

# Treatment Algorithm for Multiple Sclerosis Disease-Modifying Therapies

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## Contents

1. Purpose of this algorithm.....	3
2. Principles of organisation of MS disease-modifying therapy services.....	3
3. Definitions.....	4
4. Starting criteria common to all DMTs.....	4
5. Suggested common stopping criteria for all DMTs.....	5
6. General principles of drug switching.....	5
7. Inappropriate DMTs.....	5
8. Treatment algorithm for single clinical episode with radiological activity .....	6
9. Treatment algorithm for first-line therapy of relapsing-remitting multiple sclerosis (RRMS) ...	7
10. Treatment algorithm for intolerance to first line therapy .....	8
11. Treatment algorithm for second-line therapy of RRMS, with disease activity on first line therapy.....	9
12. Treatment algorithm for disease activity on second-line therapy.....	10
13. Treatment algorithm for relapsing progressive multiple sclerosis .....	11
Addendum 1: Table of drug authorisation, NICE indication and NHS England positioning .....	12
Addendum 2: Indications not currently approved by NHS England, but considered by the authors .....	16
Addendum 3: Authors of the algorithm.....	17
Addendum 4: Voting of membership .....	18
Appendix 1: Acronyms and abbreviations.....	23
Summary of changes to this document .....	24

## 1. Purpose of this algorithm

The purpose of this algorithm is to provide a framework to aid decision-making for multiple sclerosis (MS) specialists and patients, to help reduce excessive variation in practice, and ensure safe and effective prescribing. It is understood that there may be situations where there is no single 'right' or 'wrong' therapeutic approach, and different experts may reasonably hold different views.

This algorithm is constrained by the regulatory status, NICE approvals and commissioning status, of the disease-modifying drugs licensed for MS in England. Other guidance on disease-modifying drugs in MS, such as the Association of British Neurologists' guidelines<sup>1</sup> are different in scope and may make recommendations applying to the devolved administrations, outside the geographical and National Institute for Health and Care Excellence (NICE) constraints applying to NHS England.

NHS England's Neuroscience Clinical Reference Group (CRG) will review this algorithm to reflect any new NICE Technology Appraisal Guidance or approvals within 3 months of guidance publication.

## 2. Principles of organisation of MS disease-modifying therapy services

The patient should be at the centre of any service for disease-modifying therapies. These services should be organised to optimise timely and equitable access of people with MS to disease-modifying therapies (DMTs).

Every region should make all licensed MS drugs available to all people with MS in that region. It is expected that all DMT prescribers in a region will participate in a network of audit, quality control and education.

The minimum team for any prescribing service is a MS specialist consultant neurologist and a MS specialist nurse, working with support from a specialist MS centre and its multi-disciplinary team.

Complex cases or those where higher-risk DMTs (for instance cladribine and the monoclonal antibody therapies) are proposed, should be discussed at a multi-disciplinary team (MDT) meeting, defined as a minimum of at least two MS specialist consultant neurologists plus at least one specialist MS nurse, with access to neuro-radiology expertise. Ideally the MDT would also incorporate additional specialist healthcare professionals, including a neuropharmacist.

At each prescribing centre, there should be an individual or team responsible for the governance of safety monitoring.

Services should be organised to facilitate collection of data for mandatory requirements (for instance, annual Expanded Disability Status Scale (EDSS) for reporting on a web-based clinical decision support system) and voluntary MS registers.

This treatment algorithm applies to all age groups, including children. Children may receive DMTs if;

- (i) they are licensed for children,  
or
- (ii) they have a recognised dose for children (for instance are cited in the British National Formulary)

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<sup>1</sup> Scolding N, Barnes D, Cader S, Chataway J, Chaudhuri A, Coles A, Giovannoni G, Miller D, Rashid W, Schmierer K, Shehu A, Silber E, Young C, Zajicek J. Association of British Neurologists: revised (2015) guidelines for prescribing disease-modifying treatments in multiple sclerosis. *Pract Neurol*. 2015 Aug;15(4):273-9

- (iii) OR: if neither of the previous two criteria apply the child is post-pubescent. The management of pre-pubescent children with MS should be discussed at the meetings of the national network of paediatric MS centres.

### 3. Definitions

The definitions below are taken from the [Clinical Commissioning Policy for the use of Disease Modifying Therapies for patients with Multiple Sclerosis](#), published by NHS England in 2014. They represent useful explanations of terms used by the regulatory authorities, which were translated into NICE approvals. However, there is no difference in biological significance between relapses causing differing varying degrees of disability; all indicate disease activity.

**Clinically significant relapse:** All relapses are clinically significant, but in usual practice relapses contributing to the eligibility for Disease Modifying Therapies are:

- Any motor relapse
- Any brainstem relapse
- A sensory relapse if it leads to functional impairment
- Relapse leading to sphincter dysfunction
- Optic neuritis
- Intrusive pain lasting more than 48 hours.

**Disabling relapse:** A disabling relapse is defined as any relapse which fulfils one or more of the following criteria:

- Affects the patient's social life or occupation, or is otherwise considered disabling by the patient
- Affects the patient's activities of daily living as assessed by an appropriate method
- Affects motor or sensory function sufficiently to impair the capacity or reserve to care for themselves or others
- Needs treatment/hospital admission.

**Highly active disease:** Patients with an unchanged or increased relapse rate or ongoing severe relapses compared with the previous year despite treatment with beta interferon.<sup>2</sup> The NICE appraisal on cladribine offers a slightly different definition: "defined as 1 relapse in the previous year and magnetic resonance imaging (MRI) evidence of disease activity." [From NICE Technical Advice (TA) 254: Fingolimod for the treatment of highly active relapsing-remitting multiple sclerosis]

**Rapidly evolving severe (RES) relapsing–remitting disease:** Defined by two or more disabling relapses in one year and one or more gadolinium-enhancing lesions on brain MRI or a significant increase in T2 lesion load compared with a previous MRI. [From NICE Technical Advice (TA) 127: Natalizumab for the treatment of adults with highly active relapsing-remitting multiple sclerosis]

### 4. Starting criteria common to all DMTs

In general, treatment should be recommended as soon as a patient becomes eligible. For a patient to be eligible for any DMT, they must fulfil the following criteria:

- Sustained disability due to multiple sclerosis is less than Expanded Disability Status Scale (EDSS) 7.0, i.e. at least ambulant with two crutches. (Patients experiencing a relapse

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<sup>2</sup> We note that later definitions of Highly Active Disease incorporate the requirement for a certain number of T2 lesions. We do not think this is necessary.

may transiently have disability greater than EDSS 7.0; if they recover to a sustained EDSS less than 7.0, they are eligible for DMTs)

- No evidence of non-relapsing progressive multiple sclerosis.

It is important that, at the start of treatment, the patient understands that treatment may be stopped if it is ineffective, intolerable adverse events arise, the patient becomes pregnant or they develop progressive disease or fixed disability above EDSS 6.5.

## 5. Suggested common stopping criteria for all DMTs

The current DMT should be stopped if any of the following criteria are met:

1. No reduction in frequency or severity of relapses compared with pre-treatment phase following adequate exposure to the DMTs (which varies for each DMT, but should be a minimum of 6 months)
2. Intolerable adverse effects of the drug
3. Development of inability to walk (EDSS 7.0), persistent for more than 6 months due to MS
4. Confirmed secondary progressive disease with an observable increase in disability for more than a 12 month period, in the absence of relapse activity. Secondary progressive disease would usually only be diagnosed in patients with an EDSS of 6.0 or greater. (Except for the rare phenotype of “relapsing-progressive multiple sclerosis” detailed in section 13).

Criteria 1 and 2 might lead to switching to alternative DMTs. Criteria 3 and 4 will lead to stopping all DMTs.

Past criteria have included pregnancy, breast feeding or attempting conception, but increasing evidence shows that some DMTs may be considered safe in these situations.

Stopping DMTs should lead to continued care within the MS team or transfer of care to services which can provide appropriate support, such as neuro-rehabilitation.

If a drug is stopped for a reason other than intolerance or lack of efficacy, then it may be restarted at a later date, even though the patient may not have “requalified” through new lesions. This may apply, for instance, to people who come off a drug during pregnancy or to take an experimental drug in a trial.

## 6. General principles of drug switching

Switching can be done for reasons of intolerance (which includes burdensome modes of administration), or disease activity. None of the drugs promise 100% efficacy and some patients and physicians may choose to tolerate some disease activity without changing drugs.

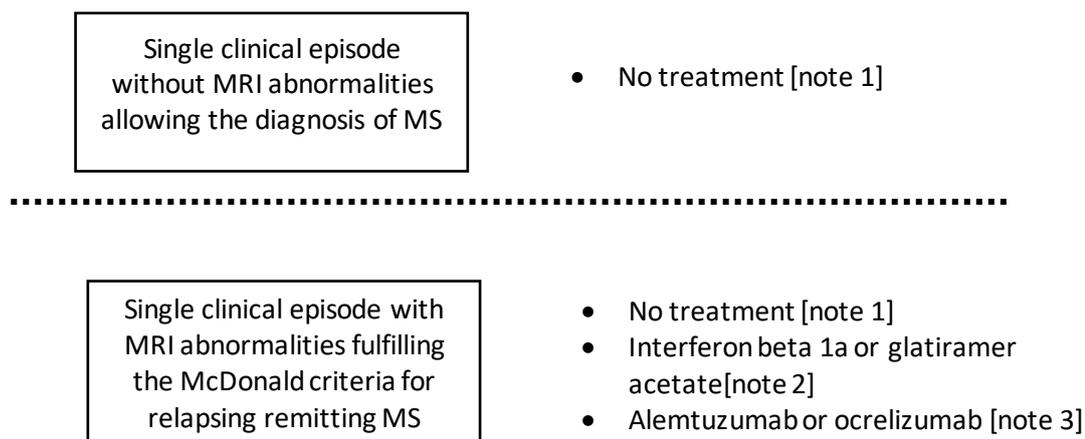
Disease activity should prompt consideration of switching only if there has been adequate exposure, with good adherence, to the DMT (which varies for each DMT, but should be a minimum of 6 months).

Evidence for disease activity that should prompt consideration of switching for all DMTs is clinical relapses; MRI evidence of disease activity usefully supplements this assessment. NICE has approved the use of alemtuzumab based on radiological disease activity alone; we suggest this means 2 or more new MS lesions on MRI over a year.

## 7. Inappropriate DMTs

- Corticosteroids and plasma exchange have roles in the treatment of acute relapses of multiple sclerosis, but do not have long-term disease-modifying efficacy.
- Intravenous immunoglobulin has no place in the treatment of multiple sclerosis.

## 8. Treatment algorithm for single clinical episode with radiological activity



### Notes:

1. Trials of first-line therapies in people with the original definition of Clinically Isolated Syndrome (CIS) at high risk of conversion have NOT shown a convincing long-term effect on the accumulation of disability. In 2018, NICE concluded that it was “unable to make recommendations for treating clinically isolated syndrome because the diagnostic criteria for multiple sclerosis and clinically isolated syndrome have changed and the treatment pathway has evolved”. These new diagnostic criteria are the 2010 and 2017 Mc Donald criteria.
2. Under 2018 NICE guidance: interferon beta 1a and glatiramer acetate can be offered to people with “relapsing-remitting” multiple sclerosis under the new diagnostic criteria.
3. In exceptional circumstances, where clinical or radiological markers indicate a poor prognosis for rapidly developing permanent disability, alemtuzumab or ocrelizumab may be considered after a single clinical episode with MRI activity. Physicians and patients should weigh up the considerable risks and burden of monitoring associated with this drug, against the potential benefit.

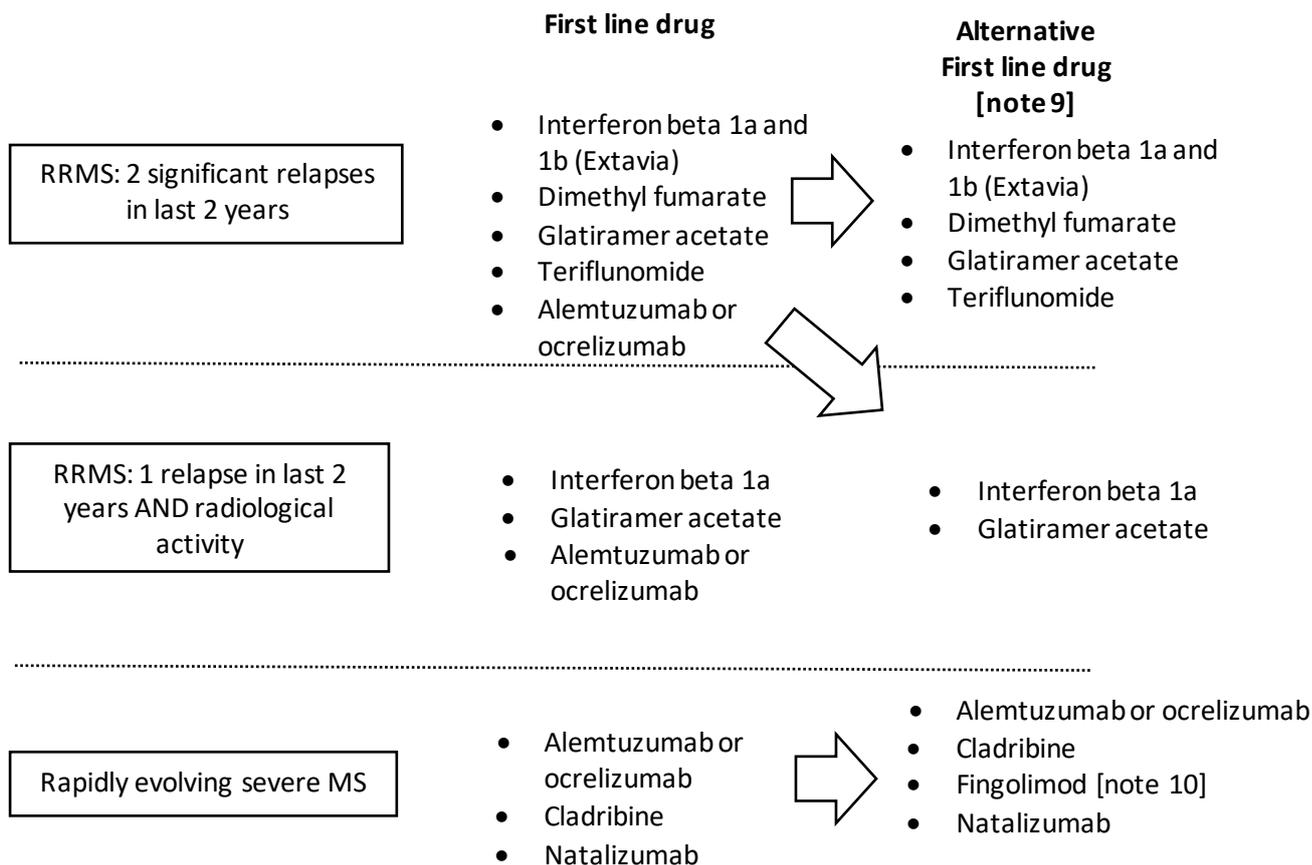
## 9. Treatment algorithm for first-line therapy of relapsing-remitting multiple sclerosis (RRMS)

RRMS: 2 significant relapses in last 2 years	<ul style="list-style-type: none"> <li>• Interferon beta 1a and 1b (Extavia)</li> <li>• Dimethyl fumarate [note 5]</li> <li>• Glatiramer acetate</li> <li>• Teriflunomide</li> <li>• Alemtuzumab or ocrelizumab [note 7]</li> </ul>
RRMS: 1 relapse in last 2 years AND radiological activity	<ul style="list-style-type: none"> <li>• Interferon beta 1a and glatiramer acetate [note 6]</li> <li>• Alemtuzumab or ocrelizumab [note 7]</li> </ul>
Rapidly evolving severe MS	<ul style="list-style-type: none"> <li>• Alemtuzumab or ocrelizumab [note 8]</li> <li>• Cladribine [note 8]</li> <li>• Natalizumab</li> </ul>

### Notes:

4. For RRMS (that is not rapidly evolving severe (RES) RRMS), beta-interferon, glatiramer acetate and teriflunomide are effective and safe.
5. There is some evidence that dimethyl fumarate may be more effective at suppressing relapses than beta-interferon, glatiramer and teriflunomide.
6. The clinical commissioning policy for the use of Disease Modifying Therapies for patients with Multiple Sclerosis, published by NHS England in 2014 allowed the use of beta-interferon in “patients with only a single major relapse in the preceding two years, but combined with MRI evidence of continuing disease activity”. The NICE 2018 guidance suggests glatiramer acetate may also be used in this context.
7. For RRMS (that is not RES), alemtuzumab is an option that may be considered, but we note it is considerably more high-risk than the other options. It should be used only when the patient and MS specialists accept the significant risks and burden of monitoring.
8. Alemtuzumab or ocrelizumab and cladribine may be considered - by some patients and physicians - a safer option than natalizumab when John Cunningham (JC) virus serology is high-index positive.

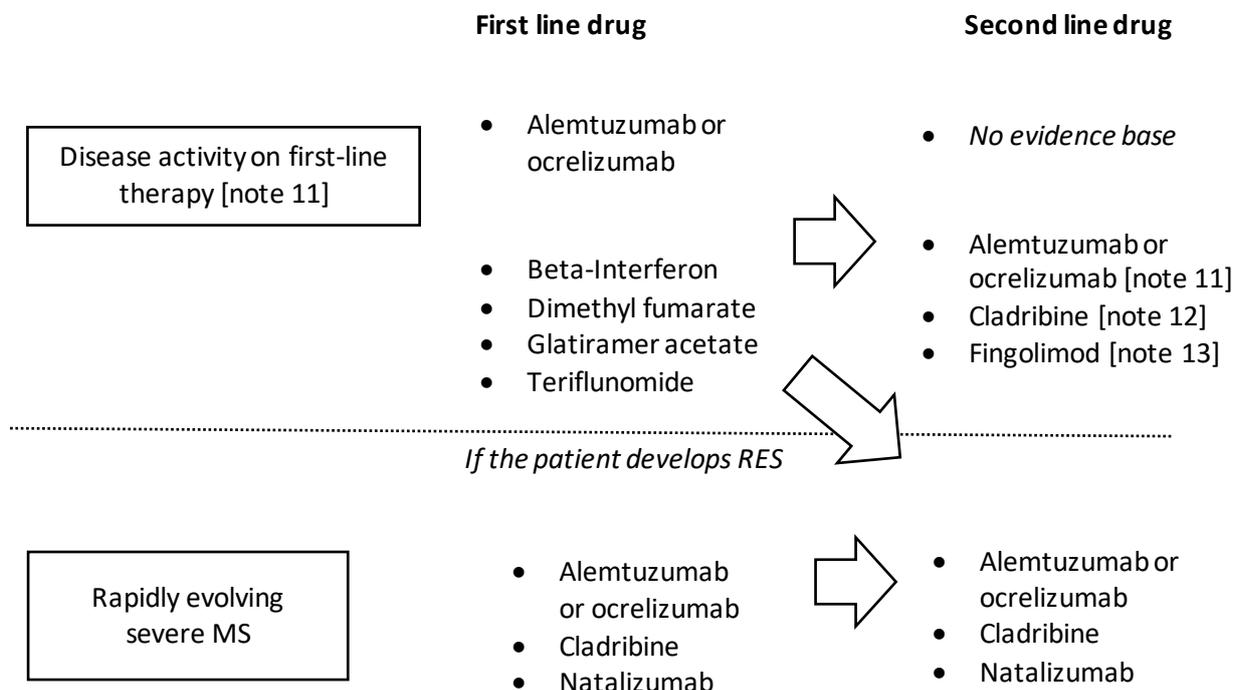
## 10. Treatment algorithm for intolerance to first line therapy



### Notes:

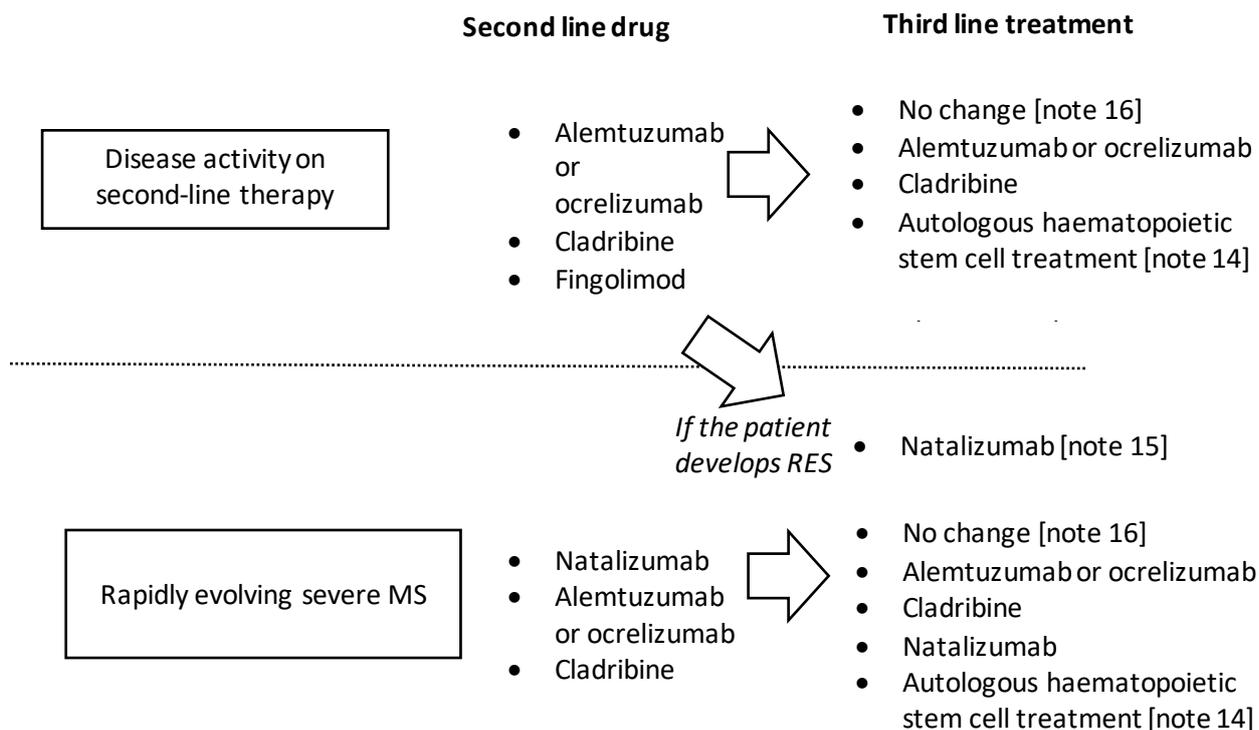
9. If a patient satisfies the eligibility criteria for a first-line therapy, and then is relapse-free on a drug to which he/she becomes intolerant, they may be switched to another DMT even though their relapses may now fall outside the eligibility window.
10. NHS England 2014 policy states that fingolimod can be used as an alternative to natalizumab for those patients receiving natalizumab who are at high risk of developing progressive multifocal leukoencephalopathy (PML) as defined by the following:
  - (i) JCV exposure indicated by anti-JCV antibody positive status,
  - (ii) Receiving an immunosuppressant prior to receiving natalizumab, or
  - (iii) Natalizumab treatment duration of >2 years. If patients develop a severe adverse effect to natalizumab (e.g. anaphylaxis), and they have not previously received fingolimod, then it may be appropriate to use fingolimod.

## 11. Treatment algorithm for second-line therapy of RRMS, with disease activity on first line therapy



11. Definition of disease activity: treatment failure may be indicated by either clinical or radiological relapse-related changes, after significant exposure to the treating drug, with changes indicating a poor prognosis for future disability. For instance, alemtuzumab is specifically licensed for “active disease defined by clinical or imaging features”.
12. For cladribine, NICE specifically defined treatment failure as “1 relapse in the previous year and MRI evidence of disease activity.”
13. For fingolimod: under previous guidance, fingolimod may be given if patients have an unchanged or increased relapse rate or ongoing severe relapses compared with the previous year despite treatment with beta interferon or glatiramer acetate. This is now extended to include disease activity on teriflunomide and dimethyl fumarate (DMF).

## 12. Treatment algorithm for disease activity on second-line therapy



14. Autologous haematopoietic stem cell treatment for autoimmunity is commissioned at specialised centres and is currently being offered to some people with MS in some parts of the UK. But there is not yet an adequately controlled trial of its efficacy relative to other potent therapies. We recommend that it is made available equitably to all people with MS, but we propose that it should only be considered for people with relapsing disease (not progressive) who have failed high-activity licensed disease-modifying therapies, and are prepared to accept the significant risks of the procedure and are eligible under European Group for Blood and Marrow Transplantation (EBMT) guidelines. We recommend that this treatment is offered only by units with expertise both in the management of aggressive multiple sclerosis and the use of autologous haematopoietic stem treatment.
15. The risk of PML on natalizumab is likely to be increased after alemtuzumab or cladribine, given the prolonged lymphopenia induced by these drugs. But, where the patient is negative for JC serology, this may rarely be appropriate.
16. After considering all these options, it may be appropriate to continue the second-line therapy, despite evidence of disease activity. None of the drugs promise 100% efficacy and some patients and physicians may choose to tolerate some disease activity without changing drugs.

### 13. Treatment algorithm for relapsing progressive multiple sclerosis

Only interferon beta 1b (Extavia) is approved by NICE for relapsing-progressive disease, under these criteria (NHS England 2014 policy):

#### Starting Criteria

All of the following criteria must be met. The patient:

- has had at least two disabling relapses in two years
- is able to walk 10m or more (EDSS less than 7.0)
- has had minimal increase in disability due to progression over the past 2 years
- is aged over 18 years
- has no contra-indications.

We recommend that patients fulfilling these criteria are investigated for MRI evidence of disease activity. If a high load of active inflammation is seen, the classification of “progressive relapsing” should be reconsidered by the MDT.

#### Stopping Criteria

One or more of the following criteria are met:

- No reduction in frequency or severity of relapses compared with pre-treatment phase following a minimum 6 month period of beta interferon treatment
- Intolerable adverse effects of the drug
- Development of inability to walk, persistent for more than 6 months, unless unable to walk for reasons other than MS
- Stopping criteria should be made known to patients and agreed before treatment is begun.

## Addendum 1: Table of drug authorisation, NICE indication and NHS England positioning

Drug	Marketing Authorisation	NICE indication	NHS ENGLAND 2014 policy
interferon-1a	<p>AVONEX is indicated for the treatment of: I (i) Patients diagnosed with relapsing multiple sclerosis (MS). In clinical trials, this was characterised by two or more acute exacerbations (relapses) in the previous three years without evidence of continuous progression between relapses; AVONEX slows the progression of disability and decreases the frequency of relapses; (ii) Patients with a single demyelinating event with an active inflammatory process, if it is severe enough to warrant treatment with intravenous corticosteroids, if alternative diagnoses have been excluded, and if they are determined to be at high risk of developing clinically definite multiple sclerosis (see section 5.1).</p> <p>REBIF is indicated for the treatment of relapsing multiple sclerosis. In clinical trials, this was characterised by two or more acute exacerbations in the previous two years.</p> <p>PLEGRIDY is indicated in adult patients for the treatment of relapsing remitting multiple sclerosis</p>	<p>[ID1809 NICE]</p> <p>Interferon beta-1a [AVONEX and REBIF] is recommended as an option for treating multiple sclerosis, only if the person has relapsing–remitting multiple sclerosis.</p> <p>NICE is not currently in a position to make recommendations on PLEGRIDY pegylated interferon beta-1a.</p>	<p>All of the following criteria must be met. The patient: (i) has had at least 2 clinically significant relapses in previous 2 years; (ii) is able to walk 10m or more**; (iii) is not pregnant or attempting conception.</p> <p>Neurologists may, in certain other circumstances where the evidence for efficacy is less secure, also consider advising treatment after discussion with the patient concerning the risks and benefits. For example: (i) Patients within 12 months of a clinically significant clinically isolated syndrome when MRI evidence predicts a high likelihood of recurrent episodes (i.e. development of MS); (ii) patients with only a single major relapse in the preceding two years, but combined with MRI evidence of continuing disease activity (i.e. meet the revised McDonald criteria for MS); (iii) individuals aged less than 18 with relapsing remitting MS</p> <p>** For patients who can walk between 10 and 99 m (aided or unaided, EDSS 6.0 to 6.5), treatment with DMT is permitted but recommended less strongly than for patients able to walk more than 100m unaided (EDSS 5.5 or less).</p>
interferon -1b	<p>BETAFERON is indicated for the treatment of (i) patients with a single demyelinating event with an active inflammatory process, if it is severe enough to warrant treatment with intravenous corticosteroids, if alternative diagnoses have been excluded, and if they are determined to be at high risk of developing clinically definite multiple sclerosis; (ii) patients with relapsing-remitting multiple sclerosis and two or more relapses within the last two years. (iii) patients with secondary progressive multiple sclerosis with active disease, evidenced by relapses.</p> <p>EXTAVIA is indicated for the treatment of (i) Patients with a single demyelinating event with an active inflammatory process, if it is severe enough to warrant treatment with intravenous corticosteroids, if alternative diagnoses have been excluded, and if they are determined to be at high risk of developing clinically definite multiple sclerosis; (ii) Patients with relapsing remitting multiple sclerosis and two or more</p>	<p><b>BETAFERON is not recommended</b></p> <p>EXTAVIA is recommended as an option for treating multiple sclerosis, only if the person has relapsing–remitting multiple sclerosis and has had 2 or more relapses within the last 2 years or the person has secondary progressive multiple sclerosis with continuing relapses</p>	<p>As per interferon-1a guidance, but also permits the use of interferon-1b in relapsing-progressive disease.</p>

	relapses within the last two years; (iii) Patients with secondary progressive multiple sclerosis with active disease, evidenced by relapses.		
Glatiramer acetate	COPAXONE and BRABIO are indicated for the treatment of relapsing forms of multiple sclerosis (MS) (see section 5.1 for important information on the population for which efficacy has been established). Neither are indicated in primary or secondary progressive MS	Glatiramer acetate is recommended as an option for treating multiple sclerosis, only if the person has relapsing–remitting multiple sclerosis. (N.b. “Stakeholders consider glatiramer acetate to be the safest drug for anyone who is planning to become pregnant”.)	As per interferon-beta guidance, but must be able to walk 100m or more
teriflunomide	AUBAGIO is indicated for the treatment of adult patients with relapsing remitting multiple sclerosis (MS).	<i>[TA303] Published date: 22 January 2014 Last updated: 01 June 2014:</i>  Teriflunomide is recommended as an option for treating adults with active relapsing–remitting multiple sclerosis (normally defined as 2 clinically significant relapses in the previous 2 years), only if  they do not have highly active or rapidly evolving severe relapsing–remitting multiple sclerosis	
dimethyl fumarate	Tecfidera is indicated for the treatment of adult patients with relapsing remitting multiple sclerosis	<i>[TA320] Published date: 27 August 2014:</i> Dimethyl fumarate is recommended as an option for treating adults with active relapsing–remitting multiple sclerosis (normally defined as 2 clinically significant relapses in the previous 2 years), only if  they do not have highly active or rapidly evolving severe relapsing–remitting multiple sclerosis	
fingolimod	Gilenya is indicated as single disease modifying therapy in highly active relapsing remitting multiple sclerosis for the following adult patient groups:  - Patients with highly active disease despite a full and adequate course of treatment with at least one disease modifying therapy  or  - Patients with rapidly evolving severe relapsing remitting multiple sclerosis defined by 2 or more disabling relapses in one year, and with 1 or more Gadolinium enhancing lesions on brain MRI or a significant increase in T2 lesion load as compared to a previous recent MRI.	<i>[TA254] Published date: 25 April 2012:</i>  Fingolimod is recommended as an option for the treatment of highly active multiple sclerosis:  Patients have an unchanged or increased relapse rate or ongoing severe relapses compared with the previous year despite treatment with beta interferon* or glatiramer acetate	Fingolimod is recommended as an option for the treatment of highly active multiple sclerosis:  Patients have an unchanged or increased relapse rate or ongoing severe relapses compared with the previous year despite treatment with beta interferon* or glatiramer acetate  OR  As an alternative to natalizumab for those patients receiving natalizumab who are at high risk of developing progressive multifocal leukoencephalopathy (PML) as defined by the following:  o JCV exposure indicated by anti-JCV antibody positive status  o Receiving an immunosuppressant prior to receiving natalizumab  o Natalizumab treatment duration of >2 years

natalizumab	<p>Patients aged 18 years and over with highly active disease activity despite a full and adequate course of treatment with at least one disease modifying therapy (DMT), a beta-interferon or glatiramer acetate.</p> <p>These patients may be defined as those who have failed to respond to a full and adequate course (normally at least one year of treatment) of beta-interferon or glatiramer acetate. Patients should have had at least 1 relapse in the previous year while on therapy, and have at least 9 T2-hyperintense lesions in cranial Magnetic Resonance Image (MRI) or at least 1 Gadolinium-enhancing lesion. A “non-responder” could also be defined as a patient with an unchanged or increased relapse rate or ongoing severe relapses, as compared to the previous year.</p> <p>or</p> <p>Adult Patients aged 18 years and over with rapidly evolving severe relapsing remitting multiple sclerosis defined by 2 or more disabling relapses in one year, and with 1 or more Gadolinium enhancing lesions on brain MRI or a significant increase in T2 lesion load as compared to a previous recent MRI</p>	<p>[TA127] Published date: 22 August 2007: rapidly evolving severe relapsing–remitting multiple sclerosis (RES). RES is defined by two or more disabling relapses in 1 year, and one or more gadolinium-enhancing lesions on brain magnetic resonance imaging (MRI) or a significant increase in T2 lesion load compared with a previous MRI</p>	<p>For patients who</p> <ul style="list-style-type: none"> <li>has had two or more disabling relapses in the past year</li> <li>has one or more gadolinium-enhancing lesions on MRI or increase in T2 lesion load compared with previous MRI unless comparator MRI is unavailable or assessment of gadolinium-enhancement is unreliable as the patient is treated with steroids at around the time of scan.</li> <li>has had no previous disease modifying therapy OR is receiving treatment with beta interferon and does not meet the agreed stopping criteria.</li> </ul> <p>*As per NICE Technology Appraisal Guidance 127 patients with high disease activity taking beta interferon or glatiramer acetate but do not fulfil the RES criteria will not be routinely funded for natalizumab.</p>
alemtuzumab	<p>LEMTRADA is indicated for adult patients with relapsing remitting multiple sclerosis (RRMS) with active disease defined by clinical or imaging features</p>	<p>[TA312] Published date: 28 May 2014: Alemtuzumab is recommended as an option, within its marketing authorisation, for treating adults with active relapsing–remitting multiple sclerosis.</p>	<p>NHS England will fund up to three cycles of alemtuzumab. Any further 4r cycles would need to be approved by NICE under a review of TA312.</p>
cladribine	<p>MAVENCLAD is indicated for the treatment of adult patients with highly active relapsing multiple sclerosis (MS) as defined by clinical or imaging features</p>	<p>[TA493] Published date: 06 December 2017: Cladribine tablets are recommended as an option for treating highly active multiple sclerosis in adults, only if the person has: (1) rapidly evolving severe relapsing–remitting multiple sclerosis, that is, at least 2 relapses in the previous year and at least 1 T1 gadolinium-enhancing lesion at baseline MRI or (2) relapsing–remitting multiple sclerosis that has responded inadequately to treatment with disease-modifying therapy, defined as 1 relapse in the previous year and MRI evidence of disease activity.</p>	
ocrelizumab	<p>Ocrevus is indicated for the treatment of adult patients with relapsing forms of multiple sclerosis (RMS) with active disease defined by clinical or imaging features.</p> <p>Ocrevus is indicated for the treatment of adult patients with early primary progressive multiple sclerosis (PPMS) in terms of disease duration and level of</p>	<p>[TA533] Published date: 25 July 2018</p> <p>Ocrelizumab is recommended as an option for treating relapsing–remitting multiple sclerosis in adults with active disease defined by clinical or imaging features, only if</p>	

	disability, and with imaging features characteristic of inflammatory activity.	alemtuzumab is contraindicated or otherwise unsuitable.	
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## Addendum 2: Indications not currently approved by NHS England, but considered by the authors

The following use of DMTs is not currently funded and was considered by the authors of this algorithm. If an individual or institution or company wish for these to be considered, they would need to follow NHS England's policy proposition route or ask NICE to re-evaluate their guidance.

1. Although not licensed for use in the clinically isolated syndrome, we note trial data supporting glatiramer and teriflunomide's use in this context, in order to reduce subsequent relapse rate (but without an effect on disability accumulation). The committee were divided on the usefulness of these drugs in the clinically isolated syndrome.
2. Fingolimod has a licence for first-line use in RES, but is not approved for NICE for this indication. However it is being used first line in Scotland and in Wales for rapidly evolving severe multiple sclerosis. Outside the EU, it is being used as first-line therapy for regular RRMS. We propose that NHS England consider fingolimod for first-line therapy of RES.
3. NICE guidance for teriflunomide and DMF specifies they are not indicated for RES, but some of the committee requested a "de-escalation" from natalizumab to these agents when there is intolerance to natalizumab, for patients with RES.
4. DMF is currently being used, in some regions, for people who have shown break through disease on other first-line therapies, although it is not approved for this indication. A number of the group propose that NHS England adopt the use of DMF for disease activity on first-line therapy.
5. One option for people with RES and disease activity on natalizumab, for risk-averse patients for instance, is to "de-escalate" by using a drug of lesser efficacy. Fingolimod, dimethyl fumarate and teriflunomide might be useful in this context, but they are not approved for this use. We propose that NHS England consider permitting fingolimod and dimethyl fumarate for treatment of RES, after natalizumab.

### Addendum 3: Authors of the algorithm

#### Attendees at a meeting on the 12<sup>th</sup> December 2016

Alasdair Coles (Chair),	Neurologist
Sian Price	Neurologist
Gavin Giovannoni	Neurologist
Brendan Mclean	Neurologist
Neil Scolding	Neurologist
Neil Robertson	Neurologist
Claire McCarthy	Neurologist
Jo Sopala	MS Trust
Sorrel Bickley	MS Society
Malcolm Qualie	NHS England
Mandy Matthews	South Worcestershire CCG
Adrian Williams	Neurology CRG
Samantha Colhoun	Specialist MS Nurse
Jeremy Robson	Neurology Pharmacist
Rachel Dorsey	Neurology Pharmacist

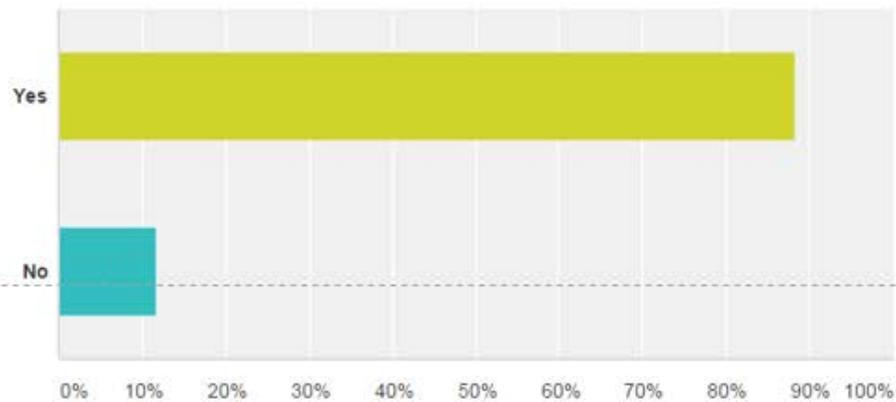
#### Members of the MS Advisory Group of the ABN, who commented on the algorithm

Waqar Rashid	Neurologist
Robert Brenner	Neurologist
Adnan Al-Araji	Neurologist
Bruno Gran	Neurologist

## Addendum 4: Voting of membership

**Do you think that dimethyl fumarate (Tecfidera) is a more efficacious treatment of MS than first-line drugs [beta-interferon, copaxone, teriflunomide]?**

Answered: 17 Skipped: 0



Based on relative reductions in relapse rate and modelling. Not sure that it is better than Teriflunomide; all the Teri trials have had positive effects on disease progression.

1/23/2017 7:48 PM [View respondent's answers](#)

Only just

1/23/2017 12:11 PM [View respondent's answers](#)

No evidence that it is. CONFIRM trial showed no superiority of DMF bd dose over copaxone (though authors state not powered). No head to head trial with IFN.

1/19/2017 8:39 PM [View respondent's answers](#)

Evidence suggests that dimethyl fumarate is more effective in reducing relapse rates and as effective for disability progression

1/16/2017 9:21 AM [View respondent's answers](#)

Data is mixed but CONFIRM trial raises issues - was not a proper comparator study and DMF showed no significant benefit in terms of disability suppression

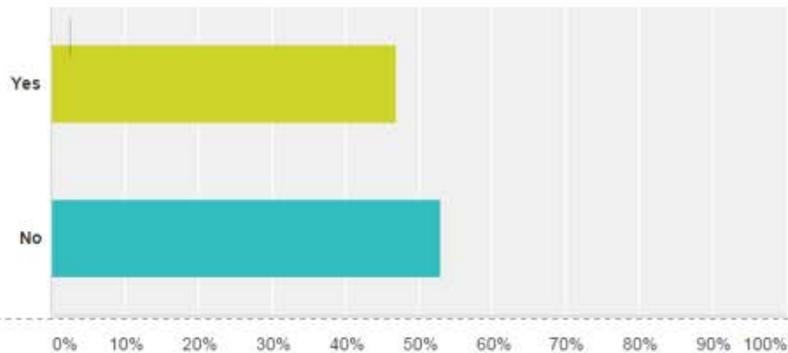
1/15/2017 9:55 PM [View respondent's answers](#)

But only on relapses

1/15/2017 10:05 AM [View respondent's answers](#)

**Do you think that dimethyl fumarate should be presented as a second-line treatment in the algorithm, alongside fingolimod and alemtuzumab?**

Answered: 17 Skipped: 0



Answer Choices	Responses	Count
Yes	47.06%	8
No	52.94%	9
Total		17

Yes, but not necessarily based on efficacy. There are many attributes that make DMF suitable for some patients.

1/23/2017 7:48 PM [View respondent's answers](#)

I like options, even if it's not as good

1/23/2017 12:11 PM [View respondent's answers](#)

No evidence for higher efficacy over other first line therapies. Fingolimod and alemtuzumab both have shown efficacy over IFN.

1/19/2017 6:39 PM [View respondent's answers](#)

gives another option if adverse effects etc with fing/alem

1/19/2017 12:53 PM [View respondent's answers](#)

I would only use it second line for tolerability switches

1/16/2017 1:14 PM [View respondent's answers](#)

Based on clinical opinion expressed - only in cases where tolerability or safety issues

1/16/2017 9:21 AM [View respondent's answers](#)

Whilst accepting the limited data on its efficacy as a second line agent, we should be allowed to have it as an option.

1/16/2017 8:56 AM [View respondent's answers](#)

It could be allowed for safety / tolerability switches and when there are patient-specific concerns about the safety of fingolimod and alemtuzumab

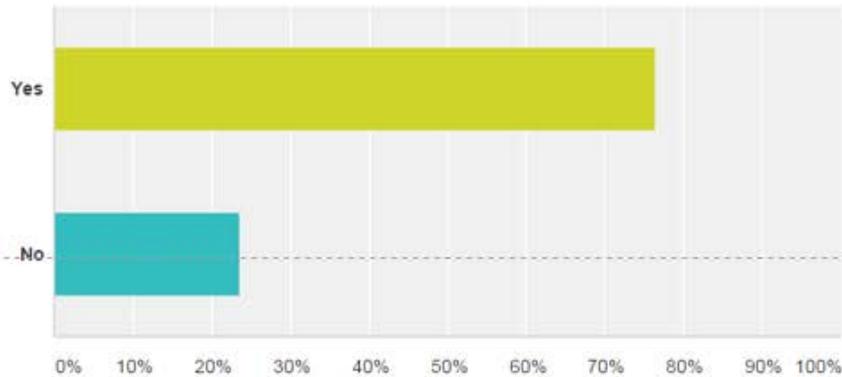
1/15/2017 11:26 PM [View respondent's answers](#)

As above - 40% RR reduction in CONFIRM is not too dissimilar to other first lines, not second line

1/15/2017 9:55 PM [View respondent's answers](#)

**Do you think that dimethy fumarate should be presented in the algorithm as intermediate in effectiveness between [beta-interferon, copaxone, teriflunomide] and [natalizumb, fingolimod, alemtuzumab]?**

Answered: 17 Skipped: 0



Answer Choices	Responses	Count
Yes	76.47%	13
No	23.53%	4
Total		17

Yes against IFN-beta and GA. Less confident against Teri. Therefore I would suggest leaving them all on one level.  
1/23/2017 7:48 PM [View respondent's answers](#)

Trial data suggests that DF and Fingolimod could be grouped together with regards to efficacy rather than Fingolimod being listed as effective as Alemtuzumab and Natalizumab  
1/23/2017 5:28 PM [View respondent's answers](#)

In MS Decisions we group dimethyl fumarate and fingolimod together as intermediate treatments  
1/23/2017 9:52 AM [View respondent's answers](#)

Although I would put Fingo in same category as DMF  
1/23/2017 8:40 AM [View respondent's answers](#)

No clear evidence of inferiority to fingo  
1/22/2017 11:17 PM [View respondent's answers](#)

I think it should sit in the same box as other DMTs but with the vague statement as in the draft protocol that 'Dimethyl fumarate may be more effective'. Based on ARR and disability reduction in DEFINE and effect on gad and T2 lesions. CONFIRM trial disappointing.  
1/19/2017 8:39 PM [View respondent's answers](#)

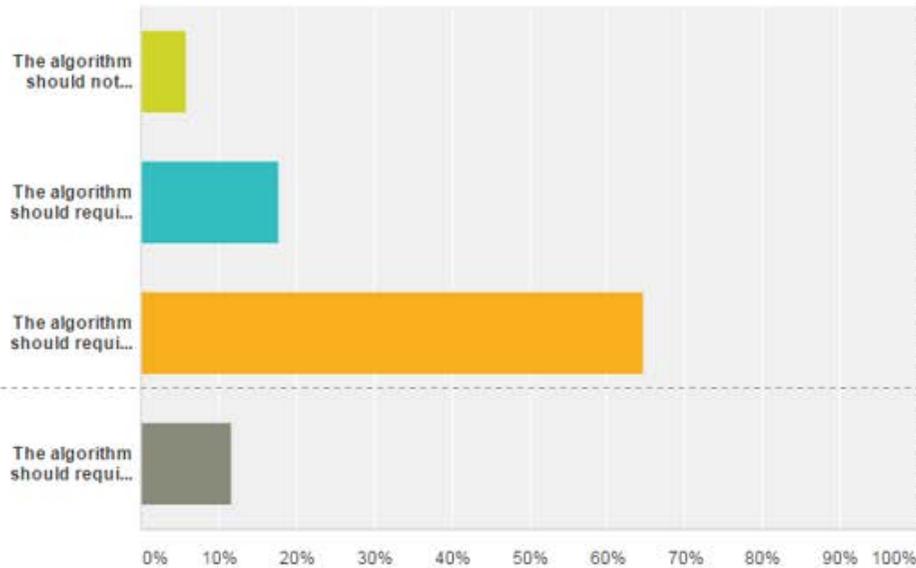
I think is a little stronger than the injectibles, but not as powerful as fingolimod.  
1/16/2017 8:56 AM [View respondent's answers](#)

Need additional data eg proper comparator study to justify this  
1/15/2017 9:55 PM [View respondent's answers](#)

this could be tucked away in the notes  
1/15/2017 10:05 AM [View respondent's answers](#)

### Which best fits your view on multi-disciplinary teams in decision-making about DMTs?

Answered: 17 Skipped: 0



Answer Choices	Responses
▼ The algorithm should not mention multi-disciplinary teams in decision-making about DMTs.	5.88% 1
▼ The algorithm should require multi-disciplinary teams in decision-making about all escalations from first-line therapy.	17.65% 3
▼ The algorithm should require multi-disciplinary teams in decision-making about all escalations to monoclonal antibody therapy.	64.71% 11
▼ The algorithm should require multi-disciplinary teams in decision-making about complex cases, not otherwise defined.	11.76% 2

We welcome initiatives that support MDTs to work more closely together and enhance care coordination. We also support the fourth option (ie. complex cases), provided clarity is given on what constitutes a complex case.  
 1/23/2017 9:28 PM [View respondent's answers](#)

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I think we need time for them to develop and it should be access to one initially  
 1/23/2017 12:11 PM [View respondent's answers](#)

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and complex cases  
 1/22/2017 10:48 PM [View respondent's answers](#)

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And complex cases.  
 1/19/2017 8:39 PM [View respondent's answers](#)

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where practical(dont want to delay treatment etc) and certainly for complex cases  
 1/19/2017 12:53 PM [View respondent's answers](#)

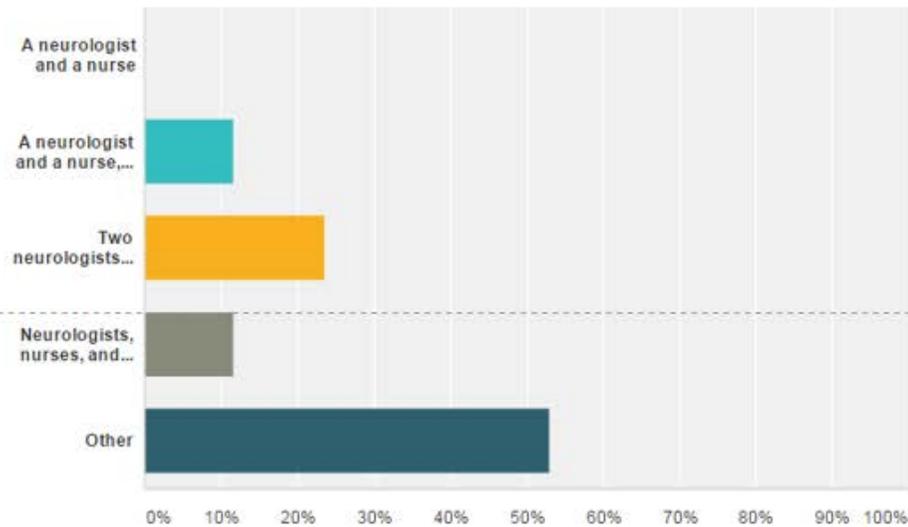
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I do nt think we could cope with an MDT that would consider all treatment induction or change - it would become apointless exercise for the reasons stated by others, and in the comment on cancer MDTs recently published.  
 1/16/2017 8:56 AM [View respondent's answers](#)

Wanted to tick first option but unlikely to fly - some escalations to MAbs will be very straightforward whilst some escalations to fingolimod (or DMF if that is what is agreed) will need MDT discussion because of individual complexity of the patient. Better to have MDT in place to discuss difficult cases without specifying further  
 1/15/2017 9:55 PM [View respondent's answers](#)

**Given the likely requirement for multi-disciplinary teams to be involved in decision-making about DMTs from April 2018, what format of MDT should the algorithm advocate?**

Answered: 17 Skipped: 0



Answer Choices	Responses
▼ A neurologist and a nurse	0.00% 0
▼ A neurologist and a nurse, both specialised in MS	11.76% 2
▼ Two neurologists and a nurse, all specialised in MS	23.53% 4
▼ Neurologists, nurses, and several other relevant healthcare professionals, all specialised in MS, including physios, OTs, pharmacists, psychologists etc	11.76% 2
▼ Other	Responses 52.94% 9

I think including a neuroradiologist is important.  
1/23/2017 7:48 PM [View respondent's answers](#)

Two neurologists and a nurse, all specialised in MS - the MS Society strongly believes however that all people with MS should have access to a wider multi-disciplinary team (regardless of whether they are on DMTs or not)  
1/23/2017 5:28 PM [View respondent's answers](#)

As a minimum, pharmacists and other AHPs welcome  
1/23/2017 12:11 PM [View respondent's answers](#)

We would advocate for a minimum of two MS specialist neurologists and and MS specialist nurse, but encourage wider participation, e.g. neuropharmacists, neuropsychologists, etc. wherever practical  
1/23/2017 9:52 AM [View respondent's answers](#)

The minimum format should be 2 neurologists and relevant nurse (i.e. their nurse) but the MDT should have access to other specialities where appropriate  
1/23/2017 8:40 AM [View respondent's answers](#)

2 neurologists & at least 1 nurse as a minimum, with reference to ideally also including others such as pharmacists, therapists & neuroradiologists  
1/19/2017 7:02 PM [View respondent's answers](#)

Should have neurologists and neuroradiologists and MS nurses.  
1/16/2017 1:14 PM [View respondent's answers](#)

Where feasible as many disciplines as can be mustered, but as a minimum one Neurologist NOT involved in the routine care of the patient, Neuroradiology input, and an MS nurse or therapist  
1/16/2017 8:56 AM [View respondent's answers](#)

Ideally with neuroradiology if practical  
1/15/2017 9:55 PM [View respondent's answers](#)

## Appendix 1: Acronyms and abbreviations

ABN	The Association of British Neurologists
CIS	Clinically Isolated Syndrome refers to a first episode of neurologic symptoms that lasts for at least 24 hours and is caused by inflammation or demyelination (loss of the myelin that covers nerve cells) in the central nervous system
CRG	Clinical Reference Group
DMT	Disease Modifying Therapies – can reduce how many relapses someone has and how serious they are
EDSS	Expanded Disability Status Scale – a method of quantifying disability in multiple sclerosis and monitoring changes in disability over time
JC virus	John Cunningham (JC) virus is a common infection completely unrelated to MS but which is normally kept under control by the immune system
MDT	Multi-disciplinary team
MRI	Magnetic resonance imaging
MS	Multiple Sclerosis involves an immune-mediated process in which an abnormal response of the body's immune system is directed against the central nervous system.
NICE	The National Institute for Health and Care Excellence
NICE TA	NICE technology appraisal guidance
PML	Progressive Multifocal Leukoencephalopathy – a rare viral disease of the brain
RES	Rapidly evolving severe relapsing-remitting MS
RRMS	Relapsing-remitting MS

## Summary of changes to this document

Describe what was stated in original document	Describe new text in the document	Section/Paragraph to which changes apply	Describe why document change required	Changes made by	Date change made
Confirmed secondary progressive disease with an observable increase in disability for more than a 12 month period, in the absence of relapse activity, and an EDSS of 6.0 or greater (except for the rare phenotype of “relapsing-progressive multiple sclerosis” detailed in section 13).	Confirmed secondary progressive disease with an observable increase in disability for more than a 12 month period, in the absence of relapse activity. Secondary progressive disease would usually only be diagnosed in patients with an EDSS of 6.0 or greater. (Except for the rare phenotype of “relapsing-progressive multiple sclerosis” detailed in section 13).	Section 5, Point 4.	Change to reflect NICE TA	Heather Shilling	04/03/2019
Alemtuzumab	“Alemtuzumab or ocrelizumab”	Sections 8, 9, 10, 11 and 12	Change to reflect NICE TA533.	Heather Shilling	04/03/2019
Alemtuzumab	“Alemtuzumab or ocrelizumab (if alemtuzumab is contra indicated or otherwise not suitable).”	Section 8, Point 3. And Section 9, Point 8.	Change to reflect NICE TA533.	Heather Shilling	04/03/2019
Alemtuzumab	“Alemtuzumab and ocrelizumab are”	Section 11, Point 12.	Change to reflect NICE TA533.	Heather Shilling	04/03/2019
N/A	[TA493] Published date: 06 December 2017	Addendum 1	Inclusion of Published date for NICE TA493	Heather Shilling	04/03/2019
N/A	Ocrelizumab  Ocrevus is indicated for the treatment of adult patients with relapsing forms of multiple sclerosis (RMS) with active disease defined	Addendum 1	Inclusion of NICE TA533.	Heather Shilling	04/03/2019

	<p>by clinical or imaging features.</p> <p>Ocrevus is indicated for the treatment of adult patients with early primary progressive multiple sclerosis (PPMS) in terms of disease duration and level of disability, and with imaging features characteristic of inflammatory activity.</p> <p>[TA533] Published date: 25 July 2018                  Ocrelizumab is recommended as an option for treating relapsing-remitting multiple sclerosis in adults with active disease defined by clinical or imaging features, only if alemtuzumab is contraindicated or otherwise unsuitable.</p>				
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