National Institute for Health and Care Excellence
Centre for Health Technology Evaluation

Pro-forma Response

ERG report

Dimethyl fumarate for the treatment of relapsing-remitting multiple sclerosis

You are asked to check the ERG report from the NHS Centre for Reviews and Dissemination and Centre for Health Economics to ensure there are no factual inaccuracies contained within it.

If you do identify any factual inaccuracies you must inform NICE by **5pm** on **6 August 2013** using the below proforma comments table. All factual errors will be highlighted in a report and presented to the Appraisal Committee and will subsequently be published on the NICE website with the Evaluation report.

The proforma document should act as a method of detailing any inaccuracies found and how and why they should be corrected.

Issue 1 Issue of hazard ratios for disability progression

<table>
<tr><th>Description of problem</th><th>Description of proposed amendment</th><th>Justification for amendment</th><th>ERG response</th></tr>
<tr>
<td>

P59. 4.4.1 Statistical methods and P112. 6.2.1.1 Drug prices.

During the clarification stage the ERG raised questions regarding modelling of the effectiveness outcome for disability progression, suggesting this had been modelled as a risk ratio, despite being referred to as a hazard ratio. We provided new code to correct the model and provided new results pertaining to disability progression.

The new results were presented as hazard ratios but in the ERG report this was questioned on the basis that time does not appear to be included in the corrected model. It was the opinion of the ERG that either the new code supplied was incorrect or the outcomes modelled are in fact rate ratios.

This assumption is incorrect as the code does include time and the outcomes are modelled as hazard ratios. The code for calculating the hazard ratios was outlined in our response to the ERGs clarification queries as follows:

</td>
<td>

We propose that tables 43-45 should be replaced.

Using the corrected model with all available discounted prices and the updated code supplied in response to the clarification questions we have calculated the results that are shown in the corrected tables below.

With the time and information available we were not able to recalculate the results in all the affected tables.

Table 43: The deterministic pairwise cost-effectiveness results using the list prices for all drugs and discounted prices (where possible) for all drugs

<table>
<tr><th></th><th colspan="2">ICER of DF versus comparator</th></tr>
<tr><th></th><th>List prices</th><th>Discounted prices</th></tr>
<tr><td>Rebif 22 µg</td><td>124,337</td><td>21,341</td></tr>
<tr><td>Rebif 44 µg</td><td>175,779</td><td>15,909</td></tr>
<tr><td>Avonex</td><td>154,781</td><td>DF dominates</td></tr>
<tr><td>Glatiramer acetate</td><td>102,830</td><td>19,716</td></tr>
<tr><td>Fingolimod (35% red)</td><td>DF dominates</td><td>DF dominates</td></tr>
<tr><td>Fingolimod (53% red)</td><td>DF dominates</td><td>DF dominates</td></tr>
<tr><td>Natalizumab</td><td>(146,300)</td><td>(448,729)</td></tr>
<tr><td>Betaferon</td><td>73,724</td><td>DF dominates</td></tr>
</table>

</td>
<td>

As the ERG itself identified in the clarification questions, the original model submitted was flawed. The ERG took a decision to use the original uncorrected model for its own analysis on the assumption that the new code supplied was incorrect or the outcomes modelled were in fact rate ratios.

Whilst we appreciate this decision was a pragmatic one, it does now mean that the results presented in the ERG report in Tables 43 - 45, and in most subsequent tables in this section (Tables 46-57) are now incorrect. In order to make an accurate evaluation of dimethyl fumarate these tables will need to be corrected based on the model using the new code.

</td>
<td>

Given the inconsistencies in the submission and decision model with the use of relative risks and hazard ratios, the ERG requested clarification on the intended approach and for any corrections to be made where necessary.

The manufacturer provided a new network meta-analysis (code/results) and decision model (results) based on hazard ratios in the response to the points for clarification.

It was not clear to the ERG from the SAS code and accompanying text that the outcome was hazard ratios; rather it was interpreted as rate ratios.

Following this latest clarification, an

</td>
</tr>
</table>

The indicative SAS code (PROC GLIMMIX) suitable for binomial MTC for hazards ratios is provided below:

```
proc glimmix data
=progression_free;
class treatment Study;
y = progression_free/N;
x = 0.5*(log(1/y));
model x = treatment / noint link =
log solution cl;
random intercept / subject=Study
solution;
```

A more detailed explanation is given below.

The methods for estimating relative hazard ratios for disease progression between treatment groups were based upon the assumption that progression-free survival follows an exponential distribution. The transformation of the exponential survivor function S(t) to derive relative hazard rates is shown below:

$$S(t) = 1 - e^{-\alpha t}$$

$$\ln S(t) = -\alpha t$$

Table 44: The probabilistic cost-effectiveness results using the list prices for all drugs

	Costs (£)	QALYs	ICER
Rebif 22 µg	36,089	0.2251	160,326
Rebif 44 µg	29,441	0.0937	314,210
Avonex	31,712	0.1323	239,701
Glatiramer acetate	34,882	0.2467	141,393
Fingolimod	-12,624	0.2628	DF dominates
Natalizumab	-13,936	-0.1404	(99,263)
Betaferon	28,885	0.3233	89,345

Table 45: The pairwise deterministic compared to probabilistic cost-effectiveness results using discounted prices (where possible) for each drug

	ICER of DF versus comparator	
	Deterministic (discounted prices)	PSA (discounted prices)
Rebif 22	21,341	£30,833
Rebif 44	15,909	£22,733
Avonex	DF dominates	£2,409
Glatiramer acetate	19,716	£30,182
Fingolimod (35% reduction)	DF dominates	DF dominates
Fingolimod (53% reduction)	DF dominates	DF dominates

amendment will be made to the report to make it clear that the revised network analysis did in fact calculate hazard ratios.

In addition, an addendum will be provided presenting comparative relative risk and hazard ratio results obtained from the decision model.

The ERG only has the decision model supplied with the original submission, so the new hazard ratio outcomes have been incorporated into that model and the results presented in the addendum.

$$\alpha = -\frac{1}{t}\ln\frac{1}{S(t)}$$ .....(1)

Where, S(t) is the progression-free survivor function over time t, and α is the relative hazard rate of disease progression

SAS model represents equation 1 as:

x = (1/t)*(log(1/y)).....(2)

Where, x = α, hazards of progression as calculated above

y = S(t), the progression-free survivor function over time t, calculated as

$$\frac{\text{estimated progression free}}{\text{number randomized}}$$

t= 2 years in all the studies,

Simplifying the equation using time function as 2 years:

x = (1/2)*(log(1/y))

x = (0.5)*(log(1/y))

Therefore time is included in the calculation and the data presented are hazard ratios.

Natalizumab	(448,729)	(597,824)
Betaferon	DF dominates	DF dominates

Issue 2 References to the MTC model being coded for rate ratios rather than hazard ratios.

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
Throughout the ERG report, there are several references to the model being based on rate ratios rather than hazard ratios. For example, on P21-22, section 1.5 *However, these analyses are based on a model which utilises relative risks, rather than hazard ratios … Attempts to clarify this resulted in a model which appeared to be based on rate ratios…*	According to the description of proposed amendment for issue 1 above, we would propose that any reference throughout the ERG report is amended to reflect the correct model coding for disability progression coded using hazard ratios.	According to the description of proposed amendment for issue 1 above, we would propose that any reference throughout the ERG report is amended to reflect the correct model coding for disability progression using hazard ratios.	The ERG will amend the report to reflect that the points for clarification analysis was in fact hazard ratios. In addition an addendum presenting comparative results will be provided.

Issue 3 Tables that are affected by using the correct version of the model based on hazard ratios for disability progression.

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
The following tables in the ERG report are based on the previous MTC model results before disability progression modelling was updated for hazard ratios: **Tables 1 and 2, page 17** **Table 16, page 62** **Table 29, page 88**	The affected tables should be amended according to the tables provided in the clarification response document following the update of the MTC model code for hazard ratios in disability progression.	The new MTC model code provided in the clarification response document to NICE includes hazards ratios for the analysis of disability progression.	See above

Issue 4 Other sections that are affected by using the correct version of the model based on hazard ratios for disability progression.

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
The following sections of the ERG report contain text related to ICER values and interpretation of results based on the previous version of the MTC model; not the updated version of the model based on hazard ratios for disability progression: P20, section 1.4, paragraph 3 P24, section 1.7, paragraph 3, 4	The text should be amended to show the correct ICERs and interpretation of the ICERs.	The new MTC model code provided in the clarification response document to NICE includes hazards ratios for the analysis of disability progression.	See above

and 5 P24 and P25: bullet points P 72. Section 5.1, paragraphs 3, 4 and 5. P87, section 5.3.5 P101, section 5.3.12.1, paragraph 3 and 4, Table 40 P102, section 5.3.12.2, paragraph 1 and 2 P103, section 5.3.12.2, table 41 P103, section 5.3.12.4, paragraph 1 P112, section 6.2.1.1, paragraph 4 P113, section 6.2.1.1, paragraph 1 P114, section 6.2.1.1, paragraph 5 P129, section 6.3, paragraph 4 P131, section 8, paragraph 2			

Issue 5 Probabilistic v deterministic sensitivity analysis

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
P 20 Section 1.5	We consider that the deterministic results should be used as a basis for decision-making	The rationale for the ERG's view on the probabilistic sensitivity results	This is not a factual error. The ERG believe that the non-linear

The ERG considers probabilistic sensitivity analysis results to be more appropriate rather than the deterministic results presented by the manufacturer.	since the main drivers of uncertainty (hazard ratios) have been rectified.	being more appropriate is based on the model which utilises relative risks, rather than hazard ratios for progression outcomes as the primary driver of uncertainty in the ICER. The clarification on hazard ratios has been addressed in issue 1.	nature of the model make the probabilistic results the most appropriate.

Issue 6 PAS approval

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
P32. Section 3.5. Other relevant factors. This section states that the company's PAS is awaiting Department of Health (DH) approval. **P94. Section 5.2.10.1.** This section also states that a PAS price has not been approved.	In June 2013 the company was notified be e-mail from the DH that the PAS had been approved by the Ministers as below. *'Ministers have agreed that the Patient Access Scheme (PAS) proposal for dimethyl fumarate (Tecfidera) for the treatment of relapsing multiple sclerosis may be considered by NICE as part of the relevant appraisal. We have informed NICE of this decision'.*	The Committee should be aware that the PAS is approved for their consideration.	We note that the proposed PAS price has been approved.

Issue 7 References to cases of PML are misleading

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
P17. Section 1.2	The sentences:	In its current form these statements are misleading, particularly the statement on	This is not a factual error. Page 90 of the draft EPAR states

P23 Section 1.6.2 **P65. Section 4.5** There is a specific mention of the technology under review, dimethyl fumarate, in relation to case reports of PML	'*The ERG is aware of four cases of progressive multifocal leukoencephalopathy (PML) in patients treated with fumaric esters.'* (P17) and *'However the ERG is aware of case reports of PML occurring in patients treated with fumaric acid esters including dimethyl fumarate'* (P23) and *'The ERG is aware of four cases of progressive multifocal leukoencephalopathy (PML) in patients treated with fumaric esters.'* (P65) Should be amended to: 'The ERG is aware of 4 case reports of PML occurring in patients treated with Fumaderm (3 cases) and a compounded formulation (1 case). To date there have been no reports of PML in the clinical trial programme or post-marketing setting of patients treated with Tecfidera.'[1] 1. European Medicines Agency Draft EPAR March 2013 (page 90)	P23, and imply that there has been a case(s) of PML in a patient being treated with the technology under review. To date there have been no reports of PML in the clinical trial programme or post-marketing setting of patients treated with Tecfidera. Tecfidera® and Fumaderm are distinct products with different active ingredients, active metabolites and formulation. Tecfidera® contains 100% dimethyl fumarate with a single active metabolite, monomethyl fumarate. Fumaderm has 4 active ingredients (dimethyl fumarate (56%), monoethyl fumarate calcium salt (40%), monoethyl fumarate magnesium salt (3%) and monoethyl fumarate zinc salt (1%)) and 2 active metabolites, monomethyl fumarate and monoethyl fumarate. In some countries, compounded fumarates may be available on an individual patient basis from compounding pharmacies. Compounded formulations of fumarates have uncertain purity, efficacy and safety and have not been reviewed by regulatory agencies. The distinction between the technology under review and any other fumarate esters should be made clear to the reader at all times.	[redacted] [redacted] The company is correct, based on the documentation submitted, that to date there have been no reports of PML in the clinical trial programme or post-marketing setting of

			patients treated with Tecfidera. The ERG report did not suggest otherwise but to ensure clarity have added a sentence to this effect in the relevant sections

Issue 8. PML cases not included in the Manufacturers submission

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
P69. Section 4.6. There is an implication that cases of PML have been reported in patients treated with the technology under review and not reported in the submission.	The sentence: *'Incidences of PML associated with fumaric esters have been documented* [redacted] Should be amended to: 'Incidences of PML associated with fumaric esters have been documented with Fumaderm (3 cases) and a compounded formulation (1 case). To date there have been no reports of PML in the clinical trial programme or post-marketing setting of patients treated with Tecfidera®. [redacted]	In its current form this statement is misleading and implies that there has been a case(s) of PML in a patient being treated with the technology under review and that these were omitted from the submission by the manufacturer. To date there have been no reports of PML in the clinical trial programme or post-marketing setting of patients treated with Tecfidera®.	It was not our intention to imply there has been an omission from the submission and we are happy to amend the wording to avoid any ambiguity.

Issue 9. Licensed indication and NICE approval of natalizumab and fingolimod

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
P19. Section 1.3. P45 Section 4.2.4.4. **P57. Section 4.3.1.6. P71. Section 5.1.** **P 80. Table 23.** At several points in the document reference is made to the licenced indication for fingolimod and natalizumab and the NICE recommendations for these products. All are incorrect to some extent due to an apparent error in interpretation of the licenced indication. For example on P19 Section 1.3. *'Trials of fingolimod and of natalizumab which are licensed only for patients with rapidly evolving severe (RES) or highly active disease were included in the MTC. These therapies are recommended by NICE only for highly active and RES disease respectively. '* This does not make it clear that the two products have the same licenced indication. It also suggests that RES patients are not part of	There is discussion at several points in the document of the licenced indication for natalizumab and fingolimod and the different NICE guidance relating to the populations in the separate parts of that indication. It should be clarified in each instance that : The licenced indication for natalizumab and fingolimod is the same. Both are indicated as single disease modifying therapy in highly active relapsing remitting multiple sclerosis in adult patients. NICE recommended fingolimod for patients who have high disease activity despite treatment with an interferon. Fingolimod was not recommended for RES patients. NICE recommended natalizumab for patients with rapidly evolving severe disease. Natalizumab was not recommended for patients who have high disease activity despite treatment with an interferon.	As there is considerable discussion of the different populations for treatment with natalizumab and fingolimod it is important that the indication should be correctly described.	We agree with the licensed indication and NICE recommendations as described here. We believe these have been accurately characterised in our report, though in a couple of instances there is some ambiguity in the precise wording used and we have amended these.

the highly active population. Both patients with ‘high disease activity despite treatment with an interferon’ and ‘RES disease‘ are part of the population with highly active RRMS. Fingolimod and natalizumab share a common licenced indication with both being indicated as single disease modifying therapy in highly active relapsing remitting multiple sclerosis in adult patients. The indication then splits highly active RRMS patients into two populations, again common to both drugs. One of these is characterised as patients who have high disease activity despite treatment with an interferon whilst the other is characterised as patients who have rapidly evolving severe disease (RES). NICE recommended fingolimod for patients who have high disease activity despite treatment with an interferon. Fingolimod was not recommended for RES patients. NICE recommended natalizumab for patients with rapidly evolving severe disease. Natalizumab was not recommended for patients who have high disease activity despite treatment with an interferon.			

Issue 10. Instances of incorrect data

<table>
<tr><th>Description of problem</th><th>Description of proposed amendment</th><th>Justification for amendment</th><th>ERG response</th></tr>
<tr>
<td>

P38 Section 4.2.1

Table 6 contains incorrect data

</td>
<td>

Table 6 should be amended to include the correct numbers of female subjects in the trial arms of the DEFINE and CONFIRM studies:

<table>
<tr><th></th><th colspan="3">DEFINE</th><th colspan="4">CONFIRM</th></tr>
<tr><td></td><td>Dimethyl fumarate 240mg BID</td><td>Dimethyl fumarate 240mg TID</td><td>Placebo</td><td>Dimethyl fumarate 240mg BID</td><td>Dimethyl fumarate 240mg TID</td><td>Placebo</td><td>Glatiramer acetate 20mg OD</td></tr>
<tr><td>Females: N (%)</td><td>296(72)</td><td>306(74)</td><td>306(75)</td><td>245(68)</td><td>250(72)</td><td>251(69)</td><td>247(71)</td></tr>
</table>

</td>
<td rowspan="2">

All instances listed under Issue 10 are incorrect data

</td>
<td>

Numbers of female participants corrected.

</td>
</tr>
<tr>
<td>

P44 Section 4.2.4.4

Table 8 contains incorrect data

</td>
<td>

Table 8 should be amended to include the correct values for proportion of patients relapsed for dimethyl fumarate versus placebo: HR (95% CI)

<table>
<tr><td></td><td>N</td><td>ARR for dimethyl fumarate vs placebo: rate ratio (95%CI)</td><td>Proportion of patients relapsed for dimethyl fumarate vs placebo: HR (95%CI)</td><td>Disability progression confirmed at 3 months for dimethyl fumarate vs placebo:HR (95%CI)</td></tr>
</table>

</td>
<td>

Table 8, Proportion of patients relapsed for prior and no prior treatment corrected.

</td>
</tr>
</table>

Baseline EDSS score				
EDSS score ≤2	414	0.29 (0.20 to 0.44)	0.35 (0.24 to 0.51)	0.52 (0.32 to 0.82)
EDSS score >2	403	0.70 (0.50 to 0.98)	0.71 (0.51 to 0.99)	0.73 (0.45 to 1.17)
Prior MS treatment				
No prior treatment	368	0.33 (0.21 to 0.52)	0.37 (0.24 to 0.57)	0.38 (0.22 to 0.65)
Prior treatment	450	0.61 (0.45 to 0.84)	0.65 (0.45 to 0.89)	0.83 (0.54 to 1.29)

P45. Section 4.2.4.4

Table 9 contains incorrect data and has an incorrect legend

As a result of the inaccuracies in Table 9 the preceding commentary is also inaccurate

Table 9 should be corrected as follows:

	ARR for dimethyl fumarate vs placebo: rate ratio (95% CI)*	Disability progression confirmed at 3 months for dimethyl fumarate vs placebo: HR (95% CI)**
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]

Table 9, Figures corrected. Text amended accordingly.

	*Ratio <1 favours DF **Ratio >1 favours DF [redacted]		
P50 Section 4.3.1 Table 14 contains transcription errors	Table 14 should be amended as follows: FREEDOMS II Mean or median disease duration (years) currently 41.4, should be 10.4 Knobler 1993 Relapses in previous 2 years (mean or median) currently Betaferon NR, Placebo 4, should be Betaferon 4, Placebo 2.3 MSRCG Relapses in previous 2 years (mean or median) currently 2.3, should be NR TRANSFORMS Percentage female currently 65.7, should be 65.4		Table 14, transcription errors corrected.
P42 Section 4.2.4.2	A superscript ‘1’ has been wrongly ascribed to the three month disability progression data figure instead of the six month figure which appears in the following sentence.		Footnote attribution corrected

Footnote 1 has been wrongly attributed **Section 4 Tables 15,16 & 29** There are some individual instances of errors in rounding of data extracted from the manufacturers submission **Page 64 Section 4.5 Paragraph 2**	[redacted]		Corrected

Issue 11. Discounted prices

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
P 102, Section 5.3.12.2. The list of drugs recorded as having an RSS price less than list price is incorrect. The statement on P 94. Section 5.2.10.1.is correct. However the assumption drawn from it on P 102 that ALL RSS drugs have a lower RSS price than the list price is incorrect. **P 110. Section 5.4** The statement *'…when discounted prices are available to the DoH for all comparators'* is incorrect. The prices used in Table 42, P 113 are correct. The List price quoted is from the submission and allows for precise dosage requirements. Hence the very minor variations between RSS and list price on some drugs.	The statements on P 94 and P 110 should be amended. It should be made clear that not all comparators have a discounted price. Avonex and Betaferon have an RSS price that is the same as the list price. Natalizumab is not discounted and not part of the RSS. Fingolimod is not part of the RSS but is discounted under a PAS. Rebif 22, Rebif 44 and Glatiramer acetate have an RSS price that is lower than the list price.	The company recognises the rationale that a comparison should be made against the RSS prices where appropriate but it should be made clear that this only affects the price of some, but not all, comparators in the submission.	The wording of both statements has been rephrased to better reflect that not all of the comparators have a discounted price. **P 110. Section 5.4** The statement *'…when discounted prices are available to the DoH for most of the comparators'*. P 102, Section 5.3.12.2 Avonex and Betaferon have been removed from the sentence.

Issue 12. Description of current UK prescribing guidelines

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
P23 Section 1.6.2 **P27 Section 2.2** **P28 Section 3.1** **P57 Section 4.3.1.6** Current UK beta-interferon and glatiramer acetate prescribing guidelines are incorrectly described	The statement on P23 'Patients who are eligible for current DMT's (i.e. 2 clinically significant relapses in the previous 2 years for beta-interferons and glatiramer acetate) are a subset of those who meet diagnostic criteria for RRMS.' The statement on P27 'The (ABN) Guideline states that eligible patients for treatment are normally ambulant adults (maximum EDSS score of 6.5) with active relapsing disease defined as 2 clinically significant relapses in the previous 2 years.'citing the Revised (2009) ABN Guidelines The statement on P28 'However the trial (DEFINE & CONFIRM) baseline ARR reflects the inclusion criterion that patients needed to have had ≥1 relapse in the previous 12 months. This criterion is different to UK prescribing guidelines for current DMT, which states that patients should have had ≥2 relapses in the preceding 2 years' The statement on P57 'As the manufacturer correctly noted in their characterisation of current treatment pathways, beta-interferons and glatiramer acetate have EMA licenses for all RRMS patients, although the UK prescribing guidelines indicate that treatment should only be started for patients who have had ≥2 relapses in the previous 2 years' citing the Revised (2009) Association of British Neurologists'guidelines for prescribing in multiple sclerosis as the source reference	There are several references to the Revised (2009) ABN Guidelines throughout the ERG Report. The guidelines are repeatedly summarised as patients experiencing 2 clinically significant relapses in the previous 2 years. This is an oversimplification of the guidelines and has the potential to mislead the reader to assume that 2 clinically significant relapses in 2 years must be documented in order for DMT to be prescribed. The revised 2009 ABN guidelines clearly state that DMT can be prescribed in the context of 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 multiple sclerosis). (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)	This is not a factual error. This information was added to the background section as the prescribing guidelines were not covered at all in the manufacturer's submission for interferons and glatiramer acetate. P27 of the ERG report explicitly states the eligible patients for treatment are "**normally** ambulant adults (maximum EDSS score of 6.5) with active relapsing disease defined as two clinically significant relapses in the previous two years". We have added a more extensive summary of the guideline (relevant to an adult population) to the background so that the other circumstances are explicit. Elsewhere in the report we are comparing relapse rates and we refer to that aspect of the guideline therefore it is not necessary to keep repeating this information. We have added the word "normally" to the other sections where

	In order to accurately reflect the current UK guidance these statements should be amended to include the following information from the Revised (2009) ABN Guidelines: Patients with a diagnosis of active multiple sclerosis with relapsing onset; active disease is defined by two clinically significant relapses in the previous two years. 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 multiple sclerosis). (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 multiple sclerosis.	We agree that the study populations in DEFINE and CONFIRM are representative of the patients who meet current ABN criteria but feel that these criteria should be adequately explained.	relevant.

Issue 13. Choice of glatiramer acetate as principal comparator.

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
P114. Section 6.2.1.1 The latest NICE 'Guide to	The most plausible base case ICER for dimethyl fumarate should be in comparison with Avonex which is the most frequently prescribed MS	Comparison of dimethyl fumarate with Avonex the most frequently prescribed MS therapy, plus	When undertaking an incremental analysis each comparator should be

Methods of Technology Appraisal' (2013) lists 'the established NHS practice in England' and 'cost effectiveness' as two of the principal factors in choosing comparators. The ERG has chosen Glatiramer Acetate as the main comparator for its own analysis on the basis that it is the 'next best alternative' in its cost effectiveness analysis. We believe this is factually incorrect as it does not reflect clinical practice in England and is not the most relevant comparison. Interferons are generally the first choice in therapy with Avonex and Rebif 44 being the most frequent choice of agent. This is reflected by the figures for the RRMS market share of the range of comparators. Data sources for market shares in the overall RRMS market vary from source to source as most drugs are provided by home delivery companies and there is variable reporting. Biogen Idec's own data, validated by market research, puts current market shares at :	therapy.	reference to Rebif 44, will give the most relevant view of the value and cost effectiveness of dimethyl fumarate compared to the therapies it is most likely to displace.	compared to the next best alternative. In all scenarios for dimethyl fumarate this comparator is glatiramer acetate. This not a selection by the ERG, this is a selection based on appropriate, well established methods. Any other comparison, which differs from standard methods, would be inappropriate unless a change to the scope is made.

[redacted] Even allowing for data variability it is clear that glatiramer acetate use is low and not representative of established clinical practice in England & Wales.			