NATIONAL INSTITUTE FOR HEALTH AND CLINICAL EXCELLENCE

Single technology appraisal (STA)

Fingolimod for the Treatment of Relapsing-Remitting Multiple Sclerosis in Adults

Manufacturer Response to Evidence Review Group Questions

Novartis Pharmaceuticals UK Ltd.

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REDACTED VERSION

Contents

Section A – Population

Three populations (1a, 1b and 2; first introduced on p. 27) are suggested for consideration in your submission:

1) Adult patients with relapsing-remitting multiple sclerosis (RRMS), with high disease activity despite treatment with a beta-interferon. These patients may be defined as those whose disease did not respond to a full and adequate course (normally at least 1 year of treatment) of beta-interferon.

a. Patients with at least 1 relapse in the previous year while on therapy and have had at least 9 T2-hyperintense lesions in cranial MRI or at least 1 gadolinium-enhancing lesion.

b. Patients with an unchanged or increased relapse rate or ongoing severe relapses compared with the previous year.

2) Adult patients with rapidly evolving, severe, RRMS defined by 2 or more disabling relapses in 1 year and with 1 or more gadolinium enhancing lesions on brain MRI or a significant increase in T2 lesion load compared with a previous recent MRI.

A1:

Priority request: For the individual arms of the FREEDOMS and the TRANSFORMS trials separately:

a) please state the numbers of patients and provide baseline characteristics[1] and outcome data[2] for each of the following populations:

[1] Baseline characteristics should be understood to include: age, sex, disease history (including duration of MS and prior relapse history), prior exposure to DMTs and full details of initial EDSS distribution (i.e. number of participants at each EDSS level)

[2] Outcome data should be understood to include: numbers of participants experiencing both **primary and secondary outcomes** in each trial arm, together with Annualised Relapse Rates (ARRs), Annualised Progression Rates (APRs) and **relative effect measures** (e.g. hazard ratios) with SEs or confidence intervals for inter-arm comparisons in each case. Please also include **MRI data**, **quality of life data** and **details of discontinuations** for each group.

Response:

As discussed in the submission dossier, Novartis believes the NICE appraisal should focus only on Population 1b ("non-responder") of the fingolimod licence. Below is our rationale.

Firstly, the area of greatest clinical unmet need is for patients who have had an inadequate treatment response to existing therapy and who do not qualify for natalizumab treatment (NICE TA 127), i.e. Populations 1a or 1b.

The definition of Population 1a requires an MRI in order to fulfil the lesion definition, whereas Population 1b does not. Novartis believes the use of MRI is not routine clinical practice in the UK, so identifying Population 1a would require access to an additional MRI. In the ABN 2009 multiple sclerosis (MS) guidelines it state that MRI is not part of regular practice in the UK. In addition, in the NICE clinical guideline for MS it does not support the routine use of MRI for MS (NICE CG 8). Therefore, Novartis believes that Population 1b is a more straightforward population for UK clinicians to identify because it does not rely on a recent MRI being available.

Finally, from a cost-effectiveness perspective the key input into the health economics model is disease progression. This is discussed further in Section 6 of the submission. If you compare 3-month disease progression (Cox proportional Hazard Ratio) for fingolimod vs. placebo from populations 1a and 1b, then you can see that Population 1b [redacted] is superior to Population 1a [redacted] and the CI are reduced. This means from a health economics perspective Population 1b is the population to prioritise.

Therefore, in summary Novartis believes that the appraisal should only focus on Population 1b.

- **Population 1a**

In Table 15 (TRANSFORMS) and Table 16 (FREEDOMS) of the submission dossier the baseline characteristics of Population 1a is presented. Please note that in the submission the subgroup needed to use T2 volume of ≥ 500 mm3 as a proxy of ≥ 9

T2 lesions. This was done because at the time of the submission (March 2011) T2 lesion volume, but not T2 lesion count, was only available at baseline. Novartis has now obtained the baseline T2 lesion volume for each subject and has determined that the T2 volume cut-off of ≥ 500 mm3 includes 99% of patients with ≥ 9 T2 lesions. However, since we are not progressing with Population 1a we have not prioritised obtaining and presenting the updated demographics from the study database.

- **Population 2**

Response:

There were 2564 ITT subjects in FREEDOMS and TRANSFORMS. If you consider both treatment experienced and treatment-naïve subjects then only 15% of subjects could fulfil the definition for Population 2. If you only consider treatment-naïve, then this drops to 8%. This needs to be compared to the fact that 32% of subjects could be considered Population 1a and 32% could be considered Population 1b. Therefore the greatest amount of clinical data is available for Population 1a and 1b. In addition, as discussed above the area of greatest clinical unmet is in patients who have had an inadequate treatment response to Disease Modifying Therapy (DMT) and who do not qualify for natalizumab treatment (NICE TA 127). TA 127 does not recommend natalizumab for this patient population (NICE, 2007a). So clinically the strongest case is for Population 1a or 1b, as there is no other treatment available for these patients. Finally, Population 1b has the greatest clinical efficacy so the submission is focused on Population 1b of the approved indication.

As a result, Novartis have not prioritised Population 2 since it is the smallest population of the label and has the lowest efficacy of the three subgroups.

- **Population 1a and 1b combined**

Response:

As discussed above Novartis believes this submission should focus on Population 1b. To provide all of the data requested by the ERG requires time and resources.

Novartis have prioritized the requests for data. Therefore, Novartis have not prioritised an analysis of the combined Population 1a and 1b population.

b) please also state the numbers of patients and provide baseline characteristics[1] and outcome data[2] for each of the following populations:

- **Population 1a but not 2 (i.e. excluding patients with RES)**
- **Population 1b but not 2 (i.e. excluding patients with RES).**

Response:

The data for these subgroups would have to be produced specifically to answer this question. Novartis don't see what clinical rationale there is to consider these two particular subgroups so have not prioritised these two populations.

A2:

Priority request: Please provide an updated version of the graph in figure 10, along with the underlying data table, showing

a) the distribution of patients across EDSS states separately for populations 1a, 1b and 2 from the pooled analysis of the FREEDOMS and TRANSFORMS trials, alongside the relevant populations from the London Ontario cohort, the UK MS Survey and the UK RSS prospective cohort study (with all relevant adjustments applied to each of these to give the populations as used in the model).

Response:

Figure 10 in the submission already presents the distribution of EDSS states from Population 1b from the pooled analysis of the FREEDOMS and TRANSFORMS

trials. The EDSS distributions for Population 1b from the published sources are not available to Novartis so we can not redraw Figure 10 with these.

The distribution of EDSS states for Popualtion1a is presented in Table 15 and 16 of the submission. The submission focuses only on Population 1b, so Novartis have not redrawn Figure 10 for the distribution of EDSS states for population 1a or Population 2.

b) Please also provide the same data for populations 1a and 1b excluding any RES patients.

Response:

The data for these subgroups would have to be produced specifically to answer this question. Novartis are unclear what clinical rationale there is to consider these two particular subgroups so have not prioritised this analysis.

A3:

Priority request: For each of the populations identified in A1.a and A1.b, above, please supply time-to-event data (e.g. Kaplan–Meier plots analogous to those provided in Figures 4 and 5 of your submission) for time to first relapse and time to progression. Please specify numbers at risk at each time point.

Response:

The submission focuses on Population 1b so analysing the data for that has been prioritised. Figure 1 and Figure 2 below are the Kaplan–Meier plots for time to first relapse in Population 1b, and Figure 3 and Figure 4 are the Kaplan–Meier plots for time to 3-month progression in Population 1b. Please note this data is supplied to you as academic in confidence.

Figure 1 FREEDOMS - Population 1b

Figure 2 TRANSFORMS Population 1b

Figure 3 FREEDOMS - Population 1b

Figure 4 TRANSFORMS - Population 1b

A4:

Priority request: Please report a fully incremental analysis of the cost-effectiveness results for fingolimod in population 1b compared with all relevant comparators including optimised standard care with no disease modifying therapy.

Response:

We did not run these suggested cost-effectiveness analyses for any additional comparators because there are no relevant clinical data available for these comparators in this patient sub-group (data for Avonex and Fingolimod came from the TRANSFORMS and FREEDOMS studies).

With regard to optimised standard care with no disease modifying therapy. A recent publication discussed stopping interferon therapy after 24 months in patients with high pre-treatment disease activity (Vandenbroek 2010). On discontinuation of the interferon treatment there was a resurgence of MS activity. In addition, an international consensus meeting held in 2006 suggested a pathway to manage sub-optimal responders. However, optimised standard care with no disease modifying therapy did not feature as a standalone treatment option (Karussis 2006). Steroids, physiotherapy, occupational therapy and symptomatic treatment of the manifestations of neurological deficit caused by MS were considered, but these options do not impact relapse rates or disability progression and are thus not considered an appropriate standalone alternative for sub-optimal responders.

Therefore Novartis do not believe optimised standard of care is a relevant comparator.

A5:

Priority request: Please also report a fully incremental analysis of the cost-effectiveness results for fingolimod compared with all

relevant comparators including optimised standard care with no disease modifying therapy for the following populations:

Response:

a) Population 1a

As stated in our response to question A1 and in the NICE submission dossier Novartis have prioritised Population 1b.

b) Population 2

As stated above Novartis have prioritised Population 1b.Novartis have not prioritised Population 2 since it is the smallest population of the label and has the lowest efficacy of the three populations of the label.

c) Population 1a but not 2 (i.e. excluding patients with RES)

The data for this subgroup would have to be produced specifically to answer this question. Novartis don't see what clinical rationale there is to consider this particular subgroup so have not prioritised obtaining the data for this subgroup.

d) Population 1b but not 2 (i.e. excluding patients with RES).

Similar to the response above the data for this subgroup would have to be produced specifically to answer this question. Novartis don't see what clinical rationale there is to consider this particular subgroup so have not prioritised obtaining the data for this subgroup.

A6:

Priority request: Please provide EDSS transition matrices (similar to tables 49 and 51 in the submission) and time to first progression (similar to figure 5B in the submission) derived using the data matching population 1b for each arm of the FREEDOMS trial.

Response:

The transition matrices for Population 1b are presented below for placebo (Table 1) and fingolimod 0.5 mg (Table 2).

Table 1: Patient Distribution at Trial Endpoint, FREEDOMS placebo group: Population 1b of label

	EDSS at Trial Endpoint								
EDSS	**0**	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**
0	[redacted]								
1	[redacted]								
2	[redacted]								
3	[redacted]								
4	[redacted]								
5	[redacted]								
6	[redacted]								
7	[redacted]								
8	[redacted]								

Table 2: Patient Distribution at Trial Endpoint, FREEDOMS fingolimod 0.5-mg group: Population 1b of label

EDSS	**0**	**1**	**2**	**3**	**4**	**5**	**6**	**7**
0	[redacted]							
1	[redacted]							
2	[redacted]							
3	[redacted]							
4	[redacted]							
5	[redacted]							
6	[redacted]							
7	[redacted]							

The time to first progression data for Population 1b were not generated previously as this variable was not required by the economic model. For time to progression data, please refer to response under question A3.

Section B – Comparators

B1:

Priority request: The results from the electronic model report an Incremental Cost-Effectiveness Ratio (ICER) of £279,107 per Quality Adjusted Life Year (QALY) for Avonex (interferon beta-1a) compared with best supportive care (optimised standard care with no disease modifying therapy) in the main modelled population. Please discuss the potential reasons why this estimated ICER appears significantly higher than the ICER estimates for beta interferons reported in previous NICE technology appraisals (NICE, 2002):

Response:

We believe that the main reason for the estimated ICER of £279,107 per QALY to be significantly higher than the ICER estimates for beta interferons reported previously is due to the fact that the population in the current submission is completely different to the one examined in previous NICE technology appraisal (NICE, 2002), i.e., treatment-naïve patients are considered in the previous appraisal vs. treatment experienced patients failing on a DMT in the current submission. In patients who have failed on a DMT you would expect low efficacy for Avonex in this group compared with the treatment-naïve group.

The natalizumab submission (Biogen, 2007) considered suboptimal therapy (SOT) population (defined as population 1a only), but did not present results for Avonex vs. best supportive care. The cost-effectiveness results for Avonex vs. no treatment for the 20-year time horizon in the 2002 appraisal varied between £48,085 (based on public domain data) and £106,150 (based on commercial-in-confidence data) (Tappenden et al., 2001). When we re-run the analysis for Avonex compared with

best supportive care for 20 years for first-line all RRMS population, this produced a more comparable ICER of £120,098 per QALY.

B2:

Please clarify the reasons for choosing Avonex (interferon beta-1a) as the main comparator drug for fingolimod; please make reference to Avonex's relatively small market share of RRMS treatments, as provided in table A7 and the potential generalisability of this comparison to other disease modifying treatments that are used in the NHS.

Response:

Novartis believe that patients with RRMS are initiated with one disease modifying therapy and if they fail to respond they are cycled to an alternative DMT. Thus, the treatment comparators to fingolimod for patients not responding to beta interferon consist of all other disease modifying therapies currently indicated for treatment of RRMS:

1. Interferon-beta-1a (Rebif) 22 mg,
2. Interferon-beta-1a (Rebif) 44 mg,
3. Interferon-beta-1a (Avonex),
4. Interferon-beta-1b (Betaferon, Extavia),
5. Glatiramer acetate (Copaxone).

Natalizumab (Tysabri) is also licensed for use in patients with high disease activity despite treatment with a beta-interferon. However, in 2006 NICE did not recommend the use of natalizumab in these patients so Novartis are not considering it a suitable comparator.

All of the above therapies are generally delivered to the home, so obtaining exact national English and Welsh prescribing data for their use in this population is not

readily available. Within the submission, Novartis presented an estimate of the market share derived from the reporting of prescribing from a sample of 45 UK clinicians. As stated in the submission, by its nature this data will not be an exact science but was the best data Novartis could identify at the time of the submission. Overall the table in the submission indicates that none of the six therapies is used in the majority of patients, and the greatest market share for a product was 36.1%.

Since submitting the evidence dossier to NICE in March 2011, Novartis has obtained prescribing data by means of a Freedom of Information (FOI) request from the Prescription Pricing Authority. These are market share data for DMT use for patients with RRMS from January 2008 to June 2010, for 60 primary care trusts (Table 3). As can be seen Avonex has the highest market share data.

Table 3: Market share of DMTs prescribed for RRMS from Jan 2008 to June 2010

Therapy	Patient share (%)
Interferon-beta-1a (Avonex)	33.8
Interferon-beta-1a (Rebif)	28.4
Glatiramer acetate (Copaxone)	21.3
Interferon-beta-1b (Betaferon and Extavia)	16.5

From the systematic review described in the fingolimod STA evidence submission we know that there are two phase III trials for fingolimod in an RRMS population. FREEDOMS is a placebo controlled trial, and TRANSFORMS compares fingolimod to Avonex. This means the only direct head-to-head data for fingolimod versus a DMT is from TRANSFORMS. If a comparison with any of the other DMT is desired then an indirect comparison would have to be undertaken.

The mixed treatment comparison presented in the fingolimod evidence dossier indicates that in **RRMS** all of the existing licensed DMTs (Avonex, Copaxone, Rebif, and Betaferon) have a similar efficacy in terms of annualised relapse rate and change in confirmed disability. In addition, this result is supported in the published literature. Therefore, in **RRMS** we would expect a comparison with Avonex to be generalisable to a comparison of fingolimod with one of the other DMTs.

The systematic review also revealed that for all the DMTs listed above the only available published clinical efficacy data is for RRMS. This means it is not possible to undertake an indirect comparison between fingolimod and any of the DMTs for a sub population of RRMS, e.g. Population 1b. Avonex is the comparator in TRANSFORMS, so it was possible for Novartis to undertake a comparison of fingolimod for a subpopulation of RRMS. This is what has been presented in the submission dossier.

Novartis therefore believe that choosing Avonex as a comparator is not unreasonable.

B3:

Glatiramer acetate is discussed in the submission as a treatment to be used in populations where patients do not respond to beta-interferons (e.g. p. 196). It has also been used as the comparator in similar non-responder populations in previous NICE technology appraisals (NICE, 2007). Please clarify why glatiramer acetate has not been formally included as a comparator in the economic model.

Response:

Novartis is not aware of any clinical data for glatiramer acetate in the population of interest to facilitate such analysis. Novartis have examined the previous technology appraisals and it is not clear from Biogen's submission (Biogen, 2007), the ERG assessment report of Biogen's submission (NICE, 2007b), or the reference in the Biogen's submission how these data for glatiramer acetate were calculated. If the ERG can be provided the relevant clinical data please can they highlight it to Novartis.

Section C – Health Related Quality of Life

C1:

Priority request: The submission states that EQ5D data were collected from patients in both the FREEDOMS and the TRANSFORMS trials. Please add to table 59 additional columns representing the utility estimates from the EQ5D data from the FREEDOMS and TRANSFORMS trials.

Response:

FREEDOMS

Table 4 presents baseline EQ5D by treatment and baseline EDSS score pooled for the 3 treatment arms FTY720 1.25mg, FTY720 0.5mg, and placebo from FREEDOMS. Please note the baseline EQ5D was missing for 8 subjects. The conversion to utility score is based on the list representing the EQ5D value set for the UK. An inclusion criteria for FREEDOMS was to have an EDSS score of 0 to 5.5 inclusive. This means there is no baseline utility for EDSS > 5.5.

Table 4: FREEDOMS: Baseline EQ5D by treatment and baseline EDSS score - Safety population

EDSS at baseline	Mean (SD) EQ5D Utility Score at baseline, n=1264
0.0	0.90 (0.180)
0.5 to 1.0	0.88 (0.145)
1.5 to 2.0	0.83 (0.158)
2.5 to 3.0	0.74 (0.160)
3.5 to 4.0	0.67 (0.193)
4.5 to 5.0	0.65 (0.169)
5.5 to 6.0	0.54 (0.225)

EDSS, Expanded Disability Status Scale; Statistics: mean (SD)

TRANSFORMS

Table 5 presents the baseline EQ5D by treatment and baseline EDSS score pooled for the 3 treatment arms FTY720 1.25mg, FTY720 0.5mg, and Interferon from TRANSFORMS. Please note the baseline EQ5D was missing for 49 subjects. The

conversion to utility score is based on the list representing the EQ5D value set for the UK. An inclusion criteria for TRANSFORMS was to have an EDSS score of 0 to 5.5 inclusive. This means there is no baseline utility for EDSS > 5.5.

Table 5: TRANSFORMS: Baseline EQ5D by treatment and baseline EDSS score - Safety population

EDSS at baseline	Mean (SD) EQ5D Utility Score at baseline, n=1231
0.0	0.89 (0.147)
0.5 to 1.0	0.86 (0.168)
1.5 to 2.0	0.85 (0.158)
2.5 to 3.0	0.77 (0.154)
3.5 to 4.0	0.71 (0.203)
4.5 to 5.0	0.63 (0.228)
5.5 to 6.0	0.55 (0.231)

EDSS, Expanded Disability Status Scale; Statistics: mean (SD)

C2:

Priority request: Please provide the EQ5D data for patients in the populations identified in A1.a and A1.b, above.

Response:

The EQ5D data that were required to respond to question C1 were prepared specifically for this ERG question. Novartis have prioritised the requests for data.

Section D – Economic Model

Adverse Events

D1:

Please provide more details on the specific events referred to in table 62 on utility decrements for adverse events. What events are

included and what assumptions are made about their incidence in the modelled population?

Response:

Disutility values for adverse events associated with interferon-beta-1a, interferon-beta-1b, and glatiramer acetate were derived from a study by Prosser et al. (2003) examining preferences for treatments and health states for patients with RRMS and members of the community. Prosser and colleagues (Prosser et al., 2003) report mean utility values for the following health states.

- **Treatment A:** Imagine that you take an injectable drug once per week. This requires first mixing the powdered drug with the liquid, drawing it into a syringe, and injecting it into your thigh. Often you will feel feverish and achy for about 24 hours after the injection - just as if you had the flu. The injection itself is not very painful, but sometimes the skin around the injection site will get sore. A doctor can prescribe medication to ease the soreness. Occasionally it will get infected.

- **Treatment B:** Imagine that you take an injectable drug every other day. This requires first mixing the powdered drug with the liquid, drawing it into a syringe, and injecting it into your thigh. Often you will feel feverish and achy for about 24 hours after the injection -just as if you had the flu. The injection itself is not very painful, but sometimes the skin around the injection site will get sore. A doctor can prescribe medication to ease the soreness. Occasionally it will get infected.

- **Treatment C:** Imagine that you take an injectable drug every day. This requires first mixing the powdered drug with the liquid, drawing it into a syringe, and injecting it into your thigh. The injection itself is not very painful, but sometimes the skin around the injection site will get sore. A doctor can prescribe medication to ease the soreness. Occasionally it will get infected.

We assumed interferon-beta-1a under “Treatment A”, interferon-beta-1b under “Treatment B”, and glatiramer acetate under “Treatment C”. The adverse events included were mainly associated with injection-site reactions and flu-like symptoms.

The assumption about incidence of adverse events is based on the 30% estimate used by the assessment group (ScHARR) in the original NICE appraisal of interferon-beta and glatiramer acetate (Tappenden et al., 2001) as well as in the Biogen's NICE submission for natalizumab (Biogen, 2007). We did not identify any other estimates in our literature searches

Its worth noting that in TRANSFORMS flu-like symptoms were reported in 37% of subjects receiving Interferon beta-1a whereas flu like symptoms were only reported in 3% of subjects receiving fingolimod 0.5mg. Novartis therefore believes the estimate of 30% for the adverse events associated with interferons and glatiramer acetate is not unreasonable.

Costs

D2:

Please clarify how the administration cost of natalizumab (quoted in table 68 as £16,861) has been estimated. Please report the resource use assumptions, unit costs and data sources which have been used to derive this estimate.

Response:

The administration cost of natalizumab reported in Table 68 is the annual cost and is based on cost of one administration multiplied by 13 administrations. Cost of one administration is equal to £1,293, which is the AA30Z HRG code from the 2010-11 National Tariffs (Department of Health, 2010). TA127 Multiple sclerosis – natalizumab: costing template (NICE, 2008) used A18 Multiple Sclerosis or other CNS Demyelinating conditions 2007/08 elective in-patient tariff, uplifted by average market forces factor. The A18 HRG code is superseded by AA30Z in 2010-11 National Tariffs (Department of Health, 2010). This explanation on the derivation of the administration cost of natalizumab is provided in the footnote to Table 66 of the current submission.

Please note the submission does not present a cost-effectiveness analysis for fingolimod vs. natalizumab so the main text of the submission does not discuss the costs of administering natalizumab in-depth.

Model Structure

D3:

The ERG's clinical advisor has emphasised that in RRMS, disability accumulates after relapses. Please clarify how this correlation between progression and relapses is accounted for in the decision model, taking into consideration the fact that different data sources (Ontario (Weinshenker, 1989) for progression and Patzold and Pocklington (1982) for relapse) were used for the different outcomes.

Response:

We can confirm that progression and relapses were applied separately in the model and relapses do not have a direct impact on the disease severity or the disease progression. Currently the rates of relapse are driven by the severity of the disease, i.e., the EDSS score, and the time since diagnosis. However, in the model there is no separate mechanism to adjust progression following a relapse.

Ideally in the decision model Novartis would consider the observation that in RRMS disability is accumulated after relapses. However, Novartis have not been able to identify any published data to fully support this.

Furthermore, Novartis believe that the clinical data for fingolimod suggests that including an assumption that disability accumulates after relapses would favour fingolimod. Therefore, Novartis believes the current model is conservative and underestimates the benefit of fingolimod.

The model used in this submission is the same model which was used in the previous NICE appraisal of natalizumab and is the one developed by ScHARR for the original interferon NICE appraisal.

D4:

Please explain the statement in section 6.2.3 of the submission that states: "progression and relapses are applied separately in the model so that progression has no influence on relapse events" with reference to tables 49 and 55 from the same sub-section of the submission showing that both relapse rates and progression depend on EDSS states. Additionally, please comment on the implications of using a relative measure of effectiveness for both relapse and progression.

Response:

Progression does influence the relapse events as is evident from Table 55 in the submission. Relapse is linked to progression in the model via the EDSS states and that the relative effect of progression and relapse is applied in the model.

In the model, both progression and relapse rates depend on EDSS states and there is no separate mechanism in the model to adjust progression following a relapse.

To test any potential impact on cost-effectiveness from overestimates the benefits of the treatments we re-ran the cost-effectiveness analysis applying no effect of relapse. This meant that only the effect through progression is applied in the model (and the indirect impact on relapses that this may imply). This changed the ICER from £55,634/QALY to £69,111/QALY. This shows that the inclusion of the relative effect on relapse (reducing the relapse rates within EDSS stages) is not a significant driver of cost-effectiveness.

As stated above, the model used in this submission is the same model which was used in the previous NICE appraisal of natalizumab and is the one developed by the NICE assessment group ScHARR for the original interferon NICE appraisal.

Section E – Minor queries and typographical errors

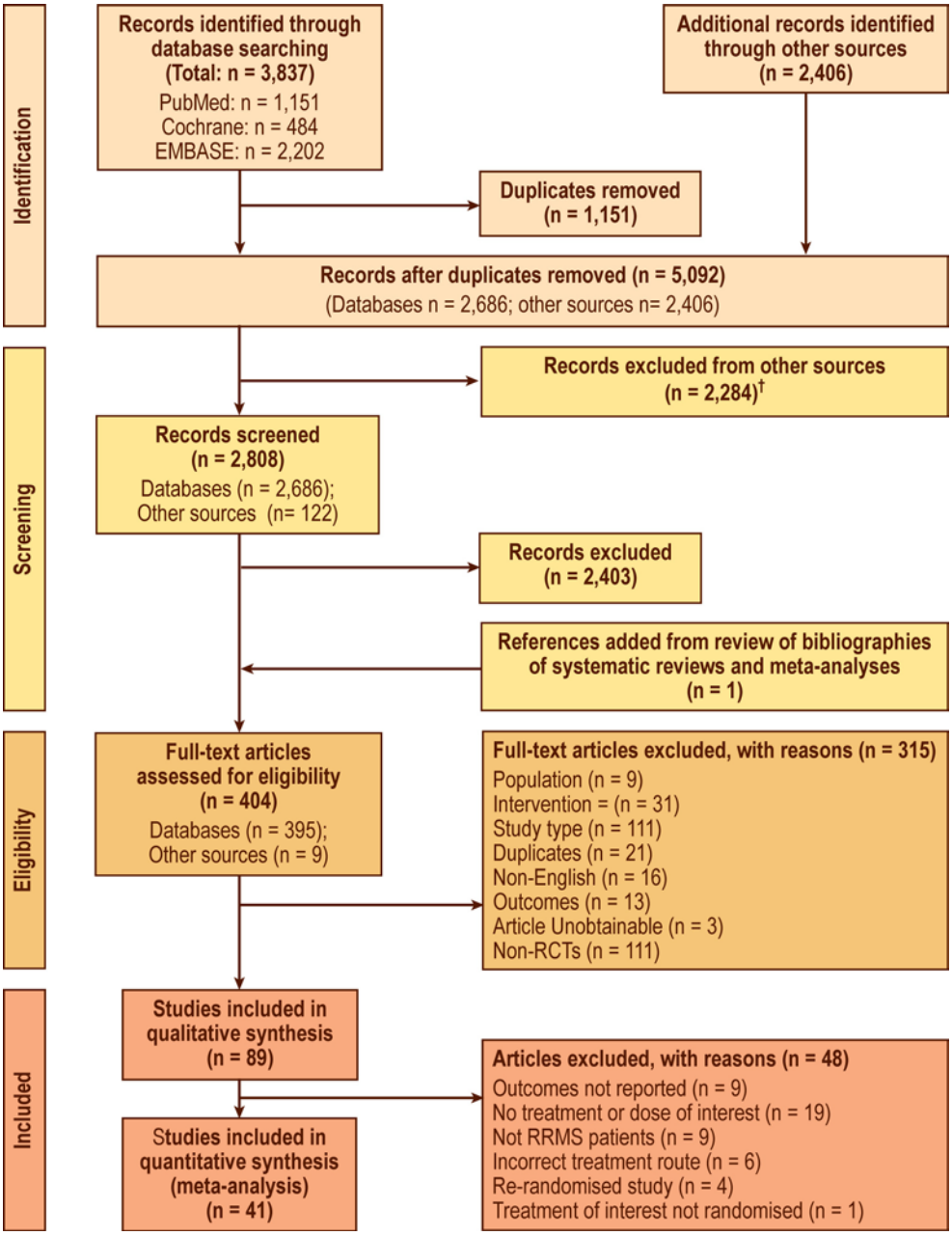
E1:

Please provide clarification of the numbers of records identified in the systematic review: there are discrepancies between figure 1 and the text and figure 1 lacks internal coherence.

Response:

We have provided further detail in Figure 5, for the “Screening” and “Identification” phases of the review, so that it is more clearly aligned with the text.

Figure 5: Study identification, inclusion and exclusion: primary systematic review (Updated)*



RCT, randomised controlled trial; RRMS, relapsing-remitting multiple sclerosis.

* Please note that of the 315 articles excluded at the level 2 screening, 111 were excluded based on “study type”, which included reviews, commentaries, diagnostics studies, genetics studies, etc; another 111 were excluded based on the study being a non-RCT, which included 90 prospective observational studies, 11 open-label follow-up studies and 10 clinical trials that were not randomised.

† Details of the reasons for exclusion of the abstracts identified from other sources (e.g. conference proceedings, abstract books and other internet sources) are not provided after the initial screening, due to the inherent difficulties in recording this information. Internet sources had varying search engines and cannot be searched in the same systematic and targeted manner as the medical databases and many of the articles initially retrieved were clearly not relevant, and only 122 studies were selected for further screening.

E2:

P45: [redacted] of subjects... qualify for either definition of high disease activity". Please clarify which figure refers to FREEDOMS and which to TRANSFORMS.

Response:

The figures on Page 45 of the dossier is the range of the overlap for each of the different treatment arms (fingolimod 0.5mg; fingolimod 1.25mg, placebo, or interferon) pooled from the two pivotal trials (FREEDOMS or TRANSFORMS). So the overlap between Population 1a and Population 1b for subjects receiving placebo is 72%, where as the overlap between Population 1a and 1b for subjects receiving fingolimod 0.5mg is 84%.

Alternatively if you consider the trials as a whole and pool the subjects for all treatment arms in the trial. Then within FREEDOMS, 79% of all the subjects in the study (all 3 arms pooled) are both Population 1a and Population 1b. And within TRANSFORMS, 84% of all the subjects in the study (all 3 arms pooled) are both Population 1a and Population 1b

E3:

For tables 26 and 28 please provide confidence intervals for the ARR in subgroups.

Response:

The confidence intervals for these two pieces of raw data have never been calculated.

E4:

Please clarify the source of the % figures in table 47.

Response:

The percentages relate to the proportion of the combined populations of FREEDOMS and TRANSFORMS that qualify for each subgroup corresponding to the three parts of the indication. To clarify, the text and table should read as follows:

"Below is a summary of identified subgroups from the FREEDOMS and TRANSFORMS studies that had the closest fit to each of the descriptions in the indication. The three subgroups partially overlap, which is why the percentages do not add up to 100%". The table title should now read "Approved indication and subgroups of FREEDOMS and TRANSFORMS trials".

E5:

The total number of patients in table 14 (Randomised population of FREEDOMS) = 1272 but table 18 (subgroup of patients with disease modifying treatment in previous year and unchanged/increased relapse rate or ongoing serious relapses) = 1292. The ERG assumes this is a typographical error; please provide the correct numbers.

Response:

This was a typographical error in Table 18 in the submission; the numbers in Table 14 are correct. The correct population numbers for Table 18 are: fingolimod 0.5 mg: 90; fingolimod 1.25 mg: 81; placebo: 79, i.e., a total of 250.

REFERENCES

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