

## Recommendations for an NHS England algorithm to use disease-modifying drugs to treat multiple sclerosis

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## 1. Purpose of this algorithm

- The purpose of this algorithm is to provide a framework to aid decision-making for multiple sclerosis specialists and patients, to help reduce excessive variations 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 multiple sclerosis in England. Other guidance on disease-modifying drugs in multiple sclerosis, such as the ABN guidelines<sup>1</sup>, are different in scope and may make recommendations outside of current approved prescribing.
- NHS England's Neuroscience CRG will review this algorithm as necessary to reflect any new NICE Technology Appraisal Guidance or approvals.

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

- The patient should be at the centre of any service for disease-modifying therapies.
- Such 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 disease-modifying therapies (currently the monoclonal antibody therapies) are proposed, should be discussed at a multi-disciplinary team meeting (MDT), 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 EDSS for BluTeq) and voluntary multiple sclerosis registers.
- This treatment algorithm applies to all age groups, including children. Children may receive disease-modifying therapies that are (i) licensed for children, (ii) have a recognised dose for children (for instance are cited in the British National Formulary) or – if neither of the previous two criteria apply – (iii) if the child is post-pubescent.

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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

### 3. Definitions

The definitions below are taken from NHS England's 2014 DMT policy. They are 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"

- [From NICE document TA254 on fingolimod] 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>

#### "Rapidly Evolving Severe Relapsing–Remitting Disease"

- [from TA127 on natalizumab] 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.

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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.

## 4. Starting criteria common to all DMTs

For a patient to be eligible for any DMT, they must fulfil the following:

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

## 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 multiple sclerosis.
4. 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 below).

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

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

We propose that 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.

## 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

Single clinical episode with  
multiple MRI lesions

- No treatment [note 1]
- Beta-interferon [note 2]

Single clinical episode with  
MRI activity fulfilling the  
McDonald criteria for  
relapsing MS

- No treatment [note 1]
- Beta-interferon [note 2]
- Alemtuzumab [note 3]

1. Trials of first-line therapies in people with CIS at high risk of conversion have NOT shown a convincing long-term effect on the accumulation of disability. Therefore it is reasonable to opt for no treatment in many patients in this situation.
2. Under 2014 NHS England guidance, beta-interferon may be offered for patients within 12 months of a clinically significant clinically isolated syndrome when MRI evidence predicts a high likelihood of recurrent episodes and thus the subsequent development of clinically definite MS).
3. Under the 2010 McDonald diagnostic criteria, relapsing multiple sclerosis may be diagnosed on the basis of a single clinical event with MRI activity. In exceptional circumstances, where clinical or radiological markers indicate a poor prognosis for rapidly developing permanent disability, alemtuzumab may be considered after a single clinical episode. 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 MS

|   |  |
|---|--|
| RRMS: 2 significant relapses in last 2 years              | <ul style="list-style-type: none"> <li>• Beta-Interferon</li> <li>• Glatiramer</li> <li>• Teriflunomide</li> <li>• Dimethyl fumarate [note 5]</li> <li>• Alemtuzumab [note 7]</li> </ul> |
| RRMS: 1 relapse in last 2 years AND radiological activity | <ul style="list-style-type: none"> <li>• Beta-Interferon [note 6]</li> <li>• Alemtuzumab [note 7]</li> </ul>   |
| Rapidly evolving severe MS                                | <ul style="list-style-type: none"> <li>• Natalizumab</li> <li>• Alemtuzumab [note 8]</li> </ul>  |

### Notes:

4. For RRMS (that is not RES), beta-interferon, glatiramer 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. NHS England 2014 policy 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”
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 is available for RES and may be considered –by some patients and physicians - a safer option than natalizumab (for instance when JC virus serology is high-index positive)

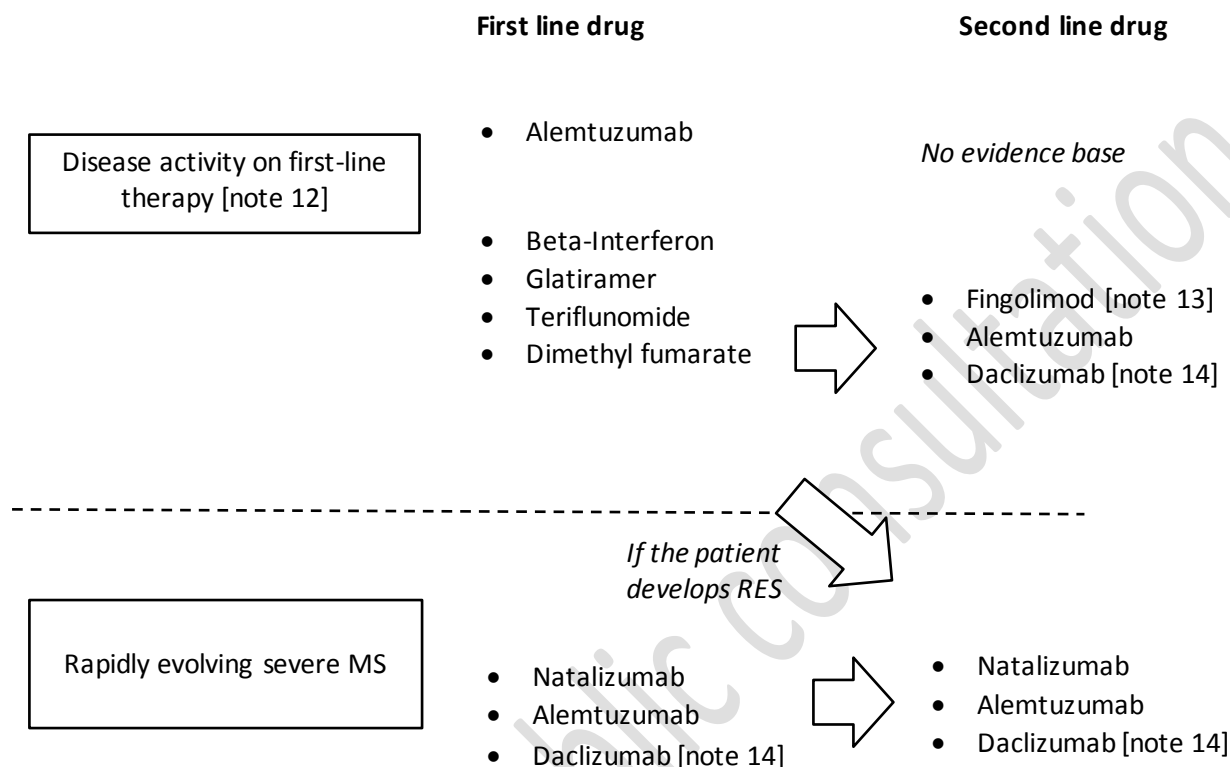
## 10. Treatment algorithm for intolerance to first line therapy

|   | First line drug  | Alternative First line drug [note 9]  |
|---|--|---|
| RRMS: 2 significant relapses in last 2 years              | <ul style="list-style-type: none"> <li>• Beta-Interferon</li> <li>• Glatiramer</li> <li>• Teriflunomide</li> <li>• Dimethyl fumarate</li> <li>• Alemtuzumab</li> </ul> | <ul style="list-style-type: none"> <li>• Beta-Interferon</li> <li>• Glatiramer</li> <li>• Teriflunomide</li> <li>• Dimethyl fumarate</li> </ul> |
| RRMS: 1 relapse in last 2 years AND radiological activity | <ul style="list-style-type: none"> <li>• Beta-Interferon</li> <li>• Alemtuzumab</li> </ul>   | No evidence base  |
| Rapidly evolving severe MS                                | <ul style="list-style-type: none"> <li>• Natalizumab</li> </ul>  | <ul style="list-style-type: none"> <li>• Fingolimod [note 10]</li> <li>• Alemtuzumab</li> <li>• Daclizumab [note 11]</li> </ul>                 |
|   | <ul style="list-style-type: none"> <li>• Alemtuzumab</li> </ul>  | <ul style="list-style-type: none"> <li>• Daclizumab [note 11]</li> <li>• Natalizumab [note 16]</li> </ul>                                       |

### Notes:

- 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 through their relapses may now fall outside the eligibility window.
- 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.
- Daclizumab is permissible under the July 2017 EMA restrictions to its licence for “adult patients with rapidly evolving severe relapsing multiple sclerosis who are unsuitable for treatment with other DMTs”.

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



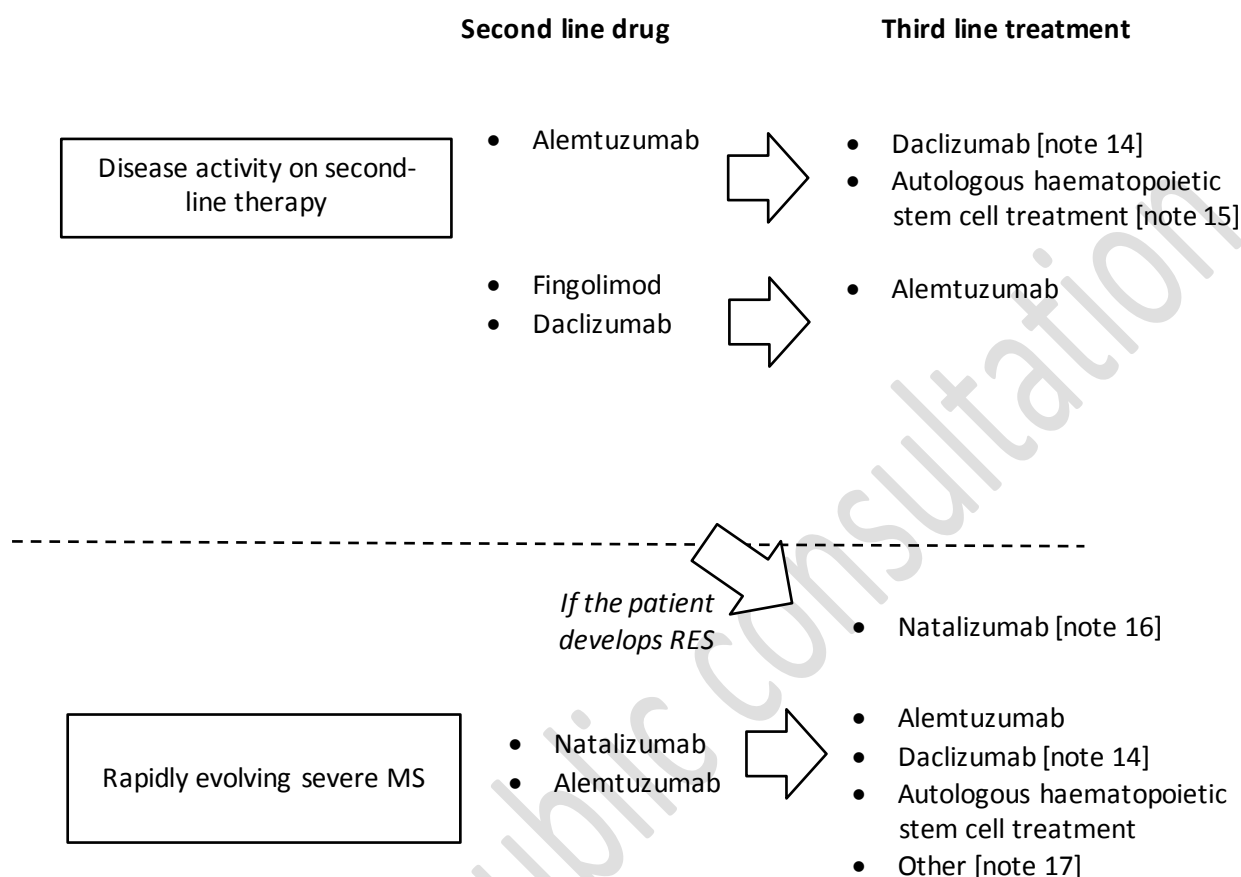
12. Definition of disease activity: treatment failure may be indicated by either clinical or radiological relapse-related changes, after significant exposure to the treating drug, with changes indicating a poor prognosis for future disability

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.

14. In July 2017, the EMA restricted the use of daclizumab to “adult patients with highly active relapsing disease despite a full and adequate course of treatment with at least one disease modifying therapy or with rapidly evolving severe relapsing multiple sclerosis who are unsuitable for treatment with other DMTs”



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



15. Autologous haematopoietic stem 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 adequate 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.
16. We do not recommend the routine use of natalizumab after alemtuzumab, given the potentially increased (but as yet undetermined) risk of PML. But, where the patient is negative for JC serology, this may rarely be appropriate.
17. 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 progressive relapsing multiple sclerosis**

Only beta-interferon (of any brand) is approved by the NHS England 2014 policy for relapsing-progressive disease, under these criteria:

#### *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   |
|------------------------------|--|--|---|
| Beta-interferon and Copaxone | <p>AVONEX is indicated for the treatment of</p> <ul style="list-style-type: none"> <li>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.</li> <li>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).</li> </ul> <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>BETAFERON is indicated for the treatment of</p> <ul style="list-style-type: none"> <li>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</li> <li>patients with relapsing-remitting multiple sclerosis and two or more relapses within the last two years.</li> <li>patients with secondary progressive multiple sclerosis with active disease, evidenced by relapses.</li> </ul> <ul style="list-style-type: none"> <li>COPAXONE is 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). Copaxone is not indicated in primary or secondary progressive MS.</li> </ul> | <p>[nil from NICE]</p> <p>DoH Risk Sharing Scheme:</p> <p>beta interferons or glatiramer acetate are indicated for all patients with relapsing remitting MS who:</p> <ul style="list-style-type: none"> <li>Can walk independently (beta-interferons) or at least 100 metres without assistance (glatiramer acetate)</li> <li>Have had at least two clinically significant relapses in the last two years</li> </ul> | <p>All of the following criteria must be met. The patient:</p> <ul style="list-style-type: none"> <li>has had at least 2 clinically significant relapses in previous 2 years*</li> <li>is able to walk 10m or more** (or 100m for glatiramer)</li> <li>is not pregnant or attempting conception</li> <li>is aged over 18 years</li> <li>has no contra-indications</li> </ul> <p>* [for interferon-beta only]<br/>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;</p> <p>(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).</p> <p>(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)</p> <p>(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 DMTs is permitted but recommended less strongly than for patients able to walk more than 100m unaided (EDSS 5.5 or less).</p> |
| teriflunomide                | AUBAGIO is indicated for the treatment of adult patients with relapsing remitting multiple sclerosis (MS).   | <p>[TA303] Published date: 22 January 2014 Last updated: 01 June 2014:</p> <p>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</p>  |   |

|                   |   |   |  |
|-------------------|---|---|--|
|                   |   | years), only if<br><br>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  | [TA320] Published date: 27 August 2014: 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<br><br>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:<br><br>- Patients with highly active disease despite a full and adequate course of treatment with at least one disease modifying therapy<br><br>or<br><br>- 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.   | [TA254] Published date: 25 April 2012:<br><br>an unchanged or increased relapse rate or ongoing severe relapses compared with the previous year despite treatment with beta interferon,   | Fingolimod is recommended as an option for the treatment of highly active multiple sclerosis:<br><br>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<br><br>OR<br><br>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:<br><br>o JCV exposure indicated by anti-JCV antibody positive status<br><br>o Receiving an immunosuppressant prior to receiving natalizumab<br><br>o Natalizumab treatment duration of >2 years |
| natalizumab       | 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.<br><br>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.<br><br>or<br><br>Adult Patients aged 18 years and over with | [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                     | For patients who <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</li> </ul>  |

|             |   |   |   |
|-------------|---|---|---|
|             | 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   |   | and does not meet the agreed stopping criteria.<br><br>*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. |
| alemtuzumab | LEMTRADA is indicated for adult patients with relapsing remitting multiple sclerosis (RRMS) with active disease defined by clinical or imaging features   | [TA312] Published date: 28 May 2014:<br>Alemtuzumab is recommended as an option, within its marketing authorisation, for treating adults with active relapsing–remitting multiple sclerosis.  |   |
| daclizumab  | Zinbrya was originally indicated “in adult patients for the treatment of relapsing forms of multiple sclerosis.” However, post-marketing concern over hepatotoxicity led to provisional EMA restrictions being placed in July 2017 to daclizumab’s use only for “adult patients with highly active relapsing disease despite a full and adequate course of treatment with at least one disease modifying therapy or with rapidly evolving severe relapsing multiple sclerosis who are unsuitable for treatment with other DMTs” | [ID 827] Daclizumab is recommended as an option for treating multiple sclerosis in adults, only if: the person has active relapsing–remitting multiple sclerosis previously treated with disease-modifying therapy, or rapidly evolving severe relapsing–remitting multiple sclerosis (that is, at least 2 relapses in the previous year and at least 1 gadolinium-enhancing lesion at baseline MRI) and alemtuzumab is contraindicated or otherwise unsuitable |   |

## **Addendum 2: Indications not correctly approved by NHS England, but considered by the committee**

The following use of DMTs are not currently funded and were considered by the committee. 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     |

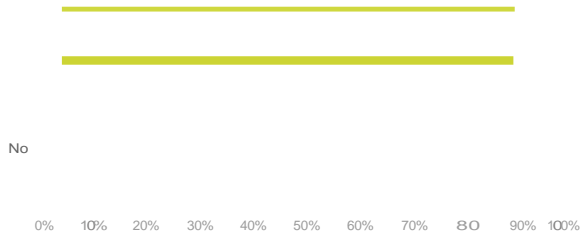
#### Members of the MS Advisory Group of the ABN, who commented on the algorithm

|                  |             |
|------------------|-------------|
| Waqar Rashid     | Neurologist |
| Robert Brenner   | Neurologist |
| Adnan Al-Araji   | Neurologist |
| Bruno Gran       | Neurologist |
| Gavin Giovannoni | Neurologist |

## Addendum 4: Voting of Membership

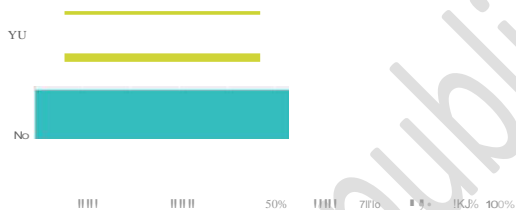
Do you think that dimethylfumarate (Tecfidera) is a more efficacious treatment of MS than first-line drugs [beta-interferon, copaxone, teriflunomide]?

Answer: 17 Skipped: 0



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

Answer: 17 Skipped: 0



| Answer Choices |    |
|----------------|----|
| Yes            | 17 |
| No             | 0  |
| Total          | 17 |

Responses

47.06%

52.94%

Based on relapse rate and disability progression, dimethylfumarate (DMF) is a more efficacious treatment of MS than first-line drugs [beta-interferon, copaxone, teriflunomide].

Only 17 responses were received.

No evidence that DMF is superior to first-line drugs in terms of relapse rate and disability progression. However, it is a more efficacious treatment of MS than first-line drugs [beta-interferon, copaxone, teriflunomide].

Evidence suggests that dimethylfumarate is more efficacious than first-line drugs in terms of relapse rate and disability progression.

Data from the CONFIRM trial shows that DMF is a more efficacious treatment of MS than first-line drugs [beta-interferon, copaxone, teriflunomide].

relapses

There are no other treatments that make DMF suitable for some patients.

17 responses were received.

No evidence that DMF is superior to first-line drugs in terms of relapse rate and disability progression. However, it is a more efficacious treatment of MS than first-line drugs [beta-interferon, copaxone, teriflunomide].

Only 17 responses were received.

17 responses were received.

17 responses were received.

Whilst accepting the limited data on its efficacy, it is a second-line treatment and should be allowed to be used.

17 responses were received.

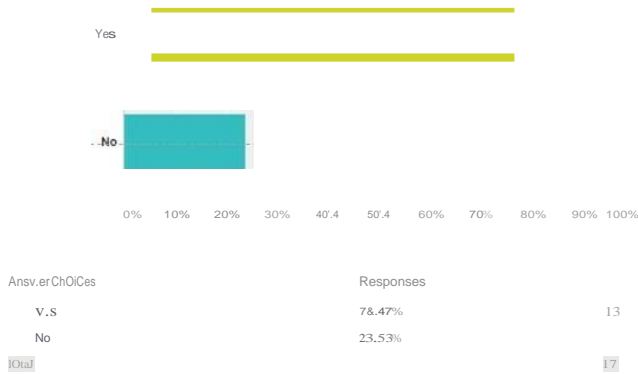
17 responses were received.

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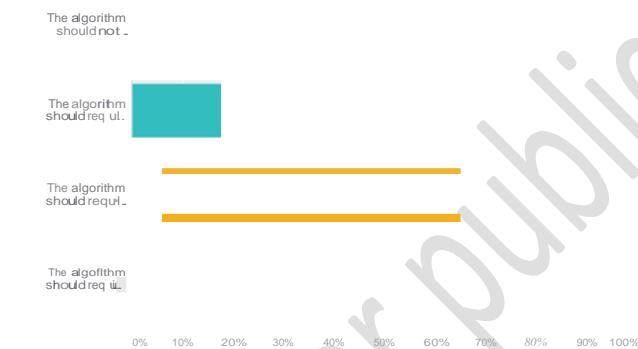
Do you think that dimethyl fumarate should be presented in the algorithm as intermediate in effectiveness between [beta-interferon, copaxone, teriflunomide] and [natalizumab, fingolimod, alemtuzumab]?

Answered: 17 Skipped: 0



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

Answered: 11 Skipped: 0



| Answer Choices  | Responses   |
|---|-------------|
| The algorithm should not mention multi-disciplinary teams in decision-making about DMTs.                            | 2 (11.76%)  |
| The algorithm should require multi-disciplinary teams in decision-making about a first-line therapy.                | 11 (64.71%) |
| The algorithm should require multi-disciplinary teams in decision-making about a first-line therapy.                | 3 (17.65%)  |
| The algorithm should require multi-disciplinary teams in decision-making about complex cases not otherwise defined. | 0 (0%)      |

Yes against IFN-beta and GA. Less confident about 31M. Ten Theleofe 1WCU suggest avfIQ it's a lon one level

1/2/2017 7:48 PM View respondent's answers

Trial data suggests IFN and GA could be grouped together with regard to efficacy rather than Fingolimod being listed as effective as Alemtuzumab and Natalizumab

1/3/2017 2:28 PM View respondent's answers

hMS OetSIOIS We group dimethyl fumarate and Fingolimod together as intermediate

1/2/2017 5:22 PM View respondent's answers

Althoough I would put Fingolimod in same category as DMTs

1/2/2017 6:10 AM View respondent's answers

Nuclearevidence of fingolimod to fingolimod

1/2/2017 11:17 PM View respondent's answers

I think it should sit in the box as other DMTs. I think the v190e supplement is the right proportion of the DMTs that may be more effective. Based on ARR adds ability to be on the DMTs and T2 lesions CONFIRMED

1/2/2017 1:17 PM View respondent's answers

I think is a little stronger than the injectables, but not as powerful as fingolimod

1/16/2017 8:56 AM View respondent's answers

Need add on. I think it's a good idea to have a box for the DMTs

1/1/2017 1:11 PM View respondent's answers

hSCOUd be in the box as other DMTs

1/1/2017 1:11 PM View respondent's answers

we were with the DMTs in the box as other DMTs. I think the v190e supplement is the right proportion of the DMTs that may be more effective. Based on ARR adds ability to be on the DMTs and T2 lesions CONFIRMED

1/1/2017 1:11 PM View respondent's answers

hSCOUd be in the box as other DMTs

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1/1/2017 1:11 PM View respondent's answers

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1/1/2017 1:11 PM View respondent's answers

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1/1/2017 1:11 PM View respondent's answers

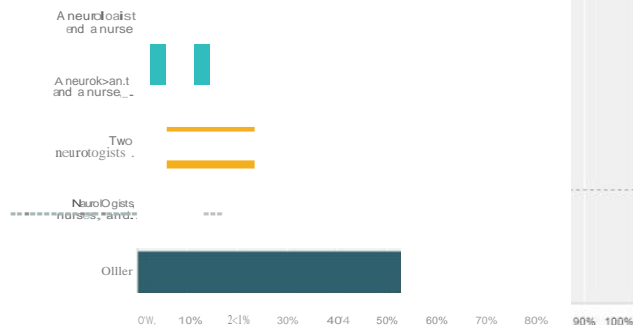
I wanted to tick first option but unlikely for some exceptions to have with the very strong evidence

what some escalation to fingolimod or DMT if that is what is agreed. I think the v190e supplement is the right proportion of the DMTs that may be more effective. Based on ARR adds ability to be on the DMTs and T2 lesions CONFIRMED

1/1/2017 1:11 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 11 Slipped



#### Answer Choices

- A neurologist and a nurse
- A neurologist and a nurse both specialising in MS
- Two neurologists and a nurse, all specialising in MS
- Neurologists, nurses and several other relevant healthcare professionals all specialising in MS including physiotherapists, psychologists etc
- Other

#### Responses

0.00%

11.76% 2

21.5% 4

11.76% 2

52.94% 9

I think we need a neurologist and a nurse

11/23/2017 7:48 AM View response

Two neurologists and a nurse, all specialising in MS. The MS society strongly believe that people with MS should have access to a wider multidisciplinary team (regardless of whether they are on MS or not)

11/23/2017 5:28 PM View response

As a clinician, pharmacist and other AHPs v. elect

11/23/2017 12:11 PM View response

We would vote for a multidisciplinary team of two MS specialist neurologists and an MS specialist nurse, but encourage wider participation, e.g. neurophysiologists, neuropsychologists etc wherever possible

11/23/2017 10:21 AM View response

The minimum team should be 2 neurologists and a relevant nurse (i.e. their nurse) but the MDT should have access to other specialities where appropriate

11/23/2017 4:40 AM View response

2 neurologists and a nurse as a minimum, with referral to specialist services such as physiotherapy, occupational therapy, speech therapy, etc

11/19/2017 7:17 PM View response

So we have neurologists and neurophysiologists and MS nurses

11/21/2017 4:40 PM View response

Where possible as many first-line services can be mustered, but as a minimum one neurologist NOT involved in the routine care of the patient, neurophysiology input and an MS nurse or therapist

11/17/2017 5:56 PM View response

Idea by v.t.j. neurologist and a nurse

11/15/2017 5:55 PM View response