Professional organisation statement template

Thank you for agreeing to give us a statement on your organisation's view of the technology and the way it should be used in the NHS.

Healthcare professionals can provide a unique perspective on the technology within the context of current clinical practice which is not typically available from the published literature.

To help you in making your statement, we have provided a template. The questions are there as prompts to guide you. It is not essential that you answer all of them.

Please do not exceed the 8-page limit.

About you

Your name: Carolyn A Young

Name of your organisation Representing:-
(1) Royal College of Physicians of London,
(2) Association of British Neurologists,
(3) British Society of Rehabilitation Medicine.

Employed by Walton Centre for Neurology & Neurosurgery NHS Trust.

Are you (tick all that apply):

- a specialist in the treatment of people with the condition for which NICE is considering this technology? **Yes**

- a specialist in the clinical evidence base that is to support the technology (e.g. involved in clinical trials for the technology)? **Yes**

- an employee of a healthcare professional organisation that represents clinicians treating the condition for which NICE is considering the technology? If so, what is your position in the organisation where appropriate (e.g. policy officer, trustee, member etc.)? **No, just NHS employee**

- other? (please specify) **-**

What is the expected place of the technology in current practice?

How is the condition currently treated in the NHS? Is there significant geographical variation in current practice? Are there differences of opinion between professionals as to what current practice should be? What are the current alternatives (if any) to the technology, and what are their respective advantages and disadvantages?

Consideration of treatments below is restricted to disease modifiers and all symptomatic and relapse treatments are omitted. Disease course, specifically relapse rate, of RRMS is treated using beta interferons, glatiramer acetate (GA) and natalizumab. In the UK the use of natalizumab is usually restricted to patients who have continued to relapse frequently on interferons and/or GA, or whose disease is deemed aggressive on the basis of early, frequent, disabling relapses and who are willing to accept the very low risk of progressive multifocal leukoencephalopathy. These patients with treatment-refractory or aggressive disease may also be offered alemtuzumab (unlicensed for this indication) or mitoxantrone (unlicensed in the UK for this indication). Such practice is in keeping national and international guidance, but there are geographical variations in use of mitoxantrone, natalizumab and alemtuzumab, largely explained by local familiarity with the drugs and variations in remuneration rates, rather than reflecting differences of opinion about the evidence base.

Fingolimod is the first oral disease modifying drug and it is significant that active comparator studies with interferon beta 1a (Avonex) over 1 year showed fingolimod to be more effective in reducing relapse rate; fingolimod 0.5 mg annualised relapse rate (ARR) 0.16 (95% confidence interval 0.12–0.21) and Avonex ARR 0.33 (95% confidence interval 0.26–0.42; P< 0.001). In the placebo controlled study, the ARR was 0.18 (95% confidence interval 0.15-0.22) for 0.5 mg fingolimod compared to 0.40 (95% confidence interval 0.34-0.47) with placebo (P< 0.001). While the placebo groups may not be exactly comparable, this reduction in relapse rate represented a relative reduction of 54% for fingolimod compared to placebo, which is greater than that found for any of the 3 interferons or GA compared to placebo. In summary, the evidence base suggests the new oral agent fingolimod is more effective at reducing relapse rates than the current first line parenteral disease modifiers, which each week require one i.m. injection or 3-7 subcutaneous injections, depending on drug. There are several other oral disease modifiers in development but not yet licensed in Europe.

Are there any subgroups of patients with the condition who have a different prognosis from the typical patient? Are there differences in the capacity of different subgroups to benefit from or to be put at risk by the technology?

Fingolimod was recently approved by the European Medicines Agency (EMA), broadly as a second line agent. It is approved for people with high disease activity despite beta interferon (normally at least one year of treatment), defined as at least 1 relapse on treatment and at least 9 T2 lesions or at least 1 Gad-enhancing lesion, or patients with rapidly evolving severe RRMS, defined as 2 or more disabling relapses in 1 year and 1 or more Gad or a “significant increase” in T2 lesions as compared to a previous recent MRI. It should be noted that the eligibility criteria for the two large phase 3 fingolimod studies were different from the type of patient for whom the EMA has approved fingolimod. For the placebo controlled study patients had to have 1 or more relapses in the previous year or 2 in the previous 2 years and could be treatment-naïve or have ceased interferon or GA 3 or more months before

randomisation. For the active comparator study patients had had at least 1 relapse in the previous year or at least 2 relapses in the previous 2 years, previous recent therapy with any interferon or GA was not a criterion for exclusion. In summary, the evidence base is wider than the licensing approval; other regulators acknowledge this and the FDA have approved fingolimod as a first line treatment.

This licensing approval covers disparate groups of patients carrying different risks of relapse–induced disability. Firstly, that large group of patients who continue to have at least one relapse per annum on treatment with beta interferon, whom most MS specialists would not consider to be necessarily showing high disease activity. Because the interferons produce a reduction in relapse rate of about 30% per annum, many patients will relapse despite being compliant with at least 1 year of treatment. In the pivotal studies the number of relapse-free patients over 2 years was:- Rebif 22 mg 27%, Rebif 44 mg 32%, Avonex 38%, Betaferon ?29%. These patients were recruited in the 1980s/1990s and current populations may differ but these data suggest the majority of patients will relapse in 2 years, in the year they have their relapse they become partially eligible for fingolimod, though not necessarily fulfilling MRI criteria (see later comments on lack of evidence for MR criteria). In terms of further relapses on treatment but possibly not MRI criteria (no data known to me), this is a large group eligible for fingolimod. One would assume their prognosis may be worse than the minority who achieve excellent disease control (i.e. no relapses) on beta interferon.

The next group covered by the EMA approval are those with rapidly evolving severe MS and I believe most MS specialists acknowledge such a group and believe their prognosis, if relapses cannot be reduced in number and/or severity, is poor. Such patients are currently treated with natalizumab, alemtuzumab or mitoxantrone and in view of the bleak prognosis, time sensitivity (the next relapse may produce long term disability) and lack of data on fingolimod in rapidly evolving MS, I suspect many MS specialists will continue to counsel patients with rapidly evolving MS to take another agent than fingolimod. Those patients who refuse or fail on other treatments will be offered fingolimod and will gradually create an evidence base for fingolimod in rapidly evolving MS. If fingolimod appears to reduce relapse rate and/or severity in rapidly evolving MS it will become a first line agent for this indication. However, at present the approval is for an indication for which there appears to be little data.

No trial has yet been run specifically on this group, and indeed some might be reluctant to consider even an active comparator trial ethical. There is post hoc analysis data available from the sponsor Novartis and presented in poster format at an international meeting. This analysis defines high disease activity MS slightly differently than the EMA approval as ≥ 1 gadolinium-enhancing lesion and ≥ 2 relapses in the year before the study, no mention of a T2 MR criterion. For the proportion of patients receiving 0.5mg fingolimod (this is the licensed dose, 0.5 mg and 1.25 mg fingolimod were used in trials) 140/841, 16.6% met the criteria above for high disease activity. For this subgroup, the ARR was 0.35 (95% confidence interval 0.25–0.48) for 0.5 mg fingolimod compared to 0.93 (95% confidence interval 0.7–1.23) for placebo (P< 0.001).

Considering future practice I foresee potential widening of usage:-

1. Patients and clinicians may consider it illogical that those who fail on interferon may receive fingolimod whilst those who fail on GA are not eligible, especially since both fingolimod studies included patients who had previously been on GA. 520/1272, 40.9% fingolimod placebo recruits had been on a previous disease modifier at some time, distribution between drugs not known

to me but certainly including GA. For the fingolimod Avonex study, there is some information available from a post hoc analysis that 732/1292, 56.7% had been on a disease modifier at any time, 641 in the year prior to the study. 635/732 had received beta interferon as a disease modifier at some time. It is not known from this how many fell into the group covered by the EMA approval of receiving beta interferon in the year leading up to fingolimod and having relapse activity in that year.

2. Clinicians may find it difficult to justify the MR other than the license requirements. Having 9 T2 lesions may not tell you if these are new or historical, Gad-enhancement is a temporary phenomenon and if the patient presents, is seen or is scanned more than a few weeks after a relapse the Gad-enhancement may be missed. In any case 61.5% of the patients in the fingolimod placebo study and 63.9% of the patients in the fingolimod Avonex study had no Gad-enhancing lesions at baseline.

3. If fingolimod proves as effective in clinical practice as it did in trials for people who have previously had other disease modifiers such as interferon, and in view of the placebo controlled data including for treatment naïve patients, patients may question why they need to take injections for a year and suffer at least 1 more relapse before being offered an effective pill.

4. There will be enormous pressure to offer fingolimod to patients who are unable to tolerate beta interferons or GA or who are needle-phobic. The ethical case to withhold an effective oral agent from people who cannot take current first line agents is untenable when one considers the evidence base from the fingolimod placebo and fingolimod Avonex studies.

In what setting should/could the technology be used – for example, primary or secondary care, specialist clinics?

Fingolimod should be initiated and monitored in specialist MS clinics by neurologists and MS nurses experienced in the care of MS.

The advantages and disadvantages of the technology

NICE is particularly interested in your views on how the technology, when it becomes available, will compare with current alternatives used in the UK. Will the technology be easier or more difficult to use, and are there any practical implications (for example, concomitant treatments, other additional clinical requirements, patient acceptability/ease of use or the need for additional tests) surrounding its future use?

Fingolimod should require less monitoring in terms of specialist nursing input as people generally need less specialist supervision to take tablets than to self inject. However I anticipate there will be clinical monitoring required, such as ophthalmology examinations; possibly skin examinations; ECG, pulse and blood pressure checking; varicella zoster immunity check and liver function tests monitoring; and specific advice and hospital work load around treatment initiation, including following a gap in treatment of 7+ days.

This initiation requires 4-6 hours of pulse, blood pressure and clinical status monitoring with capacity to keep the patient in hospital and treat symptomatic bradycardia/ hypotension/ECG abnormalities. This monitoring will likely require day case admission.

If appropriate, please give your view on the nature of any rules, informal or formal, for starting and stopping the use of the technology; this might include any requirements for additional testing to identify appropriate subgroups for treatment or to assess response and the potential for discontinuation.

Proposed starting criteria:- (additions to EMA approval in italics)

1. Patients with high disease activity despite treatment with a beta interferon *or glatiramer acetate*.
2. *Patients who have previously shown high disease activity despite treatment with beta interferons or glatiramer acetate and who have consequently withdrawn from treatment with those drugs while awaiting alternative treatments.*
3. Patients with rapidly evolving severe relapsing remitting MS.
4. *Needle-phobic patients who have been awaiting an oral treatment.*

Proposed stopping criteria

In some patients, discontinuation of treatment may become necessary because of significant adverse effects, or when a pregnancy is planned. Treatment should be discontinued when it is no longer effective. The following features indicate lack of efficacy and should be taken in to account when deciding whether treatment should be discontinued:
(i) Development of an increased number and severity of relapses or lack of relapse reduction compared with the pre-treatment 1 to 2 years, especially if MRI shows new or enhancing lesions.
(ii) Development of non-relapsing secondary progressive MS.
(iii) Loss of ability to walk, with or without assistance, persistent for at least 6 months (studies have excluded patients with such disability).
The stopping criteria should be made known to patients and agreed before treatment is begun.

If you are familiar with the evidence base for the technology, please comment on whether the use of the technology under clinical trial conditions reflects that observed in clinical practice. Do the circumstances in which the trials were conducted reflect current UK practice, and if not, how could the results be extrapolated to a UK setting? What, in your view, are the most important outcomes, and were they measured in the trials? If surrogate measures of outcome were used, do they adequately predict long-term outcomes?

The two phase 3 trials reflect current UK practice and recruited patients commonly seen in clinical practice. Their results could be extrapolated to a UK setting. The trials were standard design and unremarkable in their outcome measures. They provide a reasonable evidence base for the first few years of fingolimod use,.but long term data would be beneficial in this chronic, incurable condition. Unfortunately the approval from the EMA does not reflect the available evidence base.

Fingolimod is still being used in trials in the UK, including trials with wider eligibility than the EMA approval. Criteria from one current study include SPMS with relapses, and do not specify a relapse frequency before entry. A proportion (hopefully all) of these UK trial participants will be patients eligible for a disease modifying therapy under current Association of British Neurologists' and risk-sharing guidelines; some will be treatment failures through ongoing relapses or adverse events on existing drugs; and some will be needle-phobic. There would be a strong argument for allowing those trial participants who fulfilled 1 or more of the above criteria and have demonstrated benefit (reduced relapses) and compliance with fingolimod to remain on treatment.

What is the relative significance of any side effects or adverse reactions? In what ways do these affect the management of the condition and the patient's quality of life? Are there any adverse effects that were not apparent in clinical trials but have come to light subsequently during routine clinical practice?

In the phase 3 studies adverse events leading to drug discontinuation were similar for the 0.5 fingolimod dose (7.5%) and placebo (7.7%) in the placebo controlled study but higher for fingolimod 0.5 mg (5.6%) than Avonex (3.7%) in the active comparator study. Herpes virus infection was similar for the 0.5 mg dose between fingolimod and placebo and fingolimod and Avonex (however see comment on death below). Bradycardia, first and second degree heart block were more common with fingolimod but not clinically worrying in monitored patients. Macular oedema and laboratory abnormalities, especially decreased peripheral blood lymphocytes and liver enzyme abnormalities, were more common with fingolimod. In the fingolimod Avonex study 2 patients died, 1 of herpes simplex encephalitis (recognised significant mortality rate) and 1 of disseminated herpes zoster (unusual in immunocompetent adults), hence the requirement for herpes zoster immunity check anticipated above.

All of these adverse events are manageable in routine neurological practice but it is likely the macular oedema issue will mandate an ophthalmology check after about 4 months treatment, which is an additional consultation. If the extension studies show any later development of macular oedema the number of checks will increase. Please also note comments above about additional monitoring, eg pulse, blood pressure etc.

Any additional sources of evidence

Can you provide information about any relevant evidence that might not be found by a technology-focused systematic review of the available trial evidence? This could be information on recent and informal unpublished evidence, or information from registries and other nationally coordinated clinical audits. Any such information must include sufficient detail to allow a judgement to be made as to the quality of the evidence and to allow potential sources of bias to be determined.

Two relevant posters have been presented at international meetings, both have Novartis involvement as they required post hoc analysis of phase 3 trial data. These analyses were not all pre-specified. The study group, of which I am a member, could not anticipate the interest in specific subgroups on the part of the regulator.

1) The benefits of fingolimod (FTY720) in patients with active multiple sclerosis despite previous treatment: phase 3 results from TRANSFORMS and the TRANSFORMS extension.
J Cohen, G Francis, B Li, B Eckert

American Academy of Neurology 63rd Annual Meeting, Honolulu, Hawaii, 9–16 April 2011

2) Clinical outcomes in subgroups of patients treated with fingolimod (FTY720) or placebo: 24-month results from FREEDOMS
P von Rosenstiel, R Hohlfeld, P Calabresi, P O'Connor, C Polman, EW Radue, L Zhang-Auberson, C Agoropoulou, DA Häring, L Kappos on behalf of the FREEDOMS Study Group
26th Congress of the European Committee for Treatment and Research in Multiple Sclerosis, Gothenburg, Sweden, 13–16 October 2010

These data are in the public domain and I can provide copies of the PDFs, alternatively I am sure these are available from Novartis.

Implementation issues

The NHS is required by the Department of Health and the Welsh Assembly Government to provide funding and resources for medicines and treatments that have been recommended by NICE technology appraisal guidance. This provision has to be made within 3 months from the date of publication of the guidance.

If the technology is unlikely to be available in sufficient quantity, or the staff and facilities to fulfil the general nature of the guidance cannot be put in place within 3 months, NICE may advise the Department of Health and the Welsh Assembly Government to vary this direction.

Please note that NICE cannot suggest such a variation on the basis of budgetary constraints alone.

How would possible NICE guidance on this technology affect the delivery of care for patients with this condition? Would NHS staff need extra education and training? Would any additional resources be required (for example, facilities or equipment)?

The EMA approval terms could involve several potential changes in the delivery of care for MS patients, not all of which are clinically justifiable other than to meet these criteria:-

- It is not routine practice to repeat the MR brain scan for every patient who has an MS relapse whilst taking an interferon.

- Furthermore, part of the approval concerns Gad-enhancing lesions, Gad-enhancement fades within weeks of a relapse. Thus, those patients who are under the care of an MS centre which does not offer a MS relapse clinic (possibly the majority in the UK) are disadvantaged in being able to achieve this criterion. Commencing MS relapse clinics to provide quick access for every patient would necessitate a huge increase in workload of MS neurologists nationally. Such clinics would have to be offered to patients treated with other disease modifiers, even though under the approval they cannot access fingolimod, as a two tier service for relapsing MS patients is not justifiable.

- Doing MR brain scans in all patients who relapsed on interferon who might wish to be considered for fingolimod would increase the number of MR brain scans done, these would likely require reporting by a neuroradiologist and/or MS specialist neurologist as the criteria are very specific about number of T2 lesions and Gad-enhancement.

- Furthermore, since the approval criteria specify comparison “to a previous recent MRI”, patients who are well on beta interferon may logically request regular non-clinically indicated MR scans so they can ensure that there is always a previous recent MR available for comparison purposes.

- Finally, because of the time sensitivity of Gad-enhancement, scans done after relapse would have to be done quickly; for example, a patient commencing a relapse on 1 July, reporting it after a week, then seen within 5 working days, who then went on to have an MR brain scan, would need that scan to be done within 10 working days.

- These MRs would be a change in practice not reflecting new evidence or clinical opinion about quality care, but simply to allow EMA criteria for fingolimod to be considered. There is therefore a risk - which should be avoided - that MR scans with no clinical justification for speed would supplant scans needed by patients for whom there was a true clinical reason to do an MR quickly.