not applied and appropriate | Country:  UK  Setting:  MS centres in Hampshire and South London  Population:  People with MS, with a subgroup of people with significant distress at baseline  Intervention 1:  CBT delivered by general nurses trained to provide 8 one-to one sessions over 10 weeks (2 face to face and 6 telephone calls)  Intervention 2:  SL, with delivery and frequency as CBT  Cohort size:  94 people (n = 48 CBT, n = 46 SL)  Starting age:  CBT: 40.3, SL: 42.1  Males:  CBT: 65%, SL: 70%  Other relevant characteristics:  Married/cohabiting:  CBT: 30%, SL: 24%  White/British:  CBT: 38%, SL: 33% | Total mean costs per patient:  Intervention 1:  £306 over 12 weeks  Intervention 2:  £307 over 12 weeks  NHS perspective:  CBT: £7,331  SL: £5,026  Difference, adjusted for baseline costs: £1,610 (95% CI, -£187 to £3,771, not statistically significant)  Societal perspective: Difference in mean costs of £2,871 in favour of SL (95% CI, -£2,028 to £7,793, not statistically significant)  Currency & year:  GBP and 2008/09 | QALYS:  Change in QALYs from baseline at 12 months: CBT 0.6627 vs 0.6197 SL.  The difference (0.0053) was not statistically significant at 95% CI (-0.059 to 0.103) | ICER and CI:  Health and social care perspective:  £303,774  Societal perspective:  £541,698  Subgroup analysis reported an ICER of £126,111 from the NHS perspective and £324,630 from the societal perspective.  Analysis of uncertainty:  9% probability CBT being cost-effective at £20,000/QALY from a health and social care perspective.  Further analysis recommended:  Designing CBT trials targeted to those who need it most and using alternative utility measures validated for psychological interventions in MS people  Analysis into the cost-effectiveness of different levels of clinical expertise  Investigation into the cost-effectiveness of online therapy  Conclusion:  Nurse-led CBT compared to SL is not cost-effective for MS people using EQ-5D-3L |
| **Data sources** | | | | |
| **Heath outcomes**  Quality of life weights  EQ-5D-3L was measured at baseline, 6 months and 12 months. GHQ-12 was measured as baseline and 12 months.  Cost sources  People self-reported health (medication, inpatient, outpatient, lab tests, scans, A&E attendances and contact with community professionals), social services and informal care resources used at baseline, 6 and 12 months. Unit costs were taken from appropriate national datasets including PSSRU, National NHS reference costs and the British National Formulary. Informal care was costed using the unit cost of a local authority home care worker.  Productivity costs were estimated through a human capital approach, which applied national wage rates to days off work due to illness. | | | | |
| **Comments** Source of funds: MS Society in the UK.  Limitations: Authors Possibility of recall bias: No societal value linked to a unit improvement on the GHQ-12 score, making it hard to advice on the cost-effectiveness of CBT using this measure; Further clinical limitations listed in the clinical trial paper  YHEC No extrapolation of costs and benefits beyond 1 year of the RCT. | | | | |

Key: CBT - cognitive behavioural therapy; CI – confidence interval; CUA - cost utility analysis; EQ-5D – EuroQol-Five Dimensions; ICER – incremental cost-effectiveness ratio; GBP – British Pound Sterling; GHQ-12 - General Health Questionnaire-12; MS – multiple sclerosis; NHS – National Health Service; SL - supportive listening; QALY – quality-adjusted life-year; RCT – randomised controlled trial; QoL - quality of life; YHEC – York Health Economics Consortium

**Table D.5: Quality assessment of four economic evaluation using Drummond checklist(1996)**

| Study Reference | Das Nair 2019 | Juckes 2019 | Mosweu 2017 | Turner-Stokes 2020 |
| --- | --- | --- | --- | --- |
| Study Design | | | | |
| 1. The research question is stated. | Yes | Yes | Yes | Yes |
| 1. The economic importance of the research question is stated. | Yes | Yes | Yes | Yes |
| 1. The viewpoint(s) of the analysis are clearly stated and justified. | Yes | Yes | Yes | N/C |
| 1. The rationale for choosing alternative programmes or interventions compared is stated. | Yes | Yes | N/C | Yes |
| 1. The alternatives being compared are clearly described | Yes | Yes | No | N/C |
| 1. The form of economic evaluation used is stated. | Yes | Yes | Yes | Yes |
| 1. The choice of form of economic evaluation is justified in relation to the questions addressed. | Yes | Yes | N/C | Yes |
| **Data Collection** | | | | |
| 1. The source(s) of effectiveness estimates used are stated. | Yes | Yes | Yes | Yes |
| 1. Details of the design and results of effectiveness study are given (if based on a single study). | Yes | Yes | Yes | N/A |
| 1. Details of the methods of synthesis or meta-analysis of estimates are given (if based on a synthesis of a number of effectiveness studies). | Not Appropriate (N/A) | N/A | N/A | N/A |
| 1. The primary outcome measure(s) for the economic evaluation are clearly stated. | Yes | Yes | Yes | Yes |
| 1. Methods to value benefits are stated. | Yes | Yes | Yes | Yes |
| 1. Details of the subjects from whom valuations were obtained were given. | Yes | Yes | Yes | Yes |
| 1. Productivity changes (if included) are reported separately. | N/A | N/A | N/A | N/A |
| 1. The relevance of productivity changes to the study question is discussed. | N/A | N/A | N/A | N/A |
| 1. Quantities of resource use are reported separately from their unit costs. | Not Clear (N/C) | N/A | Yes | No |
| 1. Methods for the estimation of quantities and unit costs are described. | Yes | Yes | Yes | No |
| 1. Currency and price data are recorded. | Yes | Yes | Yes | Yes |
| 1. Details of currency of price adjustments for inflation or currency conversion are given. | Yes | Yes | N/C | Yes |
| 1. Details of any model used are given. | Yes | N/A | Yes | N/A |
| 1. The choice of model used and the key parameters on which it is based are justified. | Yes | N/A | Yes | N/A |
| **Analysis and Interpretation of Results** | | | | |
| 1. Time horizon of costs and benefits is stated. | Yes | Yes | Yes | N/C |
| 1. The discount rate(s) is stated. | Yes | Yes | N/A | N/A |
| 1. The choice of discount rate(s) is justified. | Yes | Yes | N/A | N/A |
| 1. An explanation is given if costs and benefits are not discounted. | Yes | Yes | Yes | N/C |
| 1. Details of statistical tests and confidence intervals are given for stochastic data. | Yes | Yes | Yes | Yes |
| 1. The approach to sensitivity analysis is given. | Yes | No | Yes | Yes |
| 1. The choice of variables for sensitivity analysis is justified. | No | No | N/C | N/A |
| 1. The ranges over which the variables are varied are justified. | No | No | N/C | N/A |
| 1. Relevant alternatives are compared. | No | Yes | Yes | N/A |
| 1. Incremental analysis is reported. | Yes | Yes | Yes | Yes |
| 1. Major outcomes are presented in a disaggregated as well as aggregated form. | N/C | Yes | N/C | Yes |
| 1. The answer to the study question is given. | Yes | Yes | Yes | Yes |
| 1. Conclusions follow from the data reported. | Yes | Yes | Yes | Yes |
| 1. Conclusions are accompanied by the appropriate caveats. | Yes | Yes | Yes | Yes |
| **Score: High if < 3 N/C or no** | **High** | **Moderate** | **Moderate** | **Moderate** |

The 16 papers provided by the MS Society with potentially useful evidence to include in an economic model are:

1. Ashford & St Peter’s Hospital. MS Specialist Nurse posts for ASPH. 2105.
2. British Psychological Society (2021). Psychological interventions for people with Huntington’s disease, Parkinson’s disease, motor neurone disease, and multiple sclerosis: Evidence-based guidance. Leicester: Author.
3. Evaluation of Neuro Response service (remote service to support urgent care for people with MS) <https://www.mssociety.org.uk/sites/default/files/2020-08/Evaluation-of-NeuroResponse.pdf>.
4. FACETS fatigue management programme <https://www.bournemouth.ac.uk/research/projects/reducing-impact-fatigue-people-multiple-sclerosis-using-facets-fatigue-management-programme>.
5. Harrogate and District NHS Foundation Trust. MS specialist nurse post, business case. 2106.
6. Multiple Sclerosis Clinical Working Group. The optimum clinical pathway for people with MS. 2019. [https://www.neural.org.uk/wp-content/uploads/2020/07/Optimum-pathway-for-people-with-MS\_updated.1.pdf](https://www.neural.org.uk/wp-content/uploads/2020/07/Optimum-pathway-for-patients-with-MS_updated.1.pdf).
7. MSS 2020 report on the needs of people with MS across various aspects of health, care, work etc <https://www.mssociety.org.uk/sites/default/files/2020-08/MMMN3-UK-report.pdf>.
8. MSS 2020 survey of impact of Covid on rehabilitation https://www.mssociety.org.uk/sites/default/files/2020-10/MSSociety-RehabPolicyReport-FINAL.pdf.
9. MSS 2015 review of literature on exercise and physical activity. https://www.mssociety.org.uk/sites/default/files/2020-10/MSSociety-RehabPolicyReport-FINAL.pdf.
10. MSS 2015 review of literature on emotional wellbeing, coordinated care and information & advice [not reviewed as no copy found.]
11. MS Trust, Defining the value of MS specialist nurses, 2012.
12. MS Trust and Wilmington Healthcare. Case Study Disease Insight Report — Measuring the burden of hospitalisation in multiple sclerosis. https://wilmingtonhealthcare.com/casestudy/measuring-the-burden-of-hospitalisation-in-multiple-sclerosis/.
13. NHS RightCare. Progressive Neurological Conditions Toolkit. https://www.england.nhs.uk/rightcare/products/pathways/progressive-neurological-conditions-toolkit/.
14. Sussex Community NHS Foundation Trust in partnership with the Multiple Sclerosis Society. Business Case Multiple Sclerosis Specialist Nurse Service. 2017.
15. Wilmington Healthcare. The Forgotten Many: A 2020 Vision for Secondary Progressive Multiple Sclerosis. <https://wilmingtonhealthcare.com/what-we-do/nhs-service-improvement/disease-insight-reports/the-forgotten-many-a-2020-vision-for-secondary-progressive-multiple-sclerosis/>.
16. University of Surrey. MS Models of Excellence Literature Reviews for the Multiple Sclerosis (MS) Society. 2015.

Appendix E: Evidence and Quality Assurance Tables of Three Systematic Reviews

The evidence tables for three systematic reviews addressing symptom management are presented in Tables E.1 to E.3. Table E.4 presents the completed checklist for these studies.

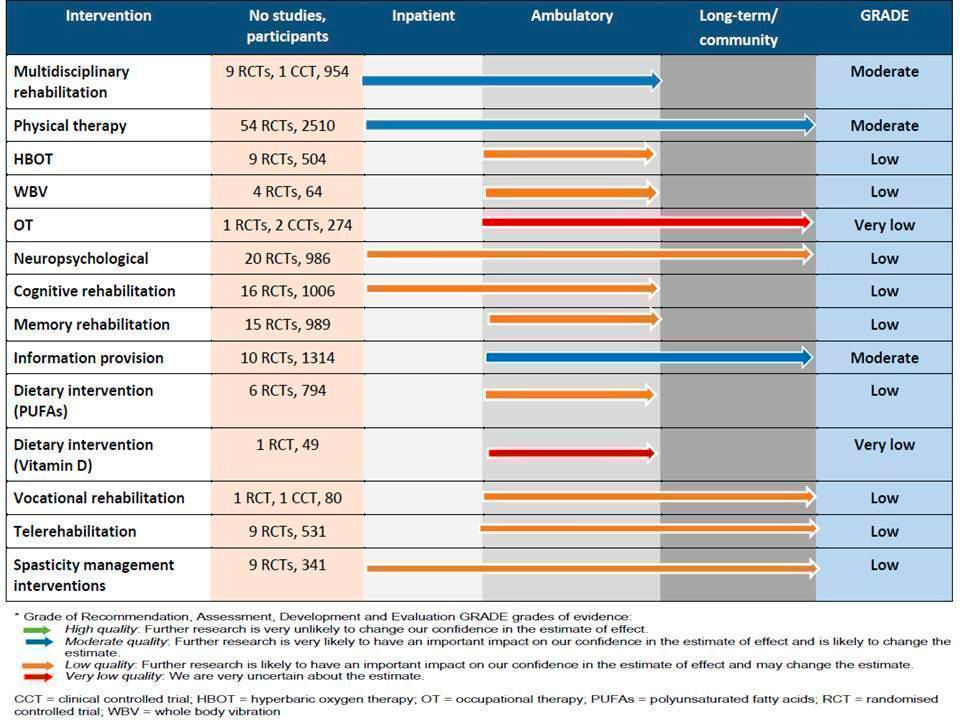
**Service: Rehabilitation**

**Table E.1: Evidence table Amatya (2019a)**

| Study details | Population & interventions | Results | Comments |
| --- | --- | --- | --- |
| Study question(s):  Do people with MS who participate in rehabilitation programmes, improve in their functional activities, disability, and quality of life compared with those who receive no rehabilitation treatment, placebo, or different types of interventions?  Study design:  To systematically evaluate evidence from published Cochrane Reviews of clinical trials to summarise the evidence regarding the  effectiveness and safety of rehabilitation interventions for people with MS, to improve patient outcomes, and to highlight evidence gaps  Search strategies:  Only the Cochrane Database of Systematic Reviews was searched,  from its start to December 2017.  Inclusion and exclusion:  Cochrane reviews of adults with MS for all rehabilitation interventions were included.  All pharmacological interventions were excluded. | Number of included studies:  15 reviews of 164 RCTs and 4 controlled clinical trials  Quality:  All high to moderate quality reviews  Number of participants:  10,396 adults with any type of MS  Characteristics  Age NR  Sex NR  Countries: NR  Settings:   * Outpatient or day treatment, community rehabilitation, or specialist rehabilitation centres * People’ own homes and community rehabilitation * Inpatient rehabilitation settings: specialised medical rehabilitation units or hospital wards   Primary outcomes:   * Function (mobility ADL) * Symptoms or impairments, e.g. pain * QoL * Adverse events   Secondary outcomes included measure of goal attainment and impact on caregivers | See Figure 1 below. The interventions with moderate quality evidence are: multidisciplinary rehab, delivered in inpatient or outpatient; physical therapy across all settings and information provision. More information is provided on these.  Multidisciplinary rehab. One review (2007) included 10 trials with 954 participants. There was strong evidence for inpatient multidisciplinary rehabilitation (3 RCTs, N = 217) improving activity (disability) and moderate evidence that it could improve symptoms, self-care, sphincter control and mobility of wheelchair users only.  Four RCTs evaluated outpatient multidisciplinary rehabilitation vs control (N = 351 participants), and found limited evidence for improved impairment, measured by the EDSS, short-term improved activity levels, improved fatigue, mood, and social function. There was no evidence on cost-effectiveness or the best ‘dose’ of therapy.  Physical therapy. One review (2015) of 45 RCTs and n = 2,250 participants, evaluated the effectiveness and safety of 69 exercise interventions: endurance training (23 interventions), muscle power training (9 interventions), task-oriented training (5 interventions), mixed training (15 interventions), or other (e.g. yoga (17 interventions)) on fatigue. The exercises with a significant benefit (p < 0.01) on fatigue were endurance training, mixed training and other training. Exercise was not associated with a significant risk of a relapse or adverse events. A second review (2005) of 9 RCTs and 260 participants examined the impact of exercise on ADL& QoL. There was strong evidence that exercise-based rehabilitation improved muscle power, exercise  tolerance, and mobility-related activities; moderate evidence that it improved mood; but no evidence for fatigue. Exercise therapy was safe, with no adverse events. There was no evidence on optimal type, duration or intensity.  Information provision was examined in one review (2014) including 10 RCTs, n = 1,314. This found moderate evidence that MS-related knowledge delivery programmes (4 RCTs) were successful in increasing participants’ knowledge but mixed results on its effects on decision making and QoL.  There was low quality evidence for neuropsychological interventions, symptom management programmes, whole body vibration, telerehabilitation and vocational interventions in improving patient outcomes. Evidence for other interventions was inconclusive. | Sources of funds:  Authors received no external funding.  Conflict of interest  Nil  Strengths:  Summarised best review evidence on multidisciplinary rehab interventions on people with MS  Limitations:  Reviews were not updated so likely to have missed relevant and recent articles.  There was bias, methodological weaknesses and inconsistencies and heterogeneity in outcomes in some of the primary studies. Many were underpowered.  Further analysis recommended:  More appropriate studies which report the type and intensity of modalities and their cost-effectiveness are needed.  Conclusion: R regular specialist evaluation and follow-up to assess the needs of people with all types of MS for appropriate  rehabilitation interventions may be of benefit, although the certainty of evidence varies across the different types of interventions. Structured, multidisciplinary rehabilitation programmes and physical therapy (exercise or physical activities) can improve functional outcomes (mobility, muscle strength, aerobic capacity), and quality of life. Overall, the evidence should be interpreted cautiously, as the reviews did not include data from current studies. |

Key: ADL – Activities of Daily Living; EDSS – Expanded Disability Status Scale; MS – multiple sclerosis; NR – not reported; QoL – quality of life; RCT – randomised controlled trial

**Figure E.1: Impact of outcomes of rehabilitation intervention based on the settings of care**



**Service: CBT**

**Table E.2: Evidence table Gutkin (2020)**

| Study details | Population & interventions | Outcomes | Comments |
| --- | --- | --- | --- |
| Study question(s): What is the efficacy of outpatient individual psychotherapy for adults with FND, using PDT and CBT.  individual psychotherapy for adults with FND, with a  focus on the evidence for PDT and CBT  Study design:  Search results were sifted using abstracts and full papers obtained where uncertainty. All studies meeting inclusion criteria were quality assessed using validated tool, with quality ratings of good, fair and poor applied. Effect sizes were expressed by calculating mean differences between groups and dividing by pooled standard deviation. No meta-analysis was undertaken due to variability in outcome measures.  Search strategies:  3 databases searched (MEDLINE, PsycINFO and Embase)  Date ranges 1980 to June 2020  Inclusion criteria:  All prospective treatment studies conducted on adults with any FND subtype. Treatment had to be psychological therapy administered to individuals in an outpatient setting. Both controlled and uncontrolled studies were included. Outcome variables measured had to include at least one of: physical symptoms, mental health symptoms, quality  of life, function, treatment satisfaction and healthcare use.  Exclusion criteria:  Primarily behavioural and hypnotic interventions & psychoeducational studies; if less than 5 participants in intervention arm; not in outpatient setting and papers not in English. | Number of included studies:  19 of which 8 were RCTs and 11 before and after studies. 9 had a follow-up of treatment end, with the longest follow-up being 5 years. 6 were rated good, 7 fair and 6 poor. 12 studies were of CBT and 7 of PCT.  Number of participants:  994  Characteristics:  The majority of people presented with psychogenic non-epileptic seizures. No further information was provided.  Countries:  8 papers from USA, 7 from UK, 1 each from Canada, Italy, Brazil and Switzerland  Settings:  All outpatient | Results were presented for each of the 5 outcome domains for before and after studies and the studies with controls.  Effect sizes in CBT studies  Physical symptoms: of the 7 before and after studies reporting this outcome, 6 reported moderate to large benefits from CBT. The 7th, study,set in Italy, reported no benefit ( n = 11 in the CBT arm) and was of motor FND. Of the 4 RCTs, 3 reported moderate to large benefits with CBT, and the same Italian study reported no benefit.  Mental health: of the 10 before and after studies,7 found moderate to large benefit from CBT and 3 no benefit. Of the 4 RCTs, 3 reported moderate to large benefits, and the same Italian study reported no benefit.  Well-being: All 4 before and after studies reported benefits with a range of effect sizes from 0.74 to 0.11.[[15]](#footnote-16) One RCT, using the EQ-5D measure, reported a large benefit from CBT relative to the control.  Function: Of the 7 before and after studies, 5 reported moderate to large benefit but the Italian study found no benefit and one reported no difference in the effect size. Of the 4 RCTs, 3 reported moderate to large benefits, the same Italian study reported no benefit.  Resource use: No studies of CBT reported resource use. At treatment end, the median pooled pre–post effect size for CBT was 0.49 with a range from 0.03 to 2.12, and at the final follow-up (excluding treatment end) it was 0.33 with a range from 0.08 to 0.71.  Summary: At treatment end, the median pooled pre–post effect size for CBT was 0.49 range (0.03 to 2.12), and at the final follow-up (excluding treatment end) it was 0.33 (0.08 to 0.71).At treatment end, the median pooled between group effect size for CBT was 0.67 (range 0.19 to 1.99) and at the final follow-up (excluding treatment end) it was 0.32 (0.13 to 0.64).  Effect sizes in PDT studies  Physical symptoms: of the 4 before and after studies reporting this outcome, 2 reported moderate to large benefit from PDT, 1 showed no benefit and it could not be calculated for one. The 1 RCT reported a small benefit at treatment end (0.84) but a large benefit at 6 months (0.38).  Mental health: of the 6 before and after studies reporting this outcome, 2 reported moderate to large benefit from PDT, 1 showed no benefit and it could not be calculated for one. Both RCTs reported small to moderate benefits.  Well-being: Both before and after studies reported benefits at treatment end but one found this benefit was not sustained to 6 or 12 months, whilst the other found the benefit was maintained at 6 months. One RCT reported a small benefit from PDT relative to the control.  Function: None of the 3 before and after studies or the RCT reported consistent benefits or disbenefit in this domain.  Resource use: Two before and after studies reported inconsistent results for resource use. One found a material reduction in GP and inpatient days, the second found lower inpatient days but more A&E attendance. The RCT reported fewer A&E visits but similar hospital days were required in the PDT arm.  Summary: At treatment end, the median pooled pre–post effect size for PDT was 0.69 (−1.68 to 2.08) and at the final follow-up (excluding treatment end) it was 0.49 (0.14 to 2.7). At treatment end, the median pooled between group effect size for the 2 RCTs of PDT was −0.03 (−0.99 to 3.76) and at the final follow-up (excluding treatment end) it was 0.11 (−1.28 to 0.98). | Sources of funds:  No external funding declared  Conflict of interest:  No conflict of interest declared  Strengths and limitations:  This is the first review of these therapies since 2005.  Limitations include the lack of good quality RCTs for PDT, the heterogeneity of the studies and that the review was conducted by a single reviewer and thus subject to potential bias.  Further analysis recommended:  RCTs of PDT against standard care and CBT and more focus on patient selection for each treatment  Conclusion:  Review supports continued use of CBT and PDT in clinical practice but more high quality evidence is needed to confirm the efficacy of PDT |

Key: CBT - cognitive behavioural therapy; EQ-5D – Euroqol-Five Dimensions; FND - functional neurological disorder; GP – general practitioner; PDT - psychodynamic therapy; RCT – randomised controlled trial

**Service: FES**

**Table E.2: Evidence table Nair (2017)**

| Study details | Population & interventions | Outcomes | Comments |
| --- | --- | --- | --- |
| Study question(s):  Is FES effective in improving gait in people with  foot drop due to MS?  Study design:  Search results were sifted using abstracts then a full text review was undertaken using 2 reviewers. Each also assessed the quality of each paper.  Search strategies:  5 databases searched (AMED, EMBASE, BNI, MEDLINE and CINAHL)  Date ranges:  2005 to June 2015  Inclusion and exclusion:  All RCTs- Non-RCTs and case series that included adults with MS using FES as one intervention were included  All non-English studies were excluded, together with all studies graded poor by reviewers | Number of included studies:  14 studies; 1 was a systematic review and 3 RCTs but all were from the same centre. Eight were before and after studies, with 1 cost effectiveness study and 1 qualitative study  Number of participants:  N = 183  Characteristics:  Adults with footdrop due to MS  Age and sex:  NR  Countries and Settings :  NR | Speed of walking  A meta-analysis of 20 studies (n =490) reported using FES improved speed of walking by 0.05 to 0.08 m/s. Two RCTs compared FES and a home exercise programme. One reported a 0.05 m/s improvement in gait speed whilst walking with FES. The second reported that while walking without FES, the exercise group showed a statistically significant increase in walking speed relative to the FES group. No p values are reported.  Energy Expenditure of Walking  Two non-RCTs found that using FES led to a significant reduction in the physiological cost of gait. A qualitative study also found that people reported reduced fatigue and falls with FES.  Gait Analysis  A before and after study found that FES increased dorsiflexion at ankle, knee flexion and reduced risk of knee hyperextension at initial contact. A second before and after study showed longer stride length and better dorsiflexion of ankle with FES.  Falls  One RCT found that participants in the FES group experienced 72% fewer falls than in the physiotherapy control. A second RCT reported that the median number of falls was significantly lower (p = 0.036) in FES group compared to an exercise only group. A cross-over trial noted that 83% of falls occurred when FES was not being used. Participants in a qualitative study to explore the impact of FES (n = 6) and ankle foot orthosis (AFO) (n = 4) described fewer falls for both interventions  ADL  One RCT noted higher performance and satisfaction scores in the FES group than the exercise group  QoL  Two case series reported that FES reduced the impact of  MS and improved QoL of People with MS  Comparison of FES with AFO  Three studies compared AFO and FES. One reported that in 3 out of 4 people with MS, FES resulted in more dorsiflexion at ankle compared to AFO. A second noted among 67 people with MS using FES, 27 had tried and rejected AFOs. The qualitative study found participants described similar positive effects for both  FES and AFO.  Cost-effectiveness of FES  A cost-effectiveness study included 39 people with MS in a cohort of 126 people. It applied the same QALY gain from stroke to people with MS. It found FES was cost-effective versus no treatment. | Sources of funds:  NR  Conflict of interest:  NR  Strengths and limitations:  This is the most recent systematic review and builds on earlier ones.  Main limitation is poor methodological quality of the RCTs and other studies. None compared FES with AFO. Most studies were done in gait laboratories using laboratory outcome measures, which may not reflect people’ experience in the community.  Further analysis recommended:  Adequately powered RCT of FES versus AFO, to include a cost effectiveness analysis.  Conclusion:  There is systematic review evidence that using FES as an orthotic device improves the speed of waking.  There is RCT evidence that FES reduces falls and improves ADL   * There is non-comparative evidence that FES improves: energy expenditure for walking * kinematics of gait * QoL |

Key: ADL – Activities of Daily Living; AFO – ankle foot orthosis; FES - functional electrical stimulation; m/s – meters per second; MS – multiple sclerosis; NR – not reported; QALY – quality-adjusted life-year; QoL – quality of life; RCT – randomised controlled trial

**Table E.3: Critical appraisal of three systematic reviews using AMSTAR 2 checklist for systematic reviews**

| Study Reference | Amatya(2019a) | Gutkin(2020) | Nair(2017) |
| --- | --- | --- | --- |
| 1. Did the research questions and inclusion criteria for the review include the components of PICO? | Yes | Yes | Yes |
| 1. Did the report of the review contain an explicit statement that the review methods were established prior to the conduct of the review and did the report justify any significant deviations from the protocol? | Yes - Protocol was developed but no deviations noted. | Yes, states registered on PROSPERO but no deviations noted. | No |
| 1. Did the review authors explain their selection of the study designs for inclusion in the review? | Yes | No | Yes |
| 1. Did the review authors use a comprehensive literature search strategy? | Yes | Yes reported in online version which has supplementary materials. | No |
| 1. Did the review authors perform study selection in duplicate? | Yes | No | Yes |
| 1. Did the review authors perform data extraction in duplicate? | Yes | No | Not Stated (No) |
| 1. Did the review authors provide a list of excluded studies and justify the exclusion? | No | No | No |
| 1. Did the review authors describe the included studies in adequate detail? | Yes | Yes | No |
| 1. Did the review authors use a satisfactory technique for assessing the risk of bias (RoB) in individual studies that were included in the review? | Yes | Yes | Yes |
| 1. Did the review authors report on the sources of funding for the studies included in the review? | Yes | Yes | No |
| 1. If meta-analysis was performed, did the review authors use appropriate methods for statistical combination of results? | Not Applicable (N/A) | N/A | N/A |
| 1. If meta-analysis was performed, did the review authors assess the potential impact of RoB in individual studies on the results of the meta-analysis or other evidence synthesis? | N/A | N/A | N/A |
| 1. Did the review authors account for RoB in individual studies when interpreting/discussing the results of the review? | Yes | Yes | No |
| 1. Did the review authors provide a satisfactory explanation for, and discussion of, any heterogeneity observed in the results of the review? | Yes | No | No |
| 1. If they performed quantitative synthesis did the review authors carry out an adequate investigation of publication bias (small study bias) and discuss its likely impact on the results of the review? | N/A | N/A | N/A |
| 1. Did the review authors report any potential sources of conflict of interest, including any funding they receive for conducting the review? | Yes | No | No |
| **Scores** | Yes = 12  No = 1  N/A = 3 | Yes = 7  No = 6  N/A = 3 | Yes = 4  No = 9  N/A = 3 |
| **Rating** | High | Moderate | Low |

Adapted from: Shea BJ, Reeves BC, Wells G, Thuku M, Hamel C, Moran J, Moher D, Tugwell P, Welch V, Kristjansson E, Henry DA. AMSTAR 2: a critical appraisal tool for systematic reviews that include randomised or non-randomised studies of healthcare interventions, or both. BMJ. 2017 Sep 21;358:j4008.

Appendix F: Evidence on DMTs

Table F.1 provides an overview of each of the 11 NICE DMT appraisals.

**Table F.1: Overview of 11 NICE DMT TAs**

| Drug, date NICE appraisal & decision | Comparator | Evidence | Incremental cost per quality adjusted life year (QALY) [ICER] |
| --- | --- | --- | --- |
| Alemtuzumab, 2014, yes for RRMS\* | GA & fingolimod | 3 RCTs and model | £13,600- £24,500 vs GA and £8,900 vs fingolimod |
| Cladribine, 2019, yes for RRMS\* | Alemtuzumab, natalizmab & fingolimod | 1 RCT and network meta-analysis plus model | Cladribine was less effective and cheaper than alemtuzumab and judged cost-effective. |
| Dimethyl fumarate, 2014, yes for RRMS\* | Avonex, rebif, GA, beta interferon, natalizmab & fingolimod | 2 RCTs plus model | ICER likely to be below £27,700 per QALY gained compared with GA. |
| Fingolimod, 2012, yes for RRMS\* | Avonex and rebif-44 | 2 RCTs plus model | ICER was £27,774 per QALY gained (with patient access scheme [PAS]) vs rebif 44. |
| Natalizmab, 2007, yes for RRMS\* | BI, GA and BSC | 1 RCT vs BSC plus Scharr model for GA and BI | ICER was £32,000 vs BI to £44,600 vs BSC but NICE judged in real life ICER would be lower. |
| Ocrelizumab, 2018 & 2019, yes for PPMS and RRMS | Vs placbo for PPMS & vs the 5 drugs above, BI & teriflunomide for RRMS | 2 RCTs and model | PAS in place; no ICERs stated for PPMS; ICERs < £30k except vs alemtuzumab, which dominated all comparisons, and pegylated interferon beta‑1a. |
| Peginterferon beta-1a, 2020, yes RRMS | Interferons, GA, Alemtuzumab, Dimethyl fumarate, Ocrelizumab, Teriflunomide | 2RCTs, both vs placebo and model | PAS in place; no ICERs stated. |
| Siponimod, 2020, SPMS | BI, BSC, placebo | 1 RCT vs placebo, network analysis and model | PAS in place; no ICERs stated. |
| Teriflunomide, 2014, RRMS | Blended comparator | 3 RCTs, 2 published economic evaluations and 1 model | Same efficacy as BIs and GA, ICER under £20k vs GA. |
| Avonex, BI, extavia, GA, 2018, RRMS | BSC | 4 network analyses plus RSS long term data vs a Canadian registry. Concluded hazard ratio pooling all treatments in the RSS showed treatments delayed disease progression vs BSC (HR 0.79; 95% CI 0.77 to 0.81). 5 economic models. Costs from UK MS Survey. | Interferon beta‑1b (Betaferon) not recommended; others are but under agreed commercial arrangements. ICERs for interferon beta‑1b (Extavia) and GA vs BSC < £30,000. ICERs for interferon beta‑1a vs BSC > £30,000 but recommended to offer alternative to extavia. All drugs had commercial arrangements in place. |
| Ozanimod, 2021, RRMS  (only at NICE consultation) | Beta interferons (1a and 1b), DF, GA, teriflunomide and peginterferon beta-1a | 2 RCTs vs interferon beta-1a + network meta- analysis. Economic model used British Columbia Multiple Sclerosis registry for comparator. | Because of confidential commercial arrangements for ozanimod and comparator treatments, the cost-effectiveness results were not reported. However, the cost-effectiveness estimates for ozanimod vs other first-line treatments for RRMS were outside what NICE normally considers an acceptable use of NHS resources. |

Key: BI – beta interferon; BSC – best supportive care; CI – confidence interval; DF - Dimethyl fumarate; GA – glatiramer acetate; HR – hazard ratio; ICER – incremental cost-effectiveness ratio; MS – multiple sclerosis; NHS – National Health Service; NICE – National Institute for Health and Care Excellence; PAS – Patient Access Scheme; PPMS – primary progressive multiple sclerosis; QALY – quality-adjusted life-year; RCT – randomised controlled trial; RRMS – relapsing-remitting multiple sclerosis; RSS – Risk Sharing Scheme; SPMS – secondary progressive multiple sclerosis

\* Disease presentation suitable for this drug is defined in NICE recommendation.

These 17 papers may be useful to inform the costs and utilities of MS states in future models.

1. Dorsey-Campbell R. MS Variance: Monitoring DMTs and the costs associated with good care. <https://neurologyacademy.org/articles/monitoring-dmts-and-the-costs-associated-with-good-care>.
2. MS Society. Prescribing behaviours study: Study on what influences professionals prescribing of DMTs <https://www.mssociety.org.uk/sites/default/files/2020-08/Prescribers-Research-Report-Dec2017.pdf>.
3. MS Trust report on [improving efficiency of DMT provision](https://mstrust.org.uk/health-professionals/resources/service-development/improving-efficiency-dmd-provision).
4. Manzano et al. [Patient perspective on decisions to switch disease-modifying treatments in relapsing-remitting multiple sclerosis.](https://pubmed.ncbi.nlm.nih.gov/32979733/)Mult Scler Relat Disord. 2020 Nov;46:102507. doi: 10.1016/j.msard.2020.102507. Epub 2020 Sep 19.PMID: 32979733.
5. Mynors G et al for MS Trust. Improving the efficiency of DMT provision Nov 2016.
6. NHS England: Treatment Algorithm for Multiple Sclerosis Disease-Modifying Therapies. 2019.
7. NHS RightCare. Progressive Neurological Conditions Toolkit. https://www.england.nhs.uk/rightcare/products/pathways/progressive-neurological-conditions-toolkit/.
8. NICE Pathways. Disease-modifying therapies for multiple sclerosis, at: <https://pathways.nice.org.uk/pathways/multiple-sclerosis>.
9. Navarro CE, Ordóñez-Callamand E, Alzate JP. Disease modifying therapies in multiple sclerosis: cost-effectiveness systematic review.Farm Hosp. 2020;44(2):68-76.
10. Wilmington Healthcare Improvement Scenario: Relapsing Remitting MS. Rachael’s story. June 2020.
11. Petruzzo MP, Raffaele; Nardone, Antonio; Nozzolillo, Agostino; Servillo, Giuseppe; Orlando, Valentina; De Angelis, Marcello; Lanzillo, Roberta; Brescia Morra, Vincenzo; Moccia, Marcello. The impact of diagnostic criteria and treatments on the 20-year costs for treating relapsing-remitting multiple sclerosis. Mult Scler Relat Disord. 2020;38:101514.
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13. Hawton AJG, C. Multiple Sclerosis: Relapses, Resource Use, and Costs. Eur J Health Econ. 2016;17(7):875-84.
14. Neuberger EEA, Ibrahim M.; Jones, Eddie; Engmann, Natalie J. Work Productivity Outcomes Associated with Ocrelizumab Compared with Other Disease-Modifying Therapies for Multiple Sclerosis. Neurol Ther. 2020;26:2.
15. Nicholas JAE, Natalie C.; Edwards, Roger A.; Dellarole, Anna; Grosso, Megan; Phillips, Amy L. Real-world adherence to, and persistence with, once- and twice-daily oral disease-modifying drugs in people with multiple sclerosis: a systematic review and meta-analysis. BMC Neurol. 2020;20(1):281.
16. Piena MAH, M.; Wormhoudt, L. W.; Wingerden, J. van; Frequin, S. T. F. M.; Uitdehaag, B. M. J. Cost-minimization analysis of alemtuzumab compared to fingolimod and natalizumab for the treatment of active relapsing-remitting multiple sclerosis in the Netherlands. J Med Econ. 2018;21(10):968-7.
17. Versteegh M. Impact on the Incremental Cost-Effectiveness Ratio of Using Alternatives to EQ-5D in a Markov Model for Multiple Sclerosis. Pharmacoeconomics. 2016;34(11):1133-44.

Tables F.2 to F.5 are evidence table for four NICE TAs.

**Study reference: NICE (2018)**

**Table F.2:** **Beta interferon and glatiramer acetate versus best supportive care**

| Study details | Population & interventions | Costs | Health outcomes per patient | Cost effectiveness |
| --- | --- | --- | --- | --- |
| Economic analysis:  CUA of DMTs (Interferon β-1a, Pegylated interferon β-1a, Interferon β-1b and GA) for CIS and RRMS against BSC and each other. This updated a previous NICE technology appraisal.  Study design:  The RSS model used by Department of Health was rebuilt using the same structure. The base case used RSS data A sensitivity analysis used values from AG.  Approach to analysis:  The model used a decision-analytical modelling framework adopting longitudinal data from natural history cohorts to provide information on the progression of RRMS. Heath states were characterised by EDSS levels. Relapse frequency, by EDSS state, was the base absolute risk which was modified by applying hazard rates when treated with DMTs.  Perspective:  NHS and PSS  Time horizon:  50 years  Treatment effect duration:  Every year 5.0% (base case) & 2.3% of people (AG) discontinue treatment due to adverse events.  Annualised relapse rates for DMTs 0.72 (base case) & 0.65 (0.56, 0.76) [AG]; frequencies provided by EDSS state (Table 69).  Treatment effects on disability progression 0.79 (base case) & 0.70 (0.55, 0.87) [AG].  Discounting:  Costs and benefits 3.5% | Country:  UK  Setting:  Community  Population:  RRMS  Intervention 1:  BSC  Intervention 2:  DMTs  Cohort size:  N = 4,217 from RSS model  Starting age:  30 years  Males:  NR  Other relevant characteristics:  RRMS:  EDSS 0 3%; EDSS 1 16% ; EDSS 2 26%; EDSS 3 23%; EDSS 4 15%; EDSS 5 10%; EDSS 6 6% | Total mean costs per patient:  Intervention 1: £362,100  Intervention 2: £387,800  No p values or CIs reported  Currency & year:  £ and 2014/15 prices  Components:  Drug costs per patient  IFN B-1a £8,502 to £10,572;  Interferon β-1b £7,264  GA £6,704 to £7,264.  Pooled cost £7,300.  Management costs per patient  EDSS 0, 1 and 2 £1,164; EDSS 3 £2,147; EDSS 4 £2,225; EDSS 5 £7,840; EDSS 6 £8,746; EDSS 7 £26,688; EDSS 8 £41,439 EDSS 9 £52,679; Dead £0.  Cost of relapse £4,263  No adverse events or complications costed. | LYG:  NR  QALYs: RRMS  Intervention 1 8.66  Intervention 2 9.61  Utility values  EDSS 0 0.925; EDSS 1 0.764; EDSS 2 0.674; EDSS 3 and 4 0.564; EDSS 5 0.491; EDSS 6 0.445; EDSS 7 0.269; EDSS 8 0.008; EDSS 9 -0.230; Dead 0  Mortality: Age specific life tables  Other outcome measures:  NR | ICER: RRMS  Pooled DMTs compared to BSC gave an ICER of £27,200 per QALY  Analysis of uncertainty:  Probabilistic sensitivity analysis ICER £32,000 per QALY. There was a 37% of cost-effectiveness at £20,00 threshold.  Sensitivity analysis showed ICER was most sensitive to hazard rate for disability progression, then cost of disease  With AG assumptions ICER was £8,100 per QALY  Pegylated IFN β-1a 125μg (Plegridy) was the most cost effective option of the individual DMTs, with an ICER of £7,000 compared to BSC. Glatiramer acetate 20 mg (Copaxone) was most cost effective treatment for CIS with an ICER of £12,900 per QALY gained  Further analysis recommended:  Both RCT evidence and the RSS data are at high risk of bias. Research priorities include comparative studies with longer follow up and systematic review and meta-synthesis of studies.  Conclusion:  DMTs both separately and together are clinically and cost effective for treatment of both RRMS and CIS. |
| **Data sources** | | | | |
| **Heath outcomes**  Quality of life weights were from the RSS model and ScHARR model  **Cost sources**:  Drug costs British National Formulary 2015, Management and relapse costs from RSS model; | | | | |
| **Comments**  Source of funds: NICE  Limitations:  Authors: Absence of confidence intervals for input parameters, sparse networks of evidence, short follow-up in clinical studies, differential risk of bias across DMTs e.g. plegridy had only 1 study with follow-up at 1 year to inform evidence  YHEC: The composition of management costs is not stated but we suspect these exclude cost of managing adverse events. All these DMTs are administered by subcutaneous injection or intramuscular injection. The TA noted up to 50% of people treated with GA have injection site reactions yet there are no costs to manage these. Also the base case excluded monitoring costs. Note in the separate model for people with CIS (see below), the AG included an annual administration costs of £225, with monitoring cost of £550 to £560 in first year and £324 in subsequent years. No disutilities were applied for adverse events in either model. The drug costs are from the BNF. It is not known if these are representative of the prices paid by the NHS.  CIS: A de novo model was also developed comparing DMTs with BSC for treating CIS. GA dominated the beta-interferons, having an ICER of £12,900 compared with BSC. No probabilistic sensitivity analysis was undertaken. The major uncertainty was on the utility value of people with CIS. The AG noted until more reliable information is available on the utility values the results should be interpreted with caution. | | | | |

Key: AG – Assessment Group; BNF – British National Formulary; BSC – best supportive care; CIS – clinically isolated syndrome; CUA – cost utility analysis; DMT – disease-modifying therapy; EDSS - Expanded Disability Status Scale; GA – glatiramer acetate; ICER – incremental cost-effectiveness ratio; IFN – interferon; LYG – life years gained; NHS – National Health Service; NICE – National Institute for Health and Care Excellence; NR – not reported; PSS – Personal Social Services; QALY – quality-adjusted life-year; RCT – randomised controlled trial; RRMS – relapsing-remitting multiple sclerosis; RSS – Risk Share Scheme; TA – technology appraisal; YHEC – York Health Economics Consortium

**Study reference: NICE (2020)**

**Table F.3: Siponimod for treating secondary progressive multiple sclerosis (TA656)**

| Study details | Population & interventions | Costs | Health outcomes per patient | Cost effectiveness |
| --- | --- | --- | --- | --- |
| Economic analysis: CUA of siponimod vs IFB, GA, natalizumab, teriflunomide, dimethyl fumarate and ocrelizumab  Study design: Literature review to identify RCTs to include in mixed adjusted indirect comparison. The only RCT of Siponimod did not have a relevant control. Plus 2 reviews of economic evidence on costs and quality of life.  Approach to analysis: Markov model using natural history from London Ontario database. Disease progression modelled using EDSS states. DMTs delayed progression and reduced frequency of relapses. Treatment stopped when people was EDSS 7 or higher and s/he moved to best supportive care.  Perspective: NHS and PSS  Time horizon: 50 years  Treatment effect duration:  50% decrease from year 11  Discounting: 3.5% costs and benefits | Country: UK  Setting: primary care  Population: SPMS  Intervention 1:Siponimod  Intervention 2: RRMS DMTs  Cohort size: Not reported  Starting age: 48  Males:40%  Time since onset 16.8 years | Total mean costs per patient:  Intervention 1: NR  Intervention 2: NR  Currency & year: GBP 2017/18  Components:  Drug costs redacted for siponimod and fingolimod but provided for IFB, GA, teriflunomide, dimethyl fumarate, natalizumab, and ocrelizumab  Admin costs and adverse event costs per patient  provided for siponimod, IFB, GA, teriflunomide, dimethyl fumarate, natalizumab, and ocrelizumab  Health state management costs by EDSS 0 £965, 1 £1,004, 2 £736, 3 £4,024, 4 £1,949, 5 £3,307, 6 £4,415, 7 £11,621, 8 £28,304, 9 £22,648  Relapse £4,357 | LYG: 16.16 vs 15.86  QALYS: 4.49 vs 3.17  Other outcome measures:  Relative risk of SPMS mortality by EDSS state | ICER and CI: redacted  PSA and other sensitivity analysis results were redacted  Further analysis recommended:  None stated  Conclusion: TA Committee was satisfied that ICERS were within the range that NICE normally considers acceptable. |
| **Data sources** | | | | |
| **Heath outcomes**  Quality of life weights Expand study and Orme (2007) but those from the RCT are redacted. Disutility for adverse events by DMT also redacted. Did provide caregivers’ utility decrements from an earlier TA  Cost sources. Drug costs are redacted for siponimod and fingolimod. Other costs from earlier TAs. | | | | |
| **Comments**  Source of funds. NICE funded.  Limitations  Authors: Clinical data is key limitation due to no RCT data that directly compare siponimod to a DMT.  YHEC Clinical parameters such as relapse rates and hazard rates for progression and all results are redacted. | | | | |

Key: CI – confidence interval; CUA - cost utility analysis; DMT – disease-modifying therapy; IFB - interferon β-1b; EDSS - Expanded Disability Status Scale; GA - Glatiramer acetate; GBP – British Pound Sterling; ICER – incremental cost-effectiveness ratio; LYG – life years gained; NHS – National Health Service; NICE – National Institute for Health and Care Excellence; NR – not reported; PSA – probababilistic sensitivity analysis; PSS – Personal Social Service; QALY – quality-adjusted life year; RCT – randomised controlled trial; RRMS – relapsing-remitting multiple sclerosis; SPMS – secondary progressive multiple sclerosis; TA – technology appraisal; YHEC – York Health Economics Consortium

**Study reference: NICE (2014a)**

**Table F.4: Dimethyl fumarate for treating relapsing‑remitting multiple sclerosis**

| Study details | Population & interventions | Costs | Health outcomes per patient | Cost effectiveness |
| --- | --- | --- | --- | --- |
| Economic analysis: CUA of dimethyl fumarate versus, beta interferon-1a treatment (Avonex, Rebif-22, or Rebif-44), beta interferon-1b (Betaferon), glatiramer acetate, fingolimod and natalizumab  Study design: Company submitted a cohort-based Markov model  ERG adopted this model for analysis but kept the structure the same  Approach to analysis: De novo Markov model. 21 different health states which represented different degrees of severity through progression in EDSS score. Health and costs affected through reduction in annual relapse rate. Included progressive disability in people with RRMS and SPMS, and death.  Perspective: NHS and PSS  Time horizon: 30 years  Treatment effect duration: Extrapolated beyond the two year trial duration. On the manufacturer’s model the treatment effect on disability progression was assumed to wane after 2 years to 75% of the original effect, until the sixth year where it was reduced to 50% and maintained at that level.  Discounting:  Costs and benefits 3.5% | Country: UK  Setting: Community  Population: Adult people with relapsing-remitting multiple sclerosis  Intervention 1: Dimethyl fumarate  Intervention 2: Other DMTs  Cohort size: Not reported, general RRMS population was used  Starting age: Not reported  Males: Not reported  Clinical data were mainly redacted. These were derived from a systematic review and a mixed treatment comparison.  Movement between states informed by London Ontario data but redacted. Mortality multiplier applied. | Total mean costs per patient at list price for drugs)  Intervention 1: £269,798  Intervention 2: Refib 22 μg: £234,103 Glatiramer acetate: £234,547 Natalizumab: £284,763  No p-values or CI reported  These results are for prices that are listed, results for PAS price not available.  List prices: DF £17,900, fingolimod £19,176, GA £6,481, Avonex £8,531, Natalizumab £14,690, Betaferon £7,265, Rebif 22ug £8,149, Rebif 44ug £10,608  Currency & year: GBP and 2012 prices  MS Trust survey 2005 (n = 2,048) data used to derive EDSS health state costs.  Details for RRMS and SPMS by state are in table 38.  Discontinuation of DMTS when move to EDSS 7 or higher.  Admin costs for interferons and GA yr. 1 £99 and £0 thereafter; Natalizumab £6,224 each year (injection as a day case).  Annual monitoring costs:  Interferons £1777 yr 1 then £595; DF £1780 yr 1 then £597;Fingolomid £2,431 then £597;GA £1184 then £590; Natalizumab £1334 then £1180  Relapse costs £2028 range £228 to £3,039.  Cost of AEs on Table 39. | QALYS:  Dimethyl Fumarate: 5.73 Refib 22μg: 5.47 Glatiramer acetate: 5.50 Natalizumab: 5.81  No p-values or CI reported  Utilities were from the 2 pivotal studies: EDSS states  0 0.88, 1 0.83, 2 0.78, 3 0.69, 4 0.63, 5 0.54, 6 0.46, 7 0.34, 8 0.002, 9 -0.17  Values from MS survey used as sensitivity analysis. | ICER: Dimethyl fumarate ICER: £27,700 (compared to glatiramer acetate), comparison with rebif-22 removed as was considered a step-up in dosage  No confidence interval stated  All sensitivity analysis poorly reported and unreliable.  Main drivers were drug costs, disease progression, stopping rules and size of waning effect.  Probability of £30,000 threshold not reported  Further analysis recommended: Committee recommended better synthesis of available evidence on underlying disease progression of MS in the UK context, impact of disability and relapses on QoL, and resource use and costs.  Conclusion:  Dimethyl fumarate is recommended as an option to treat active RRMS if supplied at the patient access scheme discount and people does not have highly active or rapidly evolving severe RRMS |
| **Data sources** | | | | |
| **Heath outcomes**  Quality of life weights VAS, SF-36 and EQ-5D results from DEFINE and CONFIRM trials  Cost sources  British National Formulary (drug costs), Department of Health’s reference costs (administration and monitoring costs), Seemingly unrelated regressions derived from MS survey data and previous technology appraisals (health state costs), PSSRU 2011, NHS reference costs 2011/12 | | | | |
| **Comments**  Source of funds NICE  Limitations  Authors: Sensitivity analysis were limited, mortality data from a Danish population that is very dated, but changing mortality rates had limited impact on the ICER. The waning effect of Dimethyl fumarate is unknown beyond 2 years. Additional HRQoL benefits associated with oral treatment and short washout duration may not have been fully captured in the model. Uncertainty on progression. YHEC: Lack of robust sensitivity analysis, Lack of confidence intervals for any values, PAS price costs and QALYs commercial in confidence | | | | |

Key: AE – adverse event; CI – confidence interval; CUA - cost utility analysis; DF - dimethyl fumarate; DMTs – disease-modifying treatments; EDSS - Expanded Disability Status Scale; EQ-5D – Euroqol-Five Dimensions; ERG - Evidence Review Group; GA – glatiramer acetate; GBP – British Pound Sterling; HRQoL – health-related quality of life; ICER – incremental cost-effectiveness ratio; MS – multiple sclerosis; NHS – National Health Service; NICE – National Institute for Health and Care Excellence; PAS - Patient Access Scheme; PSS – Personal Social Services; PSSRU - Personal Social Services Research Unit; QALY – quality-adjusted life-year; RRMS – relapsing-remitting multiple sclerosis; SF-36 – 36-Item Short Form Survey; SPMS – secondary progressive multiple sclerosis; VAS – visual anologue scale; YHEC – York Health Economics Consortium

**Study reference: NICE (2007)**

**Table F.5: Natalizumab versus BSC and other DMTs for people with RRMS with high disease activity despite treatment with an IFN-beta (sub-optimal) or rapidly evolving severe RRMS**

| Study details | Population & interventions | Costs | Health outcomes per patient | Cost effectiveness |
| --- | --- | --- | --- | --- |
| Economic analysis:  A CUA of Natalizumab against BSC, BI and GA.  Study design:  A multistate Markov model predicting disability progression and disease activity, using a series of one year cycles. The clinical data came from AFFIRM study and disability progression data was derived from the London Ontario dataset (a longitudinal study of 1000 people with RRMS followed for a mean of 25 years).  Approach to analysis: Indirect comparison conducted to compare natalizumab with BI and GA.  Perspective:  NHS & carers’ disutility in manufacturer’s base case  Time horizon:  20 years  Treatment effect duration:  2 years in study and maintained thereafter  Discounting: 3.5% costs and benefits | Country:  UK  Setting:  Community  Population:  RRMS with high disease activity despite treatment with an IFN-beta (sub-optimal) or rapidly  evolving severe RRMS  Intervention 1:  BSC, BI and GA  Intervention 2:  Natalizumab 300mg  Cohort size:  Not reported  Starting age:  Not reported  Males:  Not reported | Total mean costs per patient:  Intervention 1: NR  Intervention 2: NR  Currency & year:  GBP 2007  Components:  Drugs natalizumab  £14,730 per patient per year (before discount)  No further costs reported | LYG:  NR  QALYS:  RES population with natalizumab  Intervention 1: 5.78  Intervention 2: 7.51  Suboptimal Population  Intervention 1: 6.15  Intervention 2: 7.58  No p values & CIs  No other outcome measures: | ICER and CI:  ICERs for the RES group compared with BSC, BI and GA were £44,600, £32,000 and £34,600 respectively.  For the suboptimal therapy group the ICERs were £56,100, £43,400 and £44,300 per QALY gained respectively.  Analysis of uncertainty:  Sensitivity analysis showed  ICER was sensitive to time horizon (to 30 years) and changing the source of the disability progression data. Values not reported.  Further analysis recommended: Clinical effectiveness of natalizumab to treat highly active RRMS in the suboptimal therapy group.  Conclusion:  Not cost-effective for suboptimal population but cost-effective for people with RES. |
| **Data sources** | | | | |
| **Heath outcomes**  Quality of life weights were from UK MS survey  Cost sources were from UK MS survey | | | | |
| **Comments**  Source of funds: NICE  Limitations:  Authors Uncertainty with indirect analyses, patient group was RRMS not highly active RRMS, extrapolation of 2 year daya 20 years with no waning effect, costs and utilities from MS survey and not just people with highly active RRMS. Also limitations with EDSS instrument.  YHEC: The External review group’s report was not on NICE website so information highly limited. | | | | |

Key: BI – beta interferon; BSC – best supportive care; CI – confidence interval; CUA – cost utility analysis; EDSS – Expanded Disability Status Scale; GA – glatiramer acetate; GBP – British Pound Sterling; IFN – interferon; LYG – life years gained; MS – multiple sclerosis; NHS – National Health Service; NICE – National Institute for Health and Care Excellence; NR – not reported; QALY – quality-adjusted life-year; RES – rapidly evolving severe relapsing-remitting multiple sclerosis; RRMS – relapsing-remitting multiple sclerosis; YHEC – York Health Economics Consortium

Appendix G: Prescribing Data from FOIs

**Example FOI Request**

This is an information request from York Health Economics Consortium regarding disease modifying treatments for MS. As Background the MS Society has commissioned us to support them.

**First and second line treatments**

What is first line and second line treatment for people with a diagnosis of relapsing remitting MS (RRMS)?

What is first line and second line treatment for people with a diagnosis of primary progressive MS (PPMS)?

What is first line and second line treatment for people with a diagnosis of secondary progressive MS (SPMS)?

**DMT use and costs**

Please complete Table G.1.

**Table G.1: Use of DMTs in 2020**

|  |  |  |
| --- | --- | --- |
| Drug | No of people treated with this drug in 2020 | Total cost of the treatment |
| Alemtuzumab (Lemtrada) |  |  |
| Avonex (interferon beta-1a) |  |  |
| interferon alpha |  |  |
| interferon beta |  |  |
| Cladribine (Mavenclad) |  |  |
| Daclizumab (Zinbryta) - withdrawn |  |  |
| Dimethyl fumarate (Tecfidera) |  |  |
| Extavia (beta interferon-1b) |  |  |
| Fingolimod (Gilenya) |  |  |
| Glatiramer acetate (Copaxone) |  |  |
| Natalizumab (Tysabri) |  |  |
| Ocrelizumab (Ocrevus) |  |  |
| Peginterferon alpha |  |  |
| Plegridy (peginterferon beta 1a) |  |  |
| Rebif (beta interferon-1a) |  |  |

**Prevalence of MS**

Please complete Table G.2.

**Table G.2: Prevalence of types of MS**

|  |  |
| --- | --- |
|  | Number of people with diagnosis |
| RRMS |  |
| PPMS |  |
| SPMS |  |
| Other types of MS |  |
| Total |  |

**Table G.3: People treated with DMTs by NHS Scotland health board 2020**

|  |  |  |  |  |  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- |
| DMT | Dumfries Galloway | W Isles | Forth Valley | Shetland | Tayside | Ayrshire & Arran | Borders | Grampian | Glasgow & Clyde | Lothian | Orkney | Total |
| Alemtuzumab | 0 | 0 | 0 | 0 | 0 | 8 | 0 | 7 | 12 | 35 | 0 | **62** |
| Interferon beta 1a | 7 | 1 | 15 | 0 | 25 | 25 | 2 | 46 | 258 | 15 | 0 | **394** |
| Interferon alpha | 0 | 0 | 0 | 0 |  | 2 | 0 | 0 | 0 | 0 | 0 | **2** |
| Interferon beta | 2 | 0 | 0 | 0 | 2 | 38 | 0 | 0 | 2 | 2 | 0 | **46** |
| Cladribine | 2 | 2 | 12 | 0 | 8 | 26 | 0 | 2 | 192 | 54 | 0 | **298** |
| Daclizumb |  | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 9(a) | 0 | **9(a)** |
| Dimethyl fumarate | 65 | 8 | 84 | 11 | 172 | 91 | 56 | 22 | 833 | 113 | 5 | **1460** |
| Extavia (beta interferon-1b) |  | 0 | 0 | 0 | 24 | 0 | 0 | 45 | 2 | 47 | 2 | **120** |
| Fingolimod | 33 | 2 | 29 | 1 | 59 | 39 | 2 | 24 | 236 | 2 | 2 | **429** |
| Glatiramer acetate | 7 | 1 | 42 | 2 | 242 | 2 | 2 | 0 | 260 | 3 | 0 | **561** |
| Natalizxumab | 28 | 2 | 29 | 0 | 45 | 52 | 11 | 19 | 211 | 381 | 2 | **780** |
| Ocrelizumab | 2 | 1 | 13 | 0 | 29 | 0 | 0 | 7 | 95 | 79 | 2 | **228** |
| Peginterferon alpha | 0 | 0 | 0 | 0 | 0 | 2 | 5 | 0 | 0 | 10 | 0 | **17** |
| Peginterferon beta 1a | 12 | 3 | 18 | 0 | 10 | 31 | 2 | 14 | 165 | 49 | 0 | **304** |
| Beta interferon 1a | 2 | 1 | 3 | 0 | 14 | 13 | 2 | 5 | 55 |  | 2 | **97** |
| Teriflunomide | 0 | 0 | 0 | 0 | 13 |  |  |  |  |  | 0 | **13** |
| Other drugs | 0 | 0 | 0 | 0 | 2 |  |  |  |  |  | 0 | **2** |
| **Total** | **160** | **21** | **245** | **14** | **645** | **329** | **82** | **191** | **2321** | **799** | **15** | **4,822** |
| **People with MS** |  | **101** | **776** | **80** | **1,407** | **0** | **0** | **346 (a)** | **0** | **2,698** | **110** | **5,518** |
| **DMTs as % People with MS** |  | **21%** | **32%** | **18%** | **46%** |  |  | **55%** |  | **30%** | **14%** | **35%** |

Note: Daclizumab is now withdrawn.

Data being checked

**First and Second Line Treatments**

Responses on treatment lines were available for seven Scottish NHS boards and the Northern Irish board. The other Scottish boards advised they do not use the terms 1st line and 2nd line treatment.

**RRMS**

NHS Greater Glasgow & Clyde the largest health board, provided its clinical pathway for RRMS for West Scotland (see Annex G). For active RRMS the following DMTs are considered first line treatments:

* Beta-interferon
* Glatiramer acetate
* Dimethyl fumarate
* Teriflunomide
* Ocrelizumab (may be considered as an alternative first line treatment in complex cases)

If treatment fails, the clinician will try an alternative first line treatment.

For Rapidly Evolving severe RRMS (RES-RRMS) or highly active RRMS despite treatment the following DMTs are recommended:

* Alemtuzumab
* Cladribine
* Fingolimod
* Natalizumab
* Ocrelizumab

The other Scottish boards also use the drugs above for RRMS. Indeed some advised they use any of the 14 DMTs approved by the Scottish Medicines Consortium.

In Northern Ireland only interferons and glatiramer acetate are used first line, with natalizumab, fingolimod, teriflunomide, cladribine, dimethyl fumarate, ocrelizumab and alemtuzumab all considered second line.

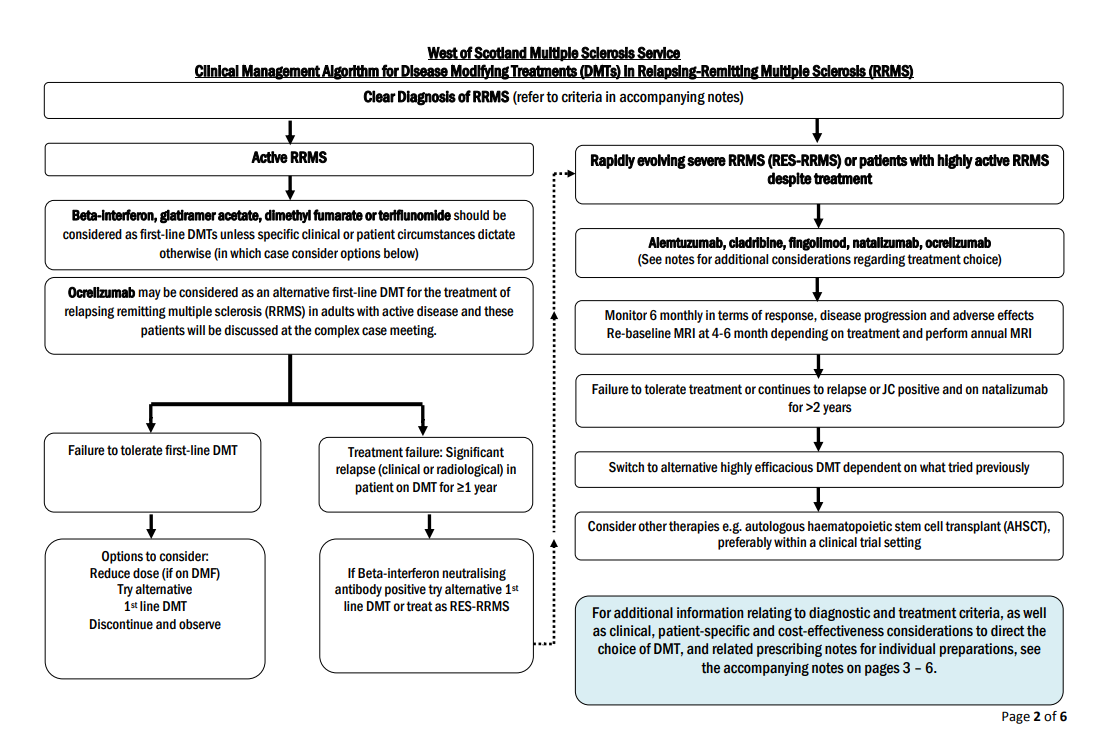
**PPMS**

There was a clear consensus across the five Scottish boards and the Northern Irish Board answering this question that ocrelizumab was the DMT of choice for people with PPMS.

**SPMS**

Siponimod was the preferred DMT to treat SPMS in Scotland and Northern Ireland, with NHS Tayside also having an interferon as an option.

**Annex: G1**



1. The final protocols are available by emailing joyce.craig@york.ac.uk [↑](#footnote-ref-2)
2. Western Europe is defined as: [Austria](https://en.wikipedia.org/wiki/Austria), [Belgium](https://en.wikipedia.org/wiki/Belgium), [Czech Republic](https://en.wikipedia.org/wiki/Czech_Republic), [France](https://en.wikipedia.org/wiki/France), [Germany](https://en.wikipedia.org/wiki/Germany), [Ireland](https://en.wikipedia.org/wiki/Republic_of_Ireland), [Liechtenstein](https://en.wikipedia.org/wiki/Liechtenstein), [Luxembourg](https://en.wikipedia.org/wiki/Luxembourg), [Monaco](https://en.wikipedia.org/wiki/Monaco), [Netherlands](https://en.wikipedia.org/wiki/Netherlands), [Switzerland](https://en.wikipedia.org/wiki/Switzerland), [United Kingdom](https://en.wikipedia.org/wiki/United_Kingdom). https://en.wikipedia.org/wiki/Western\_Europe [↑](#footnote-ref-3)
3. Observational studies includes cohort studies, case control studies and cross sectional studies. [↑](#footnote-ref-4)
4. Only costs from UK settings are relevant. Thus data extraction will be limited for non-UK studies [↑](#footnote-ref-5)
5. Western Europe is defined as: [Austria](https://en.wikipedia.org/wiki/Austria), [Belgium](https://en.wikipedia.org/wiki/Belgium), [Czech Republic](https://en.wikipedia.org/wiki/Czech_Republic), [France](https://en.wikipedia.org/wiki/France), [Germany](https://en.wikipedia.org/wiki/Germany), [Ireland](https://en.wikipedia.org/wiki/Republic_of_Ireland), [Liechtenstein](https://en.wikipedia.org/wiki/Liechtenstein), [Luxembourg](https://en.wikipedia.org/wiki/Luxembourg), [Monaco](https://en.wikipedia.org/wiki/Monaco), [Netherlands](https://en.wikipedia.org/wiki/Netherlands), [Switzerland](https://en.wikipedia.org/wiki/Switzerland), [United Kingdom](https://en.wikipedia.org/wiki/United_Kingdom). https://en.wikipedia.org/wiki/Western\_Europe [↑](#footnote-ref-6)
6. Only costs from UK settings are relevant. Thus data extraction will be limited for non-UK studies [↑](#footnote-ref-7)
7. [↑](#footnote-ref-8)
8. See reports dated 23 February 2021 and 3 March 2021 for initial findings of the symptom management services and DMTs respectively [↑](#footnote-ref-9)
9. https://www.crd.york.ac.uk/crdweb/searchstrategies.asp#nhseedmedline [↑](#footnote-ref-10)
10. https://www.crd.york.ac.uk/crdweb/searchstrategies.asp#daremedline. [↑](#footnote-ref-11)
11. Lefebvre C, Glanville J, Briscoe S, Littlewood A, Marshall C, Metzendorf M-I, Noel-Storr A, Rader T, Shokraneh F, Thomas J, Wieland LS. Technical Supplement to Chapter 4: Searching for and selecting studies. In: Higgins JPT, Thomas J, Chandler J, Cumpston MS, Li T, Page MJ, Welch VA (eds). Cochrane Handbook for Systematic Reviews of Interventions Version 6.1 (updated September 2020). Cochrane, 2020. Available from: www.training.cochrane.org/handbook. [↑](#footnote-ref-12)
12. https://www.sign.ac.uk/assets/search-filters-observational-studies.docx [↑](#footnote-ref-13)
13. https://www.crd.york.ac.uk/crdweb/searchstrategies.asp#nhseedmedline [↑](#footnote-ref-14)
14. https://www.crd.york.ac.uk/crdweb/searchstrategies.asp#daremedline. [↑](#footnote-ref-15)
15. Note a low value indicates large benefit [↑](#footnote-ref-16)