### Question 1

In patients with CIS (regardless of whether they fulfil criteria for MS), what is the benefit of starting treatment with a disease-modifying drug (DMD) compared to no treatment?

<table>
<thead>
<tr>
<th>Population</th>
<th>Patients with a single clinical attack(^a), regardless of number of MRI lesions</th>
</tr>
</thead>
</table>
| Interventions | - interferon beta/peg-interferon  
- glatiramer acetate  
- teriflunomide  
- dimethyl fumarate  
- fingolimod  
- natalizumab  
- alemtuzumab  
- daclizumab  
- ocrelizumab  
- mitoxantrone |
| Comparators | Placebo or active comparator |
| Outcomes | Efficacy outcomes  
- Relapse (time to second relapse, % of participants with second relapse)  
- Disability worsening (measured on the EDSS)  
- Conversion to clinically definite MS  
MRI outcomes  
- New T2 lesions (presence of new T2/volume)  
- GAD lesions (presence of gad/volume)  
- Brain atrophy  
Tolerability and safety outcomes  
- Discontinuation (any reason/due to side effects)  
- Adverse events (specific events outlined for each drug – see appendix 7)  
- Mortality  
Other outcomes  
- Quality of life (patient reported)  
- Cognitive impairment |
| Exclusion | Pediatric population, studies evaluating combination of drugs, unlicensed doses, studies with <10 participants per arm, non-English language |
| Study design | RCTs with at least 1 year follow-up (48 weeks acceptable)  
Long term extensions on included RCTs |

\(^a\) Clinical definition with slight variations between studies. Generally, first isolated, well-defined unifocal or multifocal neurologic event consistent with demyelination and involving the optic nerve (unilateral optic neuritis), spinal cord (incomplete transverse myelitis), or brain stem or cerebellum (brain-stem or cerebellar syndrome) that was confirmed on ophthalmologic or neurologic examination.

### Question 2

In patients with relapsing-remitting MS and secondary progressive MS, what is the benefit of treating with a DMD compared to no treatment/another DMD?

| Population | Patients with a relapsing-remitting MS\(^a\) only, patients with secondary progressive MS\(^b\) only, studies with mixed population (both RR and SP) |

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\(^a\) Relapsing-remitting MS

\(^b\) Secondary progressive MS
<table>
<thead>
<tr>
<th>Interventions</th>
<th>Comparators</th>
</tr>
</thead>
<tbody>
<tr>
<td>interferon beta/peg-interferon</td>
<td>Placebo or any active comparator</td>
</tr>
<tr>
<td>glatiramer acetate</td>
<td></td>
</tr>
<tr>
<td>teriflunomide</td>
<td></td>
</tr>
<tr>
<td>dimethyl fumarate</td>
<td></td>
</tr>
<tr>
<td>fingolimod</td>
<td></td>
</tr>
<tr>
<td>natalizumab</td>
<td></td>
</tr>
<tr>
<td>alemtuzumab</td>
<td></td>
</tr>
<tr>
<td>daclizumab</td>
<td></td>
</tr>
<tr>
<td>ocrelizumab</td>
<td></td>
</tr>
<tr>
<td>cladribine</td>
<td></td>
</tr>
<tr>
<td>mitoxantrone</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Outcomes</th>
<th>Efficacy outcomes</th>
</tr>
</thead>
<tbody>
<tr>
<td>Relapse (% patients free of relapses, annualized relapse rate)</td>
<td></td>
</tr>
<tr>
<td>Disability worsening (measured on the EDSS)</td>
<td></td>
</tr>
<tr>
<td>Conversion to SPMS (in RR patients)</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Outcomes</th>
<th>MRI outcomes</th>
</tr>
</thead>
<tbody>
<tr>
<td>New T2 lesions (presence of new T2/volume)</td>
<td></td>
</tr>
<tr>
<td>GAD lesions (presence of gad/volume)</td>
<td></td>
</tr>
<tr>
<td>Brain atrophy</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Outcomes</th>
<th>Tolerability outcomes</th>
</tr>
</thead>
<tbody>
<tr>
<td>Discontinuation (any reason/due to side effects)</td>
<td></td>
</tr>
<tr>
<td>Adverse events (specific events outlined for each drug – see appendix 7)</td>
<td></td>
</tr>
<tr>
<td>Mortality</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Outcomes</th>
<th>Other outcomes</th>
</tr>
</thead>
<tbody>
<tr>
<td>Quality of life (patient reported)</td>
<td></td>
</tr>
<tr>
<td>Cognitive impairment</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Exclusion</th>
<th>Pediatric population, studies evaluating combination of drugs, unlicensed doses, studies with &lt;10 participants per arm, non-English language</th>
</tr>
</thead>
</table>

<table>
<thead>
<tr>
<th>Study design</th>
<th>RCTs with at least 1 year follow-up (48 weeks acceptable)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Long term extensions on included RCTs</td>
</tr>
</tbody>
</table>

*a. clinically definite or laboratory-supported definite relapsing-remitting MS according to Poser criteria in the oldest trials and according to the revised McDonald criteria (2001 or 2005) in the most recent trials. Any additional criteria of number of relapses in the years prior to inclusion is valid.

*b. clinical definition with variations between studies but all reflecting a progressive deterioration of disability with an increase in the EDSS, with or without superimposed exacerbations, following an initial RR course.*

**Question 3**

In patients with primary progressive MS what is the benefit of treating with a DMD compared to no treatment

<table>
<thead>
<tr>
<th>Population</th>
<th>Patients with primary progressive MS*</th>
</tr>
</thead>
</table>

<table>
<thead>
<tr>
<th>Intervention</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>interferon beta/peg-interferon</td>
<td></td>
</tr>
<tr>
<td>glatiramer acetate</td>
<td></td>
</tr>
<tr>
<td>teriflunomide</td>
<td></td>
</tr>
<tr>
<td>dimethyl fumarate</td>
<td></td>
</tr>
<tr>
<td>fingolimod</td>
<td></td>
</tr>
<tr>
<td>natalizumab</td>
<td></td>
</tr>
<tr>
<td>alemtuzumab</td>
<td></td>
</tr>
</tbody>
</table>
### Comparator
- Placebo or any active comparator

### Outcomes
#### Efficacy outcomes
- Disability worsening (measured on the EDSS)

#### Tolerability outcomes
- Discontinuation (any reason/due to side effects)
- Adverse events (specific events outlined for each drug – see appendix 7)
- Mortality

#### Other outcomes
- Quality of life (patient reported)
- Cognitive impairment

### Exclusion
- Pediatric population, combination of drugs, unlicensed doses, studies with <10 participants per arm, non-English language

### Review strategy
- RCTs with at least 1 year follow-up (48 weeks acceptable).
- Long term extensions on included RCTs

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**Question 4**

In patients with relapsing MS treated with DMDs, does the presence of early disease activity (relapses and/or disability progression and/or MRI activity at 6 months/12 months) predict an increased risk of future disability?

#### Population
- Patients treated with DMDs (regardless type of drug and time on treatment)

#### Predictor
- Presence of early (at 6/12 months) disease activity (relapses and/or disability accumulation and/or MRI activity*)

#### Outcomes
- Sensibility, specificity
- Long-term undesirable outcomes:
  - disability accumulation
  - secondary progressive MS

#### Exclusion
- Studies assessing early disease activity at >12 months after treatment start, studies included paediatric population, non-English language

#### Review strategy
- Systematic reviews
- RCTs
- Observational studies

*a. defined as the presence of new lesions or gadolinium enhancing lesions*

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**Question 5**

In MS patients treated with DMDs, should a follow-up MRI be performed within a prespecified time scheme to monitor treatment response?

#### Population
- Patients treated with DMDs (regardless type of drug and time on treatment)
<table>
<thead>
<tr>
<th><strong>Intervention</strong></th>
<th>MRI performed at fixed intervals to monitor treatment response</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Comparator</strong></td>
<td>MRI performed without fixed intervals to monitor treatment response</td>
</tr>
<tr>
<td><strong>Outcomes</strong></td>
<td>Monitoring MRI <em>early</em> treatment response (presence of new lesions and gad lesions)</td>
</tr>
<tr>
<td><strong>Exclusion</strong></td>
<td>Pediatric population/ MRI performed to monitor safety</td>
</tr>
<tr>
<td><strong>Review strategy</strong></td>
<td>Any study design would be valid for this question.</td>
</tr>
</tbody>
</table>

**Question 6**

In patients with relapsing MS treated with interferon or glatiramer acetate and with evidence of early disease activity (relapses and/or disability progression and/or MRI activity at 6/12 months), what is the benefit of switching between interferon and glatiramer acetate versus moving to more efficacious drugs?

**Population**
Patients treated with first line DMDs (regardless type of drug and time on treatment) and evidence of disease activity

**Intervention**
Change between fist-line DMDs

**Comparator**
Escalate to a highly efficacious DMD

**Outcomes**
- Relapse (% of participants, annualised relapse rate)
- Disability worsening (measured on the EDSS)
- MRI activity (number of new T2 lesions/gad lesions)
- Side effects

**Study design**
- Systematic reviews
- RCTs
- Observational studies (prospective and retrospective cohorts)

**Exclusion**
Pediatric population, case-control studies, case-series, studies with <10 participants per arm, non-English language

*a. such as INF, GA, teriflunomide and dimethyl fumarate.
*b. several definitions could be used between studies (EDA, MEDA, Rio score...), combining clinical (relapses and disability accumulation) and MRI parameters
*c. such as natalizumab, fingolimod, alemtuzumab, daclizumab and ocrelizumab.

**Question 7**

In patients with relapsing MS who stop taking a highly efficacious drug, is there a risk of return and/or rebound of their disease activity (increased risk of relapses, disability progression and/or MRI activity)?

**Population**
Patients with relapsing MS treated with highly efficacious DMDs for at least 12 months

**Intervention**
Treatment stop (any intervention after stop is acceptable)

**Comparator**
No comparator required

**Outcomes**
- Annualised relapse rate/% with relapse (prior to current second line drug and after drug discontinuation)
- MRI outcomes (prior to current second line drug and after drug discontinuation)

*All outcomes post-discontinuation to be reported within 6 months of stopping drug*
**Exclusion**  
Pediatric population, patients receiving second-line DMD for less than 12 months, studies reporting outcomes measured after 6 months from drug switch, studies with <10 participants per arm, non-English language

**Review strategy**
- Systematic reviews
- Observational studies (before-and-after studies)

*a. such as natalizumab, fingolimod, alemtuzumab, daclizumab and ocrelizumab
b. we will not distinguish between return or rebound. We will adopt any study definition that involves increase in relapses and/or disability progression and/or MRI activity as compared to that while on treatment

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**Question 8**  
In patients with relapsing MS who stop taking a highly efficacious drug, what is the benefit of further treatment?

**Population**
Patients with relapsing MS treated with highly efficacious DMD* for at least 12 months who stop treatment for safety issues

**Intervention**
Other highly efficacious DMD*

**Comparator**
- First line DMD
- Remain untreated

**Outcomes**
- Relapse (annualised relapse rate/% of participants with relapse)
- Disability worsening (measured on the EDSS)
- MRI activity (number of new T2 lesions/gad lesions)
- Conversion to SPMS
- Side effects

**Review strategy**
- Systematic reviews
- RCTs
- Observational studies

**Exclusion**
Pediatric population, case-control studies, case-series, studies with <10 participants per arm, non-English language

*a. such as natalizumab, fingolimod, alemtuzumab, daclizumab and ocrelizumab

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**Question 9**  
In patients with relapsing MS treated with DMDs that remain stable over a long time period, what is the benefit of continuing treatment compared to stopping?

**Population**
Patients with MS treated with any DMD who show clinical stability

**Intervention**
Discontinue DMD

**Comparator**
Continue on current DMD

**Outcomes**
- Relapse (time to relapse, annualised relapse rate, % of participants with relapse)
- Disability worsening (measured with the EDSS) (time to worsening, % of participants)
- MRI activity (number of new T2/GAD lesions)
- Conversion to SPMS

**Exclusion**
Pediatric population, case-control studies, participants with clinical stability for <3 years, studies with <10 participants per arm, non-English language
### Study design
- Systematic reviews
- RCTs
- Observational studies (prospective or retrospective cohorts)

*a. absence of relapses and disability accumulation and MRI activity (no new lesions, no gad lesions)*

### Question 10

**In women with MS treated with DMDs who wish to start a pregnancy or who have an unplanned pregnancy, what should be the therapeutic approach?**

<table>
<thead>
<tr>
<th><strong>Population</strong></th>
<th>Women with MS treated with DMDs (any type of drug and time on treatment)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Intervention</strong></td>
<td>Stop treatment before trying to become pregnant</td>
</tr>
<tr>
<td><strong>Comparator</strong></td>
<td>Stop treatment when aware of being pregnant</td>
</tr>
<tr>
<td><strong>Outcomes</strong></td>
<td>Continue treatment during pregnancy</td>
</tr>
</tbody>
</table>
| **Outcomes** | - Spontaneous abortion  
- Low birth weight  
- Infant congenital malformation  
- Neonatal death  
- Relapse (prior to pregnancy and in the post-partum period) |
| **Exclusion** | Pediatric population, case-control studies, case-series, studies with <10 participants per arm, non-English language |
| **Review strategy** | - Systematic reviews  
- Observational studies (prospective and retrospective cohorts) |