NATIONAL INSTITUTE FOR HEALTH AND CLINICAL EXCELLENCE

Natalizumab for the treatment of adults with highly active relapsing–remitting multiple sclerosis

Response to consultee, commentator and public comments that relate to the Appraisal Consultation Document (ACD)

Comments received from:
Association of British Neurologists
Biogen Idec
Patient representative 1
Department of Health, Social Services and Public Safety for Northern Ireland
Patient representative 2
Merck Serono
Multiple Sclerosis Group, Institute of Clinical Neurosciences, University of Bristol
Multiple Sclerosis Trust
Oldham Primary Care Trust
Royal College of Nursing
Royal College of Physicians

Statements of no comment received from:
Department of Health

Consultee or Commentator	Issue	Comment	Response
Association of British Neurologists	General	I am writing to you in relation to the above Appraisal Consultation Document on behalf of the Association of British Neurologists. The view expressed in this response has been seen and endorsed by members of the Association's MS guidelines panel, listed at the end of this letter (with their conflicts of interest). The panel includes David Miller, a clinical expert for this appraisal	The Committee has revised its recommendations for the RES group. Natalizumab is now recommended as a treatment option for people with RES MS.

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	The comparator used to determine cost effectiveness in the RES group	It is our view that natalizumab is an important new treatment that should be available to the RES group of people with MS as defined in the EMEA license, i.e. people with relapsing remitting MS who have had two disabling relapses in the last 12 months and an active brain MRI scan with one or more gadolinium enhancing lesions or a significant increase in T2 lesion load. People with RES MS have a poor prognosis because of their highly active disease, and for them the provision of natalizumab is acceptable and appropriate when considering the balance of clinical benefits and risks of this therapy. While we are pleased that the Appraisal Consultation Document confirms our view that natalizumab is clinically effective in people with RES MS, we are disappointed that it goes on to recommend that natalizumab is not provided to people with RES MS within the NHS because it is considered not to be cost effective. We do not understand the decision made in the Appraisal Consultation Document to use best supportive care as the comparator to determine cost effectiveness in the RES group, given the clinical reality and the expert evidence presented to the committee. This comparator is completely unrealistic as all such patients will be treated with beta interferon (if not more aggressive and unlicensed drugs). People with RES MS have frequent and disabling relapses, an active MRI scan, and a poor prognosis. Treatment with beta interferon is the currently recommended first-line standard of practice for people with RES MS, and it would not be acceptable clinical practice to offer best supportive care only to people with RES MS. The appropriate comparison for evaluating the cost effectiveness of natalizumab in RES MS should therefore be beta interferon.	Following the consultation on the ACD, the Committee agreed that the appropriate comparator for determining the cost effectiveness of natalizumab in the RES group is beta interferon.

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		We ask you to acknowledge best current practice in treating people with RES and use beta interferon (and not best supportive care) as the comparison in analysing cost effectiveness in this group. We do hope that you will then find the cost per QALY acceptable and accordingly recommend natalizumab as a treatment that is provided in the NHS for people with RES MS.	
Biogen Idec	The comparator used to determine cost effectiveness in the RES group	(Executive summary of the comments received by Biogen Idec) Further to the appraisal consultation document (ACD) dated 22 March 2007, we are pleased at the opportunity to clarify the misinterpretation within the ACD. This Executive Summary directly addresses the three headings described within the email from Laura Bridgman. The main body of the document provides evidence to support the statements within the Executive Summary. Do you consider that all of the relevant evidence has been taken into account? No. 1. The ACD has failed to consider a wide body of evidence from multiple sources showing that: a) best supportive care is not a relevant comparator in highly active relapsing remitting multiple sclerosis; b) current disease modifying treatments are the most appropriate comparators as evidenced by: the inclusion of active disease modifying treatments in the final scope (section 0)	Following the consultation on the ACD, the Committee agreed that the appropriate comparator for determining the cost effectiveness of natalizumab in the RES group is beta interferon.

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		the statement from professional/ patient groups and nominated experts in the NICE pre-meeting briefing (section 1.2.2) the MS treatment pathway produced by the ERG (section 1.2.3) current clinical opinion (section 1.2.4.1) current clinical practice (section 1.2.4.2) controlled trial evidence (section 1.2.4.3) 2. The ACD has failed to consider the high unmet need in people with highly active relapsing multiple sclerosis (section 2) Do you consider that the summaries of clinical and cost-effectiveness are reasonable interpretations of the evidence, and the preliminary views of the resource impact and implications to the NHS are appropriate? No.	The Committee has revised its recommendations for the RES group. Natalizumab is now recommended as a treatment option for people with RES MS.
	Clinical effectiveness	1. Clinical Effectiveness We agree with the committee's conclusion that, 'natalizumab is clinically effective in the [rapidly evolving severe relapsing-remitting multiple sclerosis] group'. We believe that insufficient consideration was given to the sub optimal therapy subgroup. The committee failed to recognise the subset of rapidly evolving severe patients who happen to be receiving a disease modifying treatment (i.e. those experiencing 2 or more relapse in the prior year) and therefore a subset of the sub optimal treatment group. (section 3)	The Committee reconsidered the evidence relating to the suboptimal therapy group and agreed that the clinical effectiveness of natalizumab had not been fully established and that the economic case had not been made for this group of patients.
	Cost effectiveness	2. Cost Effectiveness The Committee should recognise the appropriateness of the active comparators in the rapidly evolving severe subgroup (as outlined above). With this conclusion, natalizumab must be considered a cost-effective use of NHS resources for the	Following the consultation on the ACD, the Committee agreed that the appropriate comparator for

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	Resource implications	treatment of the high unmet medical need in this subgroup. 3. NHS Resources & Implications The committee made no specific statement about the resource implications of natalizumab use within either subgroup. If natalizumab was adopted for the treatment of rapidly evolving severe multiple sclerosis the net impact on NHS resources would be negligible compared with an NHS drug budget of £94 billion in 2005 (less than £1 million in year 1 rising to approximately than £5 million in year 5). (see original submission section 7) Do you consider that the provisional recommendations of the appraisal committee are sound and constitute a suitable basis for the preparation of guidance to the NHS? No. The provisional recommendations are based on an unfounded conclusion that is not evidence-based. Having addressed the misinterpretations within the ACD, one must conclude that… There is compelling evidence to support a decision to recommend that all eligible patients that fulfill the rapidly evolving severe relapsing-remitting multiple sclerosis indication, those naïve to treatment and the rapidly evolving severe subset of those receiving a current DMT, should be treated with natalizumab, funded by the NHS.	determining the cost effectiveness of natalizumab in the RES group is beta interferon and agreed that natalizumab should be a treatment option for people with RES MS.
Patient representative 1		As a person with HARRMS I would like to make a number of points which I feel have not been adequately covered or addressed in the above document. Do I consider that all of the relevant evidence has been taken into account?	

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		No, I do not.	
	The experiences of people with MS	The entire document makes no reference to the actual experience of MS sufferers who have received Natalizumab and I believe that this aspect of discussion has been largely ignored. We have simply been treated as statistics. Although I was invited to attend the recent NICE first appraisal (March 6th 2007) and made a considerable effort to appraise myself of the background and discussion areas, when I attended the meeting I was barely spoken to at all. In fact I felt that the entire exercise was a waste of my time. I do hope that the sentiments and experiences of MS patients will be taken into account and that NICE will not simply focus on cost above all other factors. If the latter is your only concern, perhaps you would refrain from 'going through the motions' of involving patient experts in your discussions. On that day you seemed to have forgotten that patient experts are simply that - experts in their particular disease, their treatment and their results and experiences. We are not statistical machines and we are not data driven.	The Appraisal Committee considered evidence on the nature of the condition and the value placed on the benefits of natalizumab by people with multiple sclerosis, those who represent them, and clinical specialists. It also had to be mindful of the need to take account of the effective use of NHS resources.
		I believe that it is ESSENTIAL to evaluate the experiences of patients with MS and to factor this into your deliberations. This will reinforce in your minds the stark contrast in terms of quality of life and cost to the NHS, to life with and without Natalizumab. You cannot put a price nor place greater emphasis on a sustained relapse free period - which is what Natalizumab so effectively gives us. Over a 2 year period a person with HARRMS can expect 2-3 relapses, each relapse lasting weeks or months with no guarantee of a recovery – even slight or partial. THIS is the stark reality for us - there is no guaranteed recovery, the damage has been done and there is no going back. You will appreciate that a decision made to participate in	The Institute recognises the importance of the experiences of patients. It is for this reason that patient organisations are invited to participate in the appraisal and patient representatives are invited to attend the Appraisal Committee meeting to share their experiences.

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		any drugs trial requires considerable courage and now, taking Natalizumab on the current trial is a little like being a member of 'The Last Chance Saloon' - Natalizumab IS our last chance, currently it is our ONLY chance. There is nothing else out there for us. Do I consider that the summaries of clinical and cost effectiveness are reasonable interpretations of the evidence? No, I do not.	Comments noted.
	Cost effectiveness	Whilst I appreciate that the discussion about the cost effectiveness of Natalizumab is very important, I believe - as the document explores and concludes - that it is difficult to make a realistic and accurate comparison of the cost/benefit of Natalizumab versus currently used therapies and that this relies on a great deal of subjective extrapolation. In essence, you are comparing apples with pears - different treatments which have different outcomes and different track records in terms of duration of experience. I believe it is wrong to reject the treatment on the basis that you don't have enough health economic data of the right kind at this point. By doing so you deny patients the opportunity to experience a considerably better quality of life - a treatment that is twice as effective in the reduction of relapses and in delaying the progression of disability than any currently used therapies. I know we are not living in an ideal world where every therapy can be paid for. However, I believe that the benefits of Natalizumab are considerable and that it makes sense both in a health economics and patient wellbeing context to approve the drug. I believe that if you do so - we will be able to conclude - in the fullness of time - that this does indeed make cost effective	The scope of each appraisal defines the comparators as well as the all outcomes necessary to assess all relevant effects for which the technology and the comparators are assessed.

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		as well as humanitarian sense.	
	Emotional costs of MS	There is also the issue of emotional wellbeing and the emotional cost. The financial cost of Natalizumab is freely talked of but you also have to factor in the emotional costs placed upon our husbands, wives, children and parents - plus THEIR financial costs of taking care of us. That's not just the odd day here or there, it is a consistent, relentless and unpredictable cost to them.	Comments noted. The multi-faceted impact of MS was considered by the Appraisal Committee.
		During the first appraisal a great deal of time and discussion was spent discussing the EDSS module but the results and relevance of this do not capture the essence of actually living with a progressive disease It is wrong to place emphasis and make a decision based on a result that is taken once a month during an infusion visit, under pressurised conditions and when the patient is acutely aware of 'being up against it'. Surely the results are more significant when taken on a day in day out basis of patients living their lives - day to day life just as easily provides us with cognitive, physical and mental tests as a planned testing module. The central focus for NICE should now surely be – 'How can we query value for money when Natalizumab represents the best evidence based treatment for MS in almost 30 years'? This is fact and not assumption. Do I consider that the provisional recommendations of the ACD are sound? No, I do not.	The Appraisal Committee was persuaded that the disutility of relapses may have been underestimated in the economic model submitted by the manufacturer and took this into account when revising its recommendations (see section 4.7 of FAD). The Committee was also aware, however, that relapses were not a significant driver in the model compared with disability progression.

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	The comparator used to determine cost effectiveness in the RES group	To offer 'best supportive care' is not the right comparator, therefore it is not an option. We do not have the luxury of being able to accept a 'hold off' treatment package. We cannot accept just 'holding off' until (in your opinion) a more cost effective drug is found. This will take time and that is one thing you don't have when living with a progressive disease. MS is for life. Why should we be given this life sentence of a progressive disease to endure, when there is a remedy to ease that sentence? I, and many others, stand to benefit so much from Natalizumab and we should not be let down. It is self evident that we DO benefit from Natalizumab therefore we should be allowed access to it. There is no such thing as a risk free drug and all medication nowadays comes with a health warning - but with these health warnings there has to be a sense of proportion, and no more so than with the risk of PML. But I am an educated and well-informed woman, more than capable of making an informed decision for myself and I confidently say that, if allowed Natalizumab, I have so much to gain and nothing to lose from taking it for the rest of my life. MS is a treacherous disease with a host of debilitating symptoms - but one of the worst aspects is not the disease itself but its uncertainty and unpredictability. Therefore the knowledge that Natalizumab may not be available to me is unfathomable based on the clinical and patient evidence seen.	Following the consultation on the ACD, the Committee agreed that the appropriate comparator for determining the cost effectiveness of natalizumab in the RES group is beta interferon and agreed that natalizumab should be a treatment option for people with RES MS.
Department of Health, Social Services and Public Safety for Northern Ireland		I am a consultant neurologist employed in full-time NHS practice. As such, I have a number of patients with multiple sclerosis under my care. I have not received payment in relation to the therapy (natalizumab) under appraisal. Despite the evidence produced by the pharmaceutical industry, and the beliefs of patients who have received this treatment, I am minded to agree with the determinations produced in the	Following the consultation on the ACD the Committee revised its recommendations relating to the RES group.

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	Cost effectiveness Clinical effectiveness Quality of life Disease definitions	Appraisal Consultation Document. In particular, I believe: 1. That there is insufficient evidence of long term gain in the treatment which outweighs its costs. This money could be far more effectively used elsewhere in the diagnosis, and management of multiple sclerosis. 2. That the use of the AFFIRM data, and its subgroup analysis is methodologically imperfect. There appear to be significantly unequal numbers in the treatment vs placebo groups. 3. That further use of the data from the AFFIRM trial showed an almost equal rate of steroid use in the treatment vs placebo groups. Steroid therapy is a useful surrogate marker of severity of relapse, and thus this does not show a convincing benefit for natalizumab. 4. That the discrepancy between the lack of benefit in life quality not being mirrored in both SF-36 and MS Quality of Life measures when comparing natalizumab with placebo cannot be attributed to differing constructs in the instruments used. 5. That there is a real difficulty in determining the defining rapidly evolving multiple sclerosis. This difficulty would seriously impair the just allocation of this expensive treatment. At the present time, I therefore agree that natalizumab cannot be considered a cost-effective treatment for rapidly evolving multiple sclerosis. I would like to add my voice to the calls for more rigorously designed and longer trials of this therapy so that its true worth can be determined.	
Patient representative 2		Thank you for your letter of 22 March 2007. I was very please to note that the committee concluded that Natalizumab was an effective treatment for relapsing remitting multiple sclerosis.	

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		However, I am disappointed with the outcome of the appraisal process and that the committee did not recommend using the treatment within the NHS.	
	Patient experiences of MS	As you may be aware I have made a formal complaint for amongst other things, the general treatment of patient experts and the fact that I did not feel that sufficient time was given for the meeting as the chairman made it clear that due to the late start of the meeting that we would need to speed through it. For your information, I have attached copies of my recent e-mail correspondence in respect of my formal complaint. I do accept that there may be slightly differing agendas between patient experts and NICE in respect to the fact that NICE are more likely to want to remove the emotion from decision where as the patient expert will generally be keen to share some of their personal and emotional experiences of what it is really like to live with this very demanding disease. However, I really feel that the Committee missed a good opportunity to gain a greater understanding of MS and the effects on patients and their families, from the patient experts at the committee meeting. I believe that this would have helped clear up many of the points raised in this letter. In response to your specific points I would say the following: i) I do not consider that all the evidence was taken into account, as outlined in more detail below. ii) I do not consider that the summaries of clinical and cost effectiveness are reasonable particularly when you are comparing Natalizumab with best supportive care which is not appropriate in this situation as in practice disease modifying therapies will generally always be used. I can therefore only	The complaint referred to was investigated and not upheld. The Institute recognises the importance of the experiences of patients. It is for this reason that patient organisations are invited to participate in the appraisal and patient representatives are invited to attend the Appraisal Committee meeting to share their experiences. It is part of the Appraisal Committee's role to consider evidence on the nature of the condition and the value placed on the benefits of natalizumab by people with multiple sclerosis and those who represent them. Following the consultation on the ACD, the Committee agreed that the appropriate comparator for determining the cost effectiveness of natalizumab in

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		conclude that this represents a complete misunderstanding of not only treatments of MS, but the underlying disease and risks involved with not treating patients who have an active disease. iii) There is a risk that a good opportunity to significantly reduce the number of relapses for patients with relapsing-remitting MS could be lost if the recommendations remain in their current draft form. It therefore follows that I do not consider that the provisional recommendations are sound and constitute a suitable basis for guidance for the NHS. For ease of reference I have summarised my concerns with the document in the order that they arise: 1.1 – As mentioned above, I do not agree with your recommendation. 3.3 & 3.4 – I am please that you note that the AFFIRM study demonstrates that Natalizumab significantly reduces the probability of sustained disability progression. Furthermore it is noted that results showed that Natalizumab was associated with significant reductions in relapse rates when compared to other widely used disease modifying therapies. In view of the importance of these conclusions, I think that it merits highlighting these at the very start of document so that it is more obvious to the reader.	the RES group is beta interferon and agreed that natalizumab should be a treatment option for people with RES MS.
	Clinical effectiveness		NICE guidance documents are presented in line with a standard template used for all appraisals.
	Disease labels	3.9 – I am concerned that the committee is making such a distinction between relapsing-remitting MS and highly active relapsing-remitting MS. I think that it is important to note that these are not two different types or diagnoses of the disease, they are merely labels that have been applied to peoples MS. An individual with highly active relapsing remitting MS has relapsing-remitting MS, but unfortunately, as the label suggests,	Comments noted.

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		their MS is particularly active as opposed to an individual that may be experiencing a lower number of relapses in a given period. It therefore follows that if an individual is experiencing a larger number of relapses, i.e. they may be classed as having highly active MS over a particular period when compared to another patient, then it is of greater importance for them to have access to an effective disease modifying therapy such as Natalizumab, as the Committee have, as discussed above, concluded that Natalizumab is effective in reducing the number of relapses.	
	Improvement of EDSS scores	3.11 – I seem to recall that this point was discussed in the meeting, and it was stated that it was possible for patients to actually improve on this treatment. Consequently, I am not sure that the points raised here are entirely relevant.	This has been removed from the FAD.
	The comparator used to determine cost effectiveness in the RES group	4.4 & 4.5 – It is not appropriate to use best supportive care as a comparator for patients as it is simply inconceivable that patients with a very active MS would not take any disease modifying therapies. Patients with active MS are very vulnerable to the damaging effects of this disease and it is therefore incredibly important to a patient's physical and mental health to ensure that they are actively taking steps to manage their disease. Otherwise it very quickly becomes a disease that manages them. I do not therefore agree that this treatment should fail on cost effectiveness as the basis for the greater comparator in simply not an option. 4.6 – As above, I do not agree that best supportive care is an	Following the ACD consultation, the Committee agreed that the correct comparator for determining the cost effectiveness of natalizumab in the RES group is beta interferon.

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		appropriate comparator. If it can be concluded that beta interferon are not as effective for this subgroup of patients, it surely strengthens the case for a need to have access to a drug such as Natalizumab that is effective in reducing relapses. It is not acceptable to simply ignore patients who have a highly active disease.	
		4.7 & 4.8 – For the reasons discussed above, I do not consider that these conclusions are sound. As currently drafted they demonstrate a complete misunderstanding of both the disease and the importance of having an effective therapy to reduce relapses, particularly when the disease is very active.	The recommendations relating to the RES group have been revised.
	Proposed recommendations for further research	6.1 – As discussed above, we are not dealing with patients that have a different disease, it is the same disease that is more active than another individuals disease over a give period of time. I therefore do not understand the need for further clinical research.	The Committee considered that further research is needed for people in the suboptimal therapy group since the clinical effectiveness in this group has not been fully established.
		Furthermore, the committee need to understand that patients who have a very active disease do not have time on their side with which to 'shop' around for treatments, to do so can lead to very damaging and disabling results. It therefore follows that if there is an effective treatment then patients with highly active disease should have the option of that treatment as soon as possible.	Comments noted.
		It is a very risky for patients such as my wife with very active MS to simply try differing range of treatments in the hope that they will manage the level of relapses, as each time a treatment is changed there is a risk that the MS 'rebounds' and causes severe relapses and untold damage, and may also be a risky period where no treatment is given. Therefore if we are looking	Comments noted.

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		to increase the level of a patient's independence and reduce the burden on the NHS it makes far more sense to offer a clinically effective treatment such as Natalizumab to such patients. I also question the ethics of further research on patients with a very active disease as it is incredibly important for them to be on a disease modifying therapy. Other points	Further research is recommended only for the suboptimal therapy group in whom the Appraisal Committee agreed the clinical effectiveness of natalizumab has not been fully established.
	Relapses	I think that it is important for the Committee to understand that a relapse is not a specific event where it can be easily determined when it starts and ends, the lasting effects of a relapse can be very drawn out and very debilitating and consequently the long term costs to the NHS can be extensive. Whilst some of the symptoms may respond to steroid treatment or mend in time, the lasting effects can be very dramatic. It may take many months for the physical and mental health to recover, if in deed a full recovery is achieved.	The Appraisal Committee was persuaded that the disutility of relapses may have been underestimated in the economic model submitted by the manufacturer and took this into account when revising its recommendations (see section 4.7 of FAD). The Committee was also aware, however, that relapses were not a significant driver in the model compared with disability progression.
	Mental burden of MS	Aside from the physical difficulties that this disease brings, the mental burden can be very significant. Therefore the importance of managing the disease and being in a position to try and control it goes well beyond the actual physical need. It therefore follows that it is of even greater importance for patients with	The Appraisal Committee was aware of the multifaceted nature of the condition when making its recommendations.

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		very active disease to have an effective treatment available to them to help reduce the number of relapses.	
	Effects of MS on patients and families	My wife was diagnosed with MS in 1998. For the first six years my wife was largely well, but she experienced a very active stage of her MS when disease modifying therapy was stopped in 2004 as we were planning to start a family. As a result of this, my wife's physical and mental health has deteriorated rapidly, and the effects of MS on our family numerous: • my wife is not able to do many things that a 'normal' mother would be able to do with their child such as holding our son or answering his cries, • currently need full time care, • not able to plan anything as little control of, or concept of what my wife's health will be at any point in time, • base level of health is constantly changing, so therefore not able to try to adapt to disabilities as they are constantly changing, consequently the disease has the ability to trap us. • our modest savings are currently being used to pay for childcare or personal care for my wife, • reduction of cognitive ability and confidence, so we are not always able to make decisions as a family together. • my role as a husband is constantly being eroded and removed to that of primary carer. • I have not been able to work a full week in over a year, which brings both financial and physiological difficulties. In addition to this, as a result of a very aggressive period in her MS, my wife is much more affected by infections as these tend to increase her body temperature and have a major impact has on her MS symptoms. This is a hidden cost of not effectively managing relapses and therefore the progress of the disease,	Comments noted.

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		and as a result of this, my wife has spent approximately three months out of the last five in hospital including a spell in intensive care. This further highlights the importance of the need to reduce the number and severity of relapses. In summary, the Committee have concluded that this treatment is effective in reducing the relapse rates when compared to other widely used disease modifying therapies, and it reduces the probability of sustained disability progression. Consequently, I think that it is important that patients have access to this treatment on the NHS as the risks of severe reductions in both the physical and mental health of the patient and their family are so great, that an effective treatment is vital.	The Appraisal Committee has revised its recommendations for the RES subgroup following the consultation on the ACD.
Merck Serono	Cost of treatment	i) Whether you consider that all of the relevant evidence has been taken into account; a) Paragraph 2.3. Cost of technology considerations Paragraph 2.3 includes cost considerations. Here the drug cost of £14,730 is reported as the cost for the introduction of this technology to the NHS. It is also important to assess other relevant comparative costs which may have an impact on the relevant cost effectiveness of such as: Monitoring of immunogenicity Monitoring of hypersensitivity Infusions Bed occupancy MRI scans Nursing care	Section 2.3 of the ACD/FAD specifies drug costs only. Additional costs were included in the economic model, for example, administration costs, health state costs and costs associated with managing adverse events.
	Use of ITT population	b) Paragraph 3.2: Assessment of the suboptimal therapy patient population group The ITT group from the AFFIRM study may not be a suitable	The Appraisal Committee was aware that the ITT population from the AFFIRM study was used

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	from the AFFIRM study as a proxy for the suboptimal therapy group	proxy for the suboptimal group, as they qualified by the McDonald criteria and therefore earlier/milder patients would not have been treated with beta interferon.	in the manufacturer's submission as a proxy for the suboptimal therapy group and the limitations of this.
	Quality of life measurement	c) Paragraph 3.3: QoL Assessment Presented information suggests improvement in QoL measured by the SF36 instrument but not by the MSQLI instrument. This raises questions as to the validity of; the MSQLI instrument, how the data was collected, or the overall findings. It is rare to find results in which a general QoL questionnaire showed significant findings where these could not be replicated in the disease specific equivalent.	The health state values used in the economic model are based on EQ-5D data collected in the UK MS Survey 2005.
	Modelling considerations and adverse events	d) Paragraph 3.5: Modelling considerations and Adverse events All therapies require management of potential side effects. In the case of interferons, it is mainly limited to liver enzyme monitoring at treatment initiation as well as concomitant medication with paracetamol to manage flu like symptoms, which tend to regress over time. Natalizumab will require close monitoring of patients in order to rule out potential PML. Frequent MRI as well as CSF will be required. This should be included in the model as well as the fact that interferons and glatiramer acetate are self-administrated therapies, whereas natalizumab requires patients to travel to infusion facilities.	The economic model includes an estimate of the costs associated with investigation of patients suspected of PML when on natalizumab treatment, and costs associated with testing for the presence of natalizumab anti-bodies. The economic model also estimates treatment costs for other adverse events – hypersensitivity, urticaria and anaphylactic reaction. Administration costs were also included in the model.
	Improvement	e) Paragraph 3.11: Modelling considerations and	Transition probabilities between

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	in EDSS scores	improvements in EDSS The company pharmacoeconomic model allows for improvements in the EDSS. It is not clear how this was modelled for the beta interferon component in this model.	states were based on the control arms of the AFFIRM study for the RES and SOT (placebo) populations. Therefore all treatment arms had the same underlying progression. The relative risks of the interventions (NAT beta-interferon etc) are applied to the probabilities to model their efficacy, see manufacturer's submission pages 122 to 127 and ERG report pages 52 to 55.
	Clinical effectiveness	f) Clinical data assessed The clinical benefits of natalizumab rely on post hoc analysis and relatively small sample sizes. Proper randomized, prospective studies in both indications (in the appropriate population) remain to be conducted to document natalizumab benefits. ii) whether you consider that the summaries of clinical and cost effectiveness are reasonable interpretations of the evidence and that the preliminary views on the resource impact and implications for the NHS are appropriate;	The Appraisal Committee was aware of the limitations of the evidence base.
	The comparator used to determine cost effectiveness in the RES group	g) Comparator therapy Interferons as well as glatiramer acetate are not indicated for the treatment of the defined RES population of patients and the only treatment that has been approved for a very similar population is mitoxantrone, hence comparison should be made with Standard of Care in England and Wales and with mitoxantrone.	Following the response from consultees on the ACD, the Appraisal Committee was persuaded that beta interferon is the current standard of care for people with RES MS and that it is therefore the most appropriate

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			comparator for determining cost effectiveness in this group of patients.

Multiple Sclerosis Group, Institute of Clinical Neurosciences, University of Bristol		Thank you for sending me the confidential Appraisal Consultation Document regarding Natalizumab for patients with multiple sclerosis. I note the overall negative conclusion, the Committee proposing not to recommend Natalizumab in either of the proposed treatment groups. This of course is a cause for concern, and will attract considerable adverse publicity, not least when the Committee makes it clear that it has "accepted that Natalizumab is clinically effective" for at least one of the proposed therapy groups. I have three comments to offer.	The Appraisal Committee has revised its recommendations for the RES subgroup.
	Confidential data submitted by manufacturer	First, your draft document indicates that the manufacturer has submitted disability data to NICE but has done so stipulating that these data should not be made available to other parties. This is extremely unfortunate. Inevitably one must conclude that the data showed no useful impact on disability progression – but clarification or correction of this would be welcome.	In order to aid its transparency, the Institute liaises with manufacturers to keep confidential information to an absolute minimum. The confidential data on disability progression is from an indirect comparison of natalizumab and beta interferon/glatiramer acetate carried out by the manufacturer and is pending publication.
	The comparator used to determine cost effectiveness in the RES group	Secondly, the conclusion concerning the "RES Group" (rapidly evolving severe disease) I suspect may be based on a flawed premise. In section 4.8, it is said that "the appropriate comparator in current UK practice is best supportive care", and that because Natalizumab is (naturally) far more expensive than "best supportive care", Natalizumab cannot be recommended. This is mistaken. It is my belief that the great majority of neurologists in the United Kingdom would prescribe treatment with either interferon or Copaxone to individuals with rapidly	Following the consultation on the ACD, the Committee agreed that the appropriate comparator for determining the cost effectiveness of natalizumab in the RES group is beta interferon.

	Cost of natalizumab	evolving severe multiple sclerosis; these individuals would not be left on no disease modifying treatments. What is more, the defining characteristics of individuals in the RES group clearly and explicitly fall within the Guidelines for the recommended prescription of interferons or Copaxone in multiple sclerosis issued and still pertinent under the Department of Health Risk Sharing Scheme. In other words the Department of Health would recommend treating the RES group with interferons or Copaxone. Therefore the financial comparator must surely be “treatment with current DMTs”, not “best supportive care”. Finally, this having been said, it is the case that many specialist neurologists have been both surprised and very disappointed by the decision of the manufacturer to place such high costs on Natalizumab. I wondered if there were any opportunity in this document to make even clearer than is currently the case the fact that a significant reduction in the cost would very substantially alter the equation, so placing more responsibility and onus on the manufacturer rather than NICE itself. I suspect, however, that this is beyond your brief.	The Institute has no influence on the costs of drugs.
Multiple Sclerosis Trust	Subgroups	In submitting these comments on the Appraisal Consultation Document we would like them to be taken in the context of our original submission in which we outlined the clinical relevance of natalizumab to people with multiple sclerosis and especially those with highly active relapsing remitting multiple sclerosis. We are unhappy with the current recommendation by NICE and will try to list our concerns under the headings provided in your letter of March 22nd. However, in addition we wish to make a couple of general points, which are fundamental to the assessment process. 1. Sub-groups of Multiple Sclerosis are a convenience for	Comments noted.

		clinical trials rather than a categorisation of separate diseases. MS was first described in 1868 and there are many aspects of the condition that remain a mystery. The sub-division of the condition into various labelled types is a recent phenomenon and reflects the need for categorisation required in clinical trials and clinical pathways, rather than the experience of someone living with the condition. In the assessment of natalizumab there is a suggestion in the Appraisal Consultation Document that highly active relapsing-remitting disease is a different disease – the MS Trust refutes this contention. People who have many relapses at the outset of their condition are simply progressing at a different rate, and their prognosis of disability is greater than that for individuals who have fewer relapses at the outset. These individuals are the most likely to benefit from aggressive treatment, and they are also the individuals for whom the risk benefit ratio is tipped by the very aggressive nature of their disease. 2. The situation with natalizumab is complicated by the fact that the original clinical trials were set up to study the drug in the full spectrum of relapsing remitting MS. The results as recognised by NICE were exceptional in comparison with the results seen with the current agents - a reduction in the annualised relapse rate of 68% and a reduction in disability progression of 54%. However, in the trial where combination therapy was given (natalizumab plus beta-interferon) a risk of PML emerged. Safety analyses have been undertaken but at present we do not know whether it was the combination of the two drugs that proved dangerous or whether natalizumab alone leads to an increased risk of PML. It was for this reason, not unreasonably, that the regulatory authorities have erred on the side of caution and limited the licence indication to those people who are most at risk from their MS. NICE should not now try to over-interpret the original studies drawing conclusions from data which were intended for a very different purpose at the outset.	Comments noted.

		The MS Trust asks that NICE accept that for a small group of people with MS, who have many relapses and thus a higher risk of disability, they should be given the option of being treated with the most effective licensed drug available - natalizumab. Does the MS Trust consider that all the relevant evidence been taken into account? The MS Trust does not consider that all the relevant evidence has been taken into account and would ask NICE to consider the following points:	The Appraisal Committee revised its recommendations for the RES subgroup.
	The multi-faceted impact of MS on individuals and their families	As with previous assessments of MS agents NICE has only given credence to EDSS data. Whilst the MS Trust accepts that this measure remains the mainstay of clinical trials it does not capture the multi-faceted impact of MS on the individual and their family, and it is therefore wrong to use only this assessment. NICE in clinical guideline number 8 “MS management in primary and secondary care” recognised the following impact of the condition: • weakness and cardio-respiratory impairment • fatigue (acute and chronic) • bladder problems • bowel problems • spasticity, spasms and contractures • ataxia (unsteadiness) and tremor • sensory loss • pain(including neuropathic pain) • visual loss • cognitive losses • emotionalism • depression and suicide • anxiety	The Appraisal Committee took into account evidence from a number of sources including the evidence submitted from patient organisations and patient representatives highlighting the multi-faceted nature of the MS.

		• speech difficulties • swallowing difficulties • sexual dysfunction • and pressure ulcers In a specific attempt to inform the Appraisal Committee about the full impact of MS and the positive effect of Tysabri, the MS Trust was represented at the Appraisal Committee meeting by two people with first hand knowledge. We hoped that they would be able to explain some of the effects of MS listed above, and the positive impact of natalizumab – they were not given any such opportunity. In particular they were not given time to express their views on the psychological impacts of MS, or the full impact on the life of carers. We ask NICE to remember that: • MS is probably the commonest single cause of cognitive loss in adults under 65 years • At least 50% of people with MS will be treated for depression at some stage • 30% of people with MS have lost their job within 2 years of diagnosis • Rates of suicide are 7 x 8 times higher than in age-matched controls • Rates of family break up and divorce are significantly increased It is not just that 50% of people with MS will require a walking aid or wheelchair within 10 years of diagnosis MS relapses are undervalued in all scientific evaluations. Relapses are not a defined event. Research has shown that an average relapse will last 55 days, but the range is significant anything from 2 days to 18 months. If several relapses occur in close succession as happens in highly active relapsing remitting MS the psychological and physical impact is devastating. The cumulative impact is greater than the individual relapses. No credence has been given to the risk of MS as a	The Institute recognises the importance of the experiences of patients. It is for this reason that patient organisations are invited to participate in the appraisal and patient representatives are invited to attend the Appraisal Committee meeting to share their experiences. Following the consultation on the ACD, the Appraisal Committee was persuaded that the disutility of relapses may have been underestimated in the economic model submitted by the manufacturer and took this into account when revising its recommendations (see section

		disease. People with MS should be allowed to balance the risk of their disease versus the potential risk of taking natalizumab. NICE has failed to recognise the magnitude of the QALY loss in MS. Research has now clearly shown that as a condition it is responsible for the greatest QALY loss of any condition with the exception of arthritis, which in its aggressive forms can be comparable. At high EDSS scores the relative quality of life score in MS is described as worse than death. Does the MS Trust consider that the summaries of clinical and cost effectiveness are reasonable interpretations of the evidence, and that the preliminary views on the resource impact and implications for the NHS are appropriate? The MS Trust does not consider that the clinical and cost effectiveness evidence has been correctly interpreted. We ask NICE to consider the following points:	4.7 of FAD). The Committee was also aware, however, that relapses were not a significant driver in the model compared with disability progression.
	The comparator used to determine cost effectiveness in the RES group	The Committee's conclusion that best supportive care (rather than one of the currently available disease-modifying therapies) is the most appropriate comparator in this highly vulnerable group of patients demonstrates a lack of understanding of this specialist disease area. "Best supportive care" essentially means no disease-modifying therapy, and it is inconceivable that patients with the most active multiple sclerosis should receive no disease-modifying therapy at all. Progression of disability in patients with rapidly evolving severe multiple sclerosis is approximately twice as fast as in patients with less active multiple sclerosis. Although these patients may continue to experience clinically apparent disease activity, such as relapses, whilst on currently licensed disease-modifying therapies, this does not mean that these therapies are having no clinical benefit at all. To deny effective treatment to patients with the most active disease flies in the face of	Following the consultation on the ACD, the Committee agreed that the appropriate comparator for determining the cost effectiveness of natalizumab in the RES group is beta interferon.

		current clinical practice.	
	MS Survey	The cost effectiveness data presented by Biogen Idec is an attempt to present an accurate model for the condition. NICE appears to challenge the population of people with MS used to collect the quality of life data as it may be biased. Clearly as the organisation that was involved in recruiting the people with MS, we would dispute this statement. The MS Trust is a non membership organisation and thus people who receive our newsletter, the vehicle for distributing the questionnaire, are there because they want to receive information about MS. We have now worked with this database on a number of projects and there is nothing to suggest that it in any way differs demographically from the overall population of people with MS. As NICE will recall the MS Trust submitted quality of life data for the original NICE assessment of the beta-interferons and the results we showed then have since been replicated in other studies both in the UK and Europe. The use of a similar database for the natalizumab work therefore seemed sensible. [One specific criticism was the response rate of 16% but it must be recognised that on the MS Trust database are families and friends of people with MS and a response rate of people with MS cannot be specifically calculated].	Although the Evidence Review Group highlighted the limitations of the data from the MS survey, it also recognised that the approach adopted by the manufacturer in its economic modelling was pragmatic given the absence of better quality data and this was taken into account by the Appraisal Committee.
	Modeling of MS	Modelling of MS as a condition remains fraught with difficulty and we hope that NICE will accept that at present it is still impossible to accurately model a complex and variable condition that can run over a 40 – 50 year time frame. The natalizumab model seems to capture some improvements over earlier models, (for example people with MS can improve at stages), but it is still impossible to be certain about the reliability of any of these models. NICE should therefore accept that any cost per QALY figure generated will have a level of inaccuracy and this should be taken into account when looking at finite thresholds.	Comments noted – see above. The Appraisal Committee took into account the uncertainty surrounding the calculation of the costs per QALY (see sections 4.7 and 4.8 of the FAD).

		NICE has accepted in the Appraisal Consultation Document that in the rapidly relapsing remitting group natalizumab is clinically effective. Taking on board the points above the cost effectiveness ratio is £32,000, which is within the threshold set for the current disease modifying drug therapies and at a level used in many other NICE assessments. Does the MS Trust consider that the provisional recommendations of the Appraisal are sound and constitute a sensible basis for the preparation of guidance to the NHS?	Following the consultation on the ACD, the Appraisal Committee was persuaded that natalizumab should be recommended for people with RES MS. In making this recommendation, the Committee acknowledged the uncertainty surrounding the calculation of the costs per QALY and the high degree of clinical need among people in the RES group.
	The comparator used to determine cost effectiveness in the RES group	The MS Trust does not consider that the recommendations as stated are sound. We would in particular ask NICE to reconsider their assessment on the basis that they have used the wrong comparator and this completely undermines the recommendation. People with highly active relapsing remitting MS would receive one of the current disease modifying drug therapies and to use “best supportive care” as the comparator is not an accurate reflection of good and current clinical practice. The Appraisal Consultation Document cites NICE clinical guideline 8 Multiple Sclerosis: management of multiple sclerosis in primary and secondary care issued in 2003. Research undertaken by the Royal College of Physicians in conjunction with the MS Trust shows that little progress has been made with implementation in the NHS2. People with MS still need better services including access to appropriate drug therapy. The MS Trust calls upon NICE to review its current Appraisal Consultation Document to reflect the reality of multiple sclerosis, and the availability of natalizumab which is now licensed and which could make a real difference to people living with the highly active form of the condition.	Following the consultation on the ACD, the Committee agreed that the appropriate comparator for determining the cost effectiveness of natalizumab in the RES group is beta interferon.

Oldham Primary care Trust	General	I reply on behalf of Oldham PCT. I am a general practitioner and work as an associate director for the PCT. I have responsibilities for medicine management. Natalizumab would appear to be an important new but expensive treatment for a small number of people with multiple sclerosis who have severe problems and no effective alternative therapies. The possibility of a treatment that might reduce the progression of disability would be attractive to both patients, clinicians and the PCT as commissionaires of MS services. The PCT is committed to improving services for its population, including those with multiple sclerosis. In commissioning services the PCT needs to take into account many factors in addition to the medical therapy. This would include housing and supportive services such as nursing, occupational, physiotherapy. The PCT would be concerned that the impact of any new therapy or technology should not have an adverse effect on existing services, not just services for people with MS. I welcome the advice from NICE in helping the PCT to make evidence based decisions about commissioning services. I have been asked to make comments on the following general headings Relevant evidence All relevant evidence appears to have been taken into account Summaries of clinical and cost effectiveness They appear to be reasonable interpretations of the evidence Provisional recommendations These appear to be sound given the evidence presented	Comments noted.

		I would however like more clarity Section 1 “Appraisal Committee’s recommendations” 1.1 No problems 1.2 I think PCTs and clinicians would like more specific recommendations about the appropriateness to continue therapy, in particular patients who are currently on a research programme of if any PCTs who may have funded under the exceptional use of resources rules. 1.3 You should consider including the recommendation that Natalizumab is not recommended for the suboptimal therapy group (4.7) in this section	This recommendation no longer applies – the Appraisal Committee revised its recommendations. Comment noted.
	The comparator used to determine cost effectiveness in the RES group	I also note in 4.8 that the best comparator in current UK practice is best supportive care. Would it be possible to expand on this in the final recommendations? 7.1 refer’s to the appraisal guidance and clinical guidelines. It is likely that a number of people will be disappointed with the result and a recommendation that commissioning better supportive services might at this stage be appropriate.	Following the consultation on the ACD, the Committee agreed that the appropriate comparator for determining the cost effectiveness of natalizumab in the RES group is beta interferon.
Royal College of Nursing		The preliminary recommendation from the NICE Appraisal Committee not to use Natalizumab in the treatment of patients with rapidly evolving severe multiple sclerosis is disappointing and shocking from MS Specialist Nurses’ point of view.	Comments noted.
	The comparator used to determine cost effectiveness in the RES group	We disagree with the assertion that best supportive care (BSC) is the most appropriate comparator for Tysabri in the RES group. This essentially means that treatment would be denied to those patients with aggressive active disease. This patient group has aggressive relapsing-remitting disease, experiencing highly active disease with frequent disabling relapses and rapidly accumulating severe disability. This will ultimately have an impact on the quality of life of the patient and their family and	Following the consultation on the ACD, the Committee agreed that the appropriate comparator for determining the cost effectiveness of natalizumab in the RES group is beta interferon.

		will place enormous burden on hospital and community resources with regards to health and social care services. Whilst interferon and glatiramer acetate are not generally effective in this patient group and therefore, are not used long term, this does not mean that the treatment of choice is BSC - far from it. BSC is an option only when all other therapy options have been exhausted; this is because offering best supportive care to an individual with rapidly evolving severe MS condemns them to rapid deterioration of their condition. In practice what happens in many centres is that mitoxantrone is offered to patients in the RES group - either as first line or if high dose interferon beta is not effective. Treatment may vary, for instance, in one practice, 15% of patients started on DMDs in the last 12 months were prescribed Mitoxantrone - however this is a toxic drug with limited time frame due to maximum dosing and potentially severe side effects including death from leukaemia and cardio toxicity - clinicians would much prefer to have the option of prescribing Tysabri which is a safer, condition specific and a potentially longer term medication.	
	Clinical effectiveness The comparator used to determine cost effectiveness in the RES group	We are pleased that NICE accepts the clinical effectiveness of Tysabri and have noted the impact on improvement of EDSS score in patients prescribed Tysabri which is unprecedented as a treatment effect in MS. We would however stress that using best supportive care as a comparator does not accurately represent clinical practice - whilst there is no licensed indication for RES MS patients at the moment, this does not mean that doing nothing is the preferred option - as clinicians we will prescribe high dose interferon beta (Betaferon or Rebif 44 at a cost of up to GBP12,000 pa) for as long as this is tolerated or having any measurable effect. Alternatively mitoxantrone will be	

		used in many centres though with reluctance given the risk/benefits ratio of mitoxantrone. Despite the risks, clinicians use this believing it to be a preferable option to BSC. It is imperative that NICE reconsider their assumptions around the use of BSC as a comparator to determine cost effectiveness. Conclusion We would urge NICE to review the Appraisal Consultation Document on the use of natalizumab in rapidly evolving Multiple Sclerosis and reconsider the recommendations on clinical and ethical grounds. The decision that best supportive care is the most appropriate comparator for patients with rapidly evolving severe multiple sclerosis is flawed. This should be reconsidered in the light of the impact this decision will have on the management and treatment of people with MS, who desperately deserve to be treated and to have an improved quality of life.	The recommendations for the RES subgroup have been revised.
Royal College of Physicians	General	Please accept this e-mail as an endorsement from the Royal College of Physicians relevant to the attached ABN submission for this technology.	Comments noted.

Website and public responses:

Comment From	**Comment**	**Response**
Specialist Consultant Neurologists	On behalf of a group of consultant neurologists in the UK who specialise in the treatment of multiple sclerosis I submit the attached letter to NICE. We sincerely hope that our opinion will be taken into account when the committee reviews the responses to the NICE Appraisal Consultation Document The preliminary recommendation from the NICE Appraisal Committee that natalizumab should not be used for the treatment of patients with rapidly	Comments noted.

Comment From	Comment	Response
	evolving severe multiple sclerosis has surprised neurologists treating patients with multiple sclerosis in the United Kingdom. The Committee's conclusion that best supportive care (rather than one of the currently available disease-modifying therapies) is the most appropriate comparator in this highly vulnerable group of patients demonstrates a lack of understanding of this specialist disease area. "Best supportive care" essentially means no disease-modifying therapy, and it seems inconceivable that patients with the most active multiple sclerosis should receive no disease-modifying therapy at all, particularly when the treatment in question has already received widespread publicity. Progression of disability in patients with rapidly evolving severe multiple sclerosis is approximately twice as fast as in patients with less active multiple sclerosis. Although these patients may continue to experience clinically apparent disease activity, such as relapses, whilst on currently licensed disease-modifying therapies, this does not mean that these therapies are having no clinical benefit at all. To deny effective treatment to patients with the most active disease flies in the face of current clinical practice. Natalizumab is a newly licensed therapy for patients with rapidly evolving severe multiple sclerosis. It was studied in a large phase III study (AFFIRM Study) that recruited nearly 1000 patients and followed them up for a period of two years. The results showed that natalizumab was at least twice as effective as the currently available disease-modifying therapies [1]. As a result, natalizumab therapy has now been adopted as a treatment for patients with rapidly evolving severe multiple sclerosis in many European countries and in North America. The superior efficacy of natalizumab over currently licensed therapies is acknowledged within the Appraisal Consultation Document (section 4.3): "The Committee also heard the views of the clinical and patient experts that natalizumab has a clinically important effect on disability progression in people with highly active forms of multiple sclerosis, relative to placebo, that has not	Following the consultation on the ACD, the Committee agreed that the appropriate comparator for determining the cost effectiveness of natalizumab in the RES group is beta interferon. Following the consultation on the ACD, the Appraisal Committee was persuaded that natalizumab should be recommended for use in the NHS for people with RES MS. Comments noted.

Comment From	Comment	Response
	been seen with other disease modifying therapies used to treat the condition. The Committee agreed that natalizumab is clinically effective in the rapidly evolving severe group, compared with placebo." It is clear that natalizumab, despite being acknowledged as an effective treatment for patients with rapidly evolving severe multiple sclerosis, has been rejected purely on the basis of an economic evaluation based on a flawed comparison, with “best supportive care”. The fair and clinically correct comparison is with the four licensed disease-modifying therapies, which are currently being used for treating these patients. This comparison may lead to a different conclusion regarding the cost-effectiveness of natalizumab at the thresholds used for reimbursement of the other licensed disease-modifying therapies available under the Department of Health’s risk-sharing scheme. If the recommendation contained in the Appraisal Consultation Document (ACD) concerning natalizumab was to be confirmed by NICE, treatment of MS in the UK would be below international standards of care. This would also have knock-on effects: it would become increasingly difficult for British researchers to take part in future multiple sclerosis clinical trials and it would further erode the UK’s position as a country with a track record in innovative pharmaceutical research. It would be particularly ironic if British patients were unable to benefit from this treatment, given that the early phase clinical research on natalizumab was conducted in the UK and that UK centres recruited a significant number of patients into the pivotal AFFIRM study. We therefore urge NICE to revise its current ACD on the use of natalizumab in patients with multiple sclerosis. They must reverse, on both clinical and ethical grounds, the decision to use “best supportive care” as the most appropriate comparator for patients with rapidly evolving severe multiple sclerosis. We would appreciate it if you could intervene in this matter on behalf of all UK neurologists treating patients with multiple sclerosis, and on behalf of our patients and their families.	Following the consultation on the ACD, the Committee agreed that the appropriate comparator for determining the cost effectiveness of natalizumab in the RES group is beta interferon and that natalizumab should be recommended for this group. Comments noted – please note the responses above and the changes to the recommendations for the RES subgroup.

Comment From	Comment	Response
Patient	As someone with active relapsing remitting MS, aged 24, I am appalled to hear of the announcement from NICE that Tysabri will not be available for those patients who most need it. The hope was there for many of us that the UK would follow in the foot steps of other, more forward thinking countries. This is a terrible day for the NHS, unfortunately it follows in the foot steps of seemingly endless poor decisions on treatments for those with Multiple Sclerosis. When will this change? I urge you to reconsider this decision immediately.	Following the consultation on the ACD, the recommendations for the RES subgroup have been revised.

Family of patient	1.1 An unusual recommendation, given the exact opposite conclusion has been reached by EU (inc UK) and US licensing decisions. 1.2 Clearly safety and efficacy cannot be a concern if you are allowing (rightly) those already on the drug to continue taking it. 2.2 This risk has not been illustrated as a monotherapy - no cases of PML on the trial in people using natalizumab as monotherapy. One would hope, then, that this has not been given undue attention in the deliberations of NICE. It is almost a "side issue" and would be of importance primarily for an appraisal of combination therapy. 2.3 the case for similar monitoring could be argued with currently available disease modifying drugs - indeed, it happens with some. 3.11 I would be interested to know if EDSS ratings have been retrospectively discounted from previous NICE appraisals. Whilst I accept that this would not affect the validity of the scale in this case, it would go some small way in restoring confidence in the appraisal process. In fact, given the widespread use of the EDSS (and other potentially flawed scales), should the funding for NICE instead be diverted temporarily to the design and promotion of more acceptable scales? When these have been sorted, accurate and worthwhile NICE appraisals could begin again. Another simple solution to save wasting more of my taxes would be to inform drug companies, in advance, which scales are deemed useful and which are not.	This recommendation has been revised following the consultation on the ACD. When a technology is judged not be cost effective, the Institute recommends that people currently receiving the technology should have the option to continue therapy until they and their clinicians consider it appropriate to stop. Section 2 documents background information relating to natalizumab. It does not relate to the Appraisal Committee's considerations of the evidence, which is outlined in section 4 of the ACD/FAD. Section 3 provides information relating to the manufacturer's submission and evidence from the Evidence Review Group that reviewed the manufacturer's submission. The Evidence Review Group commented on the limitations of the EDSS instrument. This does not mean that the EDSS ratings have been discounted. Information in Section 3 of the ACD/FAD does not relate to the Appraisal Committee's considerations of the evidence,

	3.12 How can one comment adequately on the manufacturer's submission in the absence of the evidence? This short consultation suddenly (at point 3.12) appears to be a sham: "Please comment on what we choose to tell you about the submission." I"d appreciate a response to this point - why only available after full guidance?	which is outlined in section 4 of the ACD/FAD. In the 'Guide to the single technology appraisal (STA) process' section 5.12 states '…The ACD [appraisal consultation document] (with an electronic comment facility) and the committee papers (with confidential material removed) are posted on the Institute's website 5 working days after they have been circulated to consultees and commentators.' See link: http://www.nice.org.uk/page.aspx?o=STAprocess For this appraisal the committee papers (comprising of the submissions received, the report from the evidence review group and various other documents) were published alongside the ACD as the 'evaluation report'. We note the misleading wording in the ACD stating that these documents become available only when the final guidance is issued and we thank you for bringing this error to our attention. The Institute will correct this error as soon as possible to ensure that the problem does not occur again.

	4.3 This is an example of inappropriate language being used by NICE in what is supposed to be a public consultation. why say "post hoc" if you expect non-medic/ research/ classically educated people to respond. It appears unthoughtful. Again, I would appreciate a response to this overriding point - which applies, I suspect to NICE consultations in general. 6.1 Surely, here should be a call for research into the use of clinical scales and ratings, as without these, all data submitted are discounted. 8.2 whether recommendation is a "yes" or a "no" , this is not nearly long enough - see my repeated points (above) about clarifying acceptable data before trials are re-run or submitted (if the decision proves to be a "no"). Equally, if a "yes", what possible long-term data could be considered in under three years? Suggests that a "no" has been reached already. Leading to more lost confidence in this consultation with the public...	Although every effort is made to make the document accessible to all and use plain English wherever possible, the ACD is a technical document and includes many technical terms that may be difficult to explain or simplify within the space available. Comment noted. The date for the review of the guidance refers to when the Institute will judge whether the guidance it has issued needs updating.
Patient	Tysabri will slow if not halt the progression of MS, thereby minimizing - dramatically, in some cases - destruction of the quality of life of MS patients. Overall net costs of MS care to the NHS, i.e. the taxpayers, will decrease with the early and continuing administration of Tysabri to MS patients who would otherwise ultimately manifest costly disabilities and fall off the tax payer rolls. Penny wise and pound foolish is a cruel and futile strategy which will allow otherwise avoidable permanent injury to savage many thousands of Britons and wreak ancillary damage upon the families and caregivers of MS sufferers deprived, irrationally so, of a best-as-yet, life changing therapy. Thank you. Biogen-Idec, co-partner with Elan in the manufacturing and marketing of Tysabri, has a vested interest in continuing to push its wholly-owned and much less effective and side effect ridden MS drug, Avonex, upon an unsuspecting public and complicit governing bodies. Manufacturers of similarly ineffective but less costly (in the very short run) MS drugs, most notoriously Teva, continue the fiction that their ""solutions"" are a better value for taxpayers while working to deprive MS sufferers of a demonstrably superior therapy. Anyone qualified to sit on a governing or advisory panel is fully aware of the long term sensibility of	Comments noted.

	providing Tysabri to MS patients; persons arguing against such dispensation can at very best be described as disingenuous and, in candor typically unknown in political discourse, are suspect of serious ethical misconduct in this author"s opinion. Immediate approval of NHS funding of Tysabri foregone, a review date any later than October 1, 2007 can only be described as malicious.	
Member of public	To anyone connected with NICE concerning the position on Tysabri therapy. First let me state I am an investor and have a monetary gain with Elan stock to promote. But now that you see the truth in me you should also consider the truth of the science. I have invested time in my investment to learn that the Tysabri works. You are making a decision for thousands of sufferers with MS. Why? Do I have better sources, do I have more time than a NICE committee member or is it that money guided my learning of Tysabri. Whichever the case you bear the responsibility for that I share no envy. Please help those in need to the best of your abilities. At first with this investment I was only concerned with me now Isee the many who have benefited from the medicine. Take a second look please. 1.2 seems appropriate. But was pulled from market to prove safety in mono. Over 6,000 infusions to date not one case PML and 6 months since relaunch of injections. Section 2: Cost should be considered in relation to 60% efficacy Section 4: Higher cost vs higher quality of life. Section 5: The wheels are turning just to slow for most MS sufferers Section 6: 2 years away to redecide? Section 7: These therapies fail over time most dont have that luxury Section 8: To far away to help some by then could help more that are not in the severe cat.	Comments noted.

Member of public	Tysabri clinical data show that it is far more effective than interferons or glatiramer acetate. It is also safer - see NEJM articles and package inserts. Twice as many people died in the placebo group as in the drug groups during trials, despite the fact that there were twice as many drug patients as placebo patients. A single statistic tells the story: the annualize relapse rate for Gd-Enhanced lesions is as folows: Tysabri = 0.1 lesions per year Avonex= 1.0 lesions per year Placebo= 1.4 lesions per year This data comes straight from the package inserts. Instead of being more expensive, Tysabri is more cost effective for the UK: it costs 30% more that INFb treatments (including infusion costs) but nearly half of patients regain the ability to walk or see or some other lost function, most see an noticable improvement in cognition, and there is a much lower relapse rate and rate of emergency steroid treatment regimen. This adds up to patients being more productive, costing less, and often coming off the dole and returning to society as tax-paying citizens. Please approve Tysabri for the benefit of the UK and UK MS patients. MS patients have an overabundance T cells and disproporationately more VLA-4 mediated T cells. Tysabri works to inactivate VLA-4 mediated T cells - 50% of them - to keep these rogue cells from attacking a patient"s own neurons. In an MS patient with an otherwise uncompromised immune system, this works to tamp down his/her overactive immune system to normal levels and permits the patient"s body to repair itself and fend off further attack. The clinical data demonstrating efficacy unequivocally puts Tysabri at the head of the class of MS treatments. The mAb is targeted specifically at the VLA-4 receptor while non-specific proteins and small molecules like INFb and glatiramer acetate mechanisms of actions are by no means well-understood (nor is there much clinical evidence that they make much difference.) I have to ask why it will cost 45,000 pounds to treat MS patients with Tysabri. In the US, Medicare and Medicaid and the Veterans Administration pay the wholesale cost of the drug plus $150 per infusion. In US dollars, the cost to the US government is US$30,000 per year with additional cost of $2,000 for annual MRI. Why will NICE expect to pay the equivalent of US$90,000 for the same treatment? Not to manage the non-pharmaceutical portion of the cost of drug administration is irresponsible.	Comments noted.

	To pay UK 35,000 for INFb treatment and have accepted on average 1.0 new Gd-Enhanced lesions per year while denying Tysabri for UK45,000 for 0.1 new lesions per year seems inconsistent. The difference between 1.4 lesions annually (Placebo) and 1.0 lesions (Avonex) annually is worth UK35000 but the difference between 1.4 lesions annually and 0.1 annually (Tysabri) is not? I respectfully submit that instead of punishing MS patients by denying them an effective treatment, why don"t you deny them the ineffective treatments (from manufacturers who were originally given approval conditional on their providing far more comprehensive and long term data which they have never done?) It is clear that NICE is considering only cost and not cost/benefit. Please reconsider and give MS patients a real chance at productive lives. This is an investment that will pay for NICE and the UK. Good idea. INFb and glatiramer acetate are grossly inadequate treatments. Copaxone has p values of 0.08 and 0.055 supporting its data analysis - very poor - and INFb manufacturers have studiously avoided making it possible to acertain the value of its treatments. High dropout rates characterize INFb trials... what happens to the dropouts? Answer: their data is dropped along with the patients. Why? Because this self-selective behaviour results in skewed trial results in INFb"s favour. Formerly, without better options, NICE and MSers were desperate for any treatment. Now, Tysabri is here: approve it and make Biogen, Serono, Schering and Teva prove again why their treatments deserve UK funding. Please take as much time as you need to reach the right conclusion.	
Patient	Section 1: I am appalled that the UK would consider accepting this unfair NICE advice going against EU and USA recommendations and is taking this move - which is in fact disabling people with MS Section_2: Individuals should be given the full information, in an accessible format and make their own decision, NICE should not presume to make it for them by not allowing its prescription Section_3: This is still not justifying removing this option from people with MS that may have their life and independence back and reduce social isolation.	Comments noted.

	NICE and the government should be ashamed of themselves Section_4: see above boxes i fully agree with the following and that what NICE the government is doing is absolutely disgusting: ""NICE is pushing this through in a timescale shorter than it declares it allows in its own guidance. We can only speculate as to why they aren't prepared to give the MS community the time it needs. The timing also coincides with Parliamentary recess, so MPs are being refused the opportunity to take part."" Section_5: allowing such a short consultation is underhand Section_7: i fully agree with the following and that what NICE and the government is doing is absolutely disgusting: ""NICE is pushing this through in a timescale shorter than it declares it allows in its own guidance. We can only speculate as to why they aren't prepared to give the MS community the time it needs. The timing also coincides with Parliamentary recess, so MPs are being refused the opportunity to take part."" Section_8: Such an atrocious decision should be reviewed and remedied immediately	
Patient	Section_1: I was diagnosed with relapsing/remitting MS a little over 4 years ago. I dutifully took Avonex (3 months) and then Rebif (3.5 years) even though they gave me nasty flu like side effects that intensified my symptoms for days afterwards. My time on these drugs can best be described as being in a glider with no plunges but the feeling of slowly losing altitude in the continuing self-assessment of my abilities. I switched to Tyabri treatment 3 months ago. It is no overstatement to say that I felt like a different person (in a good way) almost immediately. My fatigue level significantly decreased, my stiffness/spasticity significantly decreased, and my stength/muscle control improved. My Nuerologist even commented that I was walking better when I saw him on my 30 day check-up. From my experience, denying Tysabri to MS patients is akin to saying that you are not allowed to have to the best MS Medication possible and ,based on my experience, you are not allowed to feel better/enjoy life more. If you feel Tysabri is ""uneconomic"" at the price requested by the drug"s manufacturers, maybe the real issue is that the other drugs are overpriced for the benefits they provide.	Comments noted.
Patient	Evidence from MS sufferers who have received Natalizumab in the US to whom I have spoken appears to suggest that the drug is beneficial in reducing relapse rate & disability in sufferers. Given this sort of expert evidence, and the	Comments noted.

	absolutely vile nature of this disease, surely it should be down to expert practising neurologists to decide whether, based on the experiences of their colleagues and patients, Natalizumab should be prescribed to any of their patients, thus potentially enabling them to increase their contribution to society? The nature of MS is such that patients ARE prepared to take extreme risks if there is hope of improving their lot, such hope being available through this drug. Why not allow those who are prepared to take the risk to take the risk, subject only to approval of their neurologist? Section_2: Any comments I could make here would be based on opinion rather than facts. Section_3: Ditto. Section_4: Ditto. Section_5: Ditto. Section_6: EVERYTHING needs further research. (I refer you to BMJ 2003;327:1459-1461 (20 December), doi:10.1136/bmj.327.7429.1459 ""Parachute use to prevent death and major trauma related to gravitational challenge: systematic review of randomised controlled trials"") I feel you have failed to produce proof here as to why further research is needed before approval is given to funding.	
Patient	Section_1: THIS IS A DISGRACEFUL AND NOT FULLY CONSIDERED RECOMMENDATION. THE UK IS NOW THE ONLY MAJOR COUNTRY IN THE WORLD NOT TO ENDORSE THIS TREATMENT FOR SUCH A DEBILITATING DISEASE. Section_2: COST SHOULD NOT BE THE ONLY FACTOR IN DECIDING ON APPROVAL AS VERY FEW PATIENTS WILL USE IT ANYWAY AND THE NHS DOES NOT SEEM TO MIND SPENDING OUT ON UNNECESSARY TREATMENTS SUCH AS FOR INFERTILITY - WHICH IS NOT A DISEASE Section_3: THE EVIDENCE IS CLEAR THAT THIS PRODUCT DOES HELP MS SO THERE SEEMS LITTLE REASON FOR NICE (INEPTLY NAMED I FEEL) TO RULE AGAINST ITS USE - NICE IS TOTALLY WRONG Section_4: USE SHOULD BE APPROVED FOR ALL WHO MAY BENEFIT - PERIOD. Section_5: Section_6: FURTHER RESEARCH IS ALWAYS WELCOME - BUT FOR MANY THIS TREATMENT IS NEEDED NOW - NOT SOME INDETERMINATE TIME	Comments noted.

	IN THE FUTURE Section_7: Section_8: THIS IS FAR TOO LONG AWAY - ANY REVIEW SHOULD BE MUCH SOONER	
Carer	My daughter has relapsing remitting MS. Any drug that has been proven to alleviate symptoms should be approved by NICE. In cold economic terms the government will save money. And look good. Perhaps if taken to The International Court of Human Rights the government will be seen to be in dereliction of its duty. Section_1: I dont agree Section_2: I think the side effects of MS are worse . What could be worse than paralysis or incontinence. Section_3: If Tysabri reduces relapses ,as it patently does, please let it be prescribed freely on the NHS Section_4: You are talking about a small group of people. How effective is the UK"s part in the Iraqi war....How much has that cost us? Section_5: Section_6: If tysabri has been shown to reduce relapses, why do we need more research? Surely that will make it even more expensive. Section_7: By the way, since contracting MS 3 years ago, my daughter has had no drugs/support from the NHS. Section_8: This date is far too far away. With the pain and suffering involved in MS and the economic/emotional havoc this disease causes, this research , if needed should be fast tracked. Why dont you have non clinical ordinary human beings on your committee. Doctors and Medics aren"t necessarily expert in every field of the human psyche.	Comments noted.
Patient	Section_1: This treatment has been approved by both the US and EU. The UK should not deviate from this approval without further evidence. Section_4: Those with the most severe types of relapsing remitting MS deserve not to be let down by NICE. Without effective treatments they will become a financial burden to the NHS and Social Care agencies at a much earlier stage. With effective treatment they could, however, continue to be economically active. This is a small part of the MS population with much to gain from treatment. Section_7: The Risk Sharing Scheme could be extended to include Tysabri.	Comments noted.

Member of public	3.10 The extrapolation to 20-year time horizon is the only reasonable one given the data. No alternatives or error bars have been given. This statement, given without statistical backing, would not pass peer-review. Any study will always be ""short-term"" relative to the consequences. Given the proven effectiveness of the drug, it does not seem likely that a placebo-controlled trial lasting even 10 years would actually be approved from an ethical standpoint, and is therefore a catch-22 situation 3.11 The EDSS score is the only peer-reviewed, clinically-accepted measurement scale. The Committee are not justified in dismissing it without proposing an alternative measure. Furthermore, no alternative measure would be clinically accepted Whilst the EDSS score may have a moderate internal variability, this will be fully captured within the p-values quoted on the statistical evidence. This claim double-counts the statistical variance and should be withdrawn Furthermore, for those patients undergoing repeated relapses, with insufficient time to recover, one would expect a drug that increases the inter-attack time to improve the EDSS score. It certainly does not invalidate the measurement Section_4: 4.5 The Committee seems unconvinced by the long-term economic model. It has not, however, taken into account the long-term consequence of the specific drug becoming cheaper over time. By the time this occurs, significant disability will already have occurred. Therefore, waiting until the marginal (annual) rate-of-return is positive actually increases the overall economic cost to society. 4.6 If 44,600 per QALY is considered not cost-effective, it would seem reasonable to publish a statement of the currently acceptable cost-per-QALY. Other decisions for both medical and social care seem inconsistent and come out with a much higher cost-per-QALY.	The Appraisal Committee agreed that it was appropriate to evaluate costs and benefits over at least a 20-year time horizon – see section 4.7 of the FAD. The Committee has not dismissed the EDSS score. Section 3 of the ACD/FAD provides information on the manufacturer's submission and comments from the Evidence Review Group that reviewed the manufacturer's submission. Section 3 does not reflect the Appraisal Committee's considerations, which are outlined in section 4. Comment noted. Please see Guide to the Methods of Technology Appraisal section 6.2.6.10 (Available from URL http://www.nice.org.uk/page.aspx?o=201974) *"Above a most plausible ICER of £20,000/QALY, judgements about the acceptability of the technology as an effective use of NHS resources are more likely to make*

	4.8 ""Best supportive care"" is a euphemism for not treating. One would suspect that this will always be cheaper than treating. Furthermore, with an aging population, who will provide this ""best supportive care""? When the carers themselves become infirm, where will the costs lie then? This appears not to have been factored in.	*reference to explicit factors including: the degree of uncertainty surrounding the ICERs, the innovative nature of the technology, the particular features of the condition and population receiving the technology, where appropriate, the wider societal costs and benefits. Above an ICER of £30,000/QALY, the case for supporting the technology on these factors has to be increasingly strong."* Following the consultation on the ACD, the Committee was persuaded that the appropriate comparator for determining cost effectiveness in the RES group is beta interferon.
Patient	Section_1: This is appalling. How is an extra few years walking or working evaluated in economic terms? Is the cost of people staying at home longer and the social care required included in the evaluation? I assume that the additional environmental cost of keeping people at home such as more heating and more personal care outings is not included in the evaluation never mind about the additional cost of care. Section_4: It appears that the NHS is simply waiting while those who can afford it pay for it themselves and then they will be pressurised into it. Section_6: Any further research should be time limited as each delay affects lives so significantly.	Comments noted.
Patient	Section_1: How do you describe highly active relapsing-remitting multiple sclerosis. Is this one or two major relapses a years or the affects that the patient has after the relapse has passed? It is good that the people on the current trial can continue and that it will be up to their Consultant when the therapy finishes. Section_2: How many side affects does beta interferon have? I have been on	Please refer to section 2.1 of the FAD for the definition of highly active relapsing-remitting multiple sclerosis.

	the trial drug, the first once which was over two/three years, I wasn't on the placebo and again now for three months. I have not suffered any side affects. I have had treatment for my right foot/leg that cramps (I had a relapse straight after I came off the Antigren which has left my right foot/leg like this) but unfortunately drugs just made me sleepy and felt that I couldn't continue them and stay at work. I also understand that this drug might be available in tablet form eventually which surely would cut down on the costs. As I understand it there were three cases of PML in America, these people were on a drug trial which comprised of beta interfon with the Tysabri. I believe these are two strong drugs. No one was aware of how Antigren performed on its own let alone together with a beta interferon. Nobody was on a single dose. As far as I am aware nobody in England got PML although I appreciate it needs to be checked out as an extra precaution. Section_3: I think that NICE should just look at what is happening in England and comment on the previous trial with regards to that data and now look at the data from this trial. I think that it is too soon to comment. Section_4: What I would like to say is that after having the drug I feel much more alert and able and willing to participate in the community. I feel that without the drug that I wouldn't be in work and be able to enjoy myself after work. It may seem a cliche but I live a ""normal"" life. I don't feel that with the side affects of beta interferon and the fact that you have to change the injection site each time and the fact that the site then becomes weakened and bruised I don't think that you can say the same for Tysabri. My veins are not that good, they decide to delve back into my arm and just when the nurse/doctor thinks that it is a good vein it then disappears, but I have had the drug in the same site each month and there doesn't seem to be any ""damage"" to the site. Which if nothing else is a good sign to me. Section_6: I am pleased that further research will be undertaken and that this is not a complete ""No""to Tysabri (Antigren) as I feel that this is a really good drug and even if it gives a good life for a few years it is better than the prognosis at the moment. Section_8: I believe that this maybe when my drug trial finishes in which case it would be good that it is reviewed then when there is more evidence since the trial without the placebo has only just started. I can't understand why the drug is being discussed now as the trial is only just in its third month.	Comments noted. This date refers to when the Institute will judge whether it is necessary to update the guidance it has issued.

		Natalizumab is being discussed now because some trials have already completed and the drug has a UK marketing authorisation.
Patient	Reconsideration is desperately needed of NICE"s decision not to recommend Natalizumab (hereafter referred to as Tysabri) for Multiple Sclerosis patients. To effectively assess the advantages or disadvantages of Tysabri, or any disease modifying drug treatment, NICE needs to significantly recognize that once disability has set in, treatment is too late and for the person with MS, the clock cannot be turned back. Over the last decade, research shows emphatically that MS needs to be treated from the start to prevent permanent disability and slow the disease process down (which usually strikes young adults in their prime). Advantages of Natalizumab (Tysabri): Natalizumab is a welcome advance in the treatment of Multiple Sclerosis in that it 1) reduces disease progression; 2) reduces number & severity of relapses; 3) reduces use of costly & damaging steroids; 4) reduces costly hospital admissions; and 5) improves quality of life & reduced cognitive decline. Tysabri has been shown to reduce the annual rate of relapses by 68%, and after one year, 77% of patients on treatment were relapse free as compared to 56% in the placebo group. Tysabri has sustained effect on the annual relapse rate in MS patients treated for up to three years. The approximate cost per relapse avoided with Tysabri was between $13,000 (USD) & $24,000 (USD) lower than that of the other disease-modifying therapies (the ABCR"s). A reduction of the number of relapses will enable the person with MS to stay working, pay taxes, have a more meaningful family & social life. Tysabri offers an important therapeutic option for many patients living with the debilitating effects of MS. It is impossible to over-estimate the impact of a long-term condition such as MS (which is huge), just as it is impossible to under-estimate the positive impact of early treatment with Tysabri early in the disease course. Persons with MS have a much higher level of depression and suicide than the general population. Lack of work (due to the increasing disabilities of MS) and lack of effective management of their condition are major contributors to the suicide risk. The enormous benefits of Tysabri far outweigh it"s minimal .1% risk of PML, and MS patients, such as myself, are willing to take such a minimal risk in order to stop/slow our disease progression, and reduce our relapse rate with further accumulating disabilities. Further, the risks of	Comments noted.

	Mitoxantrone (Novantrone) carries a 1:200 risk of permanent cardiac damage and a 1:400 risk of promyelocytic leukaemia. This compares with the minimal 1:1000 risk of PML with Tysabri. When comparing relapse reduction rates (Tysabri-67%; Avonex (Interferon beta-1a IM) 32%; Betaseron(R) (Interferon beta-1b) 34%; Copaxone(R) (glatiramer acetate) 29%; and Rebif(R) (Interferon beta-1a SC) 32%), it is clear that Tysabri is needed in the UK to treat it"s MS patients in a cost-effective manner. Another advantage to Tysabri is that it is administered via an IV infusion every 28 days and this is another positive for persons with MS. It is not only convenient, it ensures that they will be monitored while having their monthly treatment, and it will further ensure compliance that the patient stay on their MS therapy, while removing 1) any fear of self-injection as required for the current disease modifying drug therapies, and 2) non-compliance with same due to their horrific side effects and injection site reactions. Tysabri is well tolerated, easy to administer, and adherence/compliance will be high among patients if approved by the NHS. Patients and/or carers would readily accept Tysabri if it was made available on the NHS. To not have Tysabri available by the NHS would leave persons with MS, who have highly active relapsing disease, only hopelessness and dispair, further debilitating relapses with accumulating disabilities, and a rapid decline in their health and well-being, with increased suffering. Failure of the NHS to authorize Tysabri will result in untreated highly active relapsing-remitting MS leading to repeated hospital admissions for eventual ineffective steroid treatments and increased costs to be borne by the NHS, and an ultimate showing of a wanton disregard for the complete destruction of a suffering patient"s life. Finally, give the MS patient hope and a fighting chance to live a fulfilling life and substantially contribute to society. Do the right thing, recommend Tysabri (Natalizumab) to the NHS for the treatment of highly active relapsing-remitting forms of Multiple Sclerosis. Respectfully submitted, Lauren Roberts (MS patient for 31 years & current Tysabri patient) Section_1: Reconsideration is desperately needed of NICE"s decision not to recommend Natalizumab (hereinafter referred to as Tysabri) for Multiple Sclerosis patients. To effectively assess the advantages or disadvantages of Tysabri, or any disease modifying drug treatment, NICE needs to significantly recognize that once disability has set in, treatment is too late and for the person	

	with MS, the clock cannot be turned back. Over the last decade, research shows emphatically that MS needs to be treated from the start to prevent permanent disability and slow the disease process down (which usually strikes young adults in their prime). Patients currently receiving Tysabri (who desperately need it) will not be able to afford to pay for it themselves if the NHS does not approve it, thus the NHS will be condeming them to a lifetime of suffering due to accumulating disabilities that will be increasing in severity. Loss of brain tissue due to MS lesions forming equals disability. Time Is Brain. Section_2: The technology of Tysabri (a Selective Adhesion Molecule) is the first superior effecifacy of 68% for treating relapsing (inflammatory) forms MS in over a decade. It is more effective than all of the beta interferons, glatiramer acetate, and Mitoxantrone. The minimal 0.1% risk of PML is due to a diminished immunosurveillance (per the NEJM) which is why no other immunomodulators or strong immunosuppressants should be used with it. Persons with MS have a much higher level of depression & suicide than the general population. Lack of work (due to the increasing disabilities of MS) & lack of effective management of their condition are major contributors to the suicide risk. The enormous benefits of Tysabri far outweigh it"s minimal .1% risk of PML, and MS patients, such as myself, are willing to take such a minimal risk in order to stop/slow our disease progression, and reduce our relapse rate with further accumulating disabilities. Further, the risks of Mitoxantrone (Novantrone) carries a 1:200 risk of permanent cardiac damage and a 1:400 risk of promyelocytic leukaemia. This compares with the minimal 1:1000 risk of PML with Tysabri. Section_3: 3.4: A model was constructed by Xcenda, formerly Applied Health Outcomes, to compare the cost per relapse avoided among the five disease-modifying MS therapies to treat relapsing forms of MS. Overall cost of therapy was calculated using the US wholesale acquisition drug cost, and costs associated with drug administration, patient monitoring and treatment of relapses. The costs associated with adverse events were not assessed as part of this model. Effectiveness was defined as the number of relapses avoided with treatment, which was calculated as the number of relapses for a non-treated population multiplied by published relapse rate reductions for the therapies.(1) Based on the model developed, the cost per relapse per year avoided was lowest for Tysabri. The cost per relapse avoided for TYSABRI was between $12,730 and $23,274 (USD)lower than that of the other disease-modifying	

	therapies. Highly active relapsing-remitting MS falls within the category of ""relapsing"" forms of MS. Also, severe elevated liver enzymes, severe depression (associated w/the interferons), and severe injection site reactions (assoc. w/glataimer acetate) were NOT found with Tysabri. Section_4: The NHS wastes money on INEFFECTIVELY treating relapses instead of EFFECTIVELY treating highly active R/R MS with Tysabri that PREVENTS/MINIMIZES relapses to begin with. The cost of Tysabri (approx. 14,000 per year) is LESS than the alloted 44,600 QALY for beta interferons, glatimer acetate, and best supportive care. MS patients don''t want any of this- we want to PREVENT needing any of these unnecessary and exorbhitant costs by having Tysabri therapy which has been proven to improve our Quality of Life. Another advantage to Tysabri is that it is administered via an IV infusion every 28 days and this is another positive for persons with MS. It is not only convenient, it ensures that they will be monitored while having their monthly treatment, & it will further ensure compliance that the patient stay on their MS therapy, while removing any fear of self-injection as required for the current disease modifying drug therapies, and non-compliance with same due to their horrific side effects and injection site reactions. Tysabri is well tolerated, easy to administer, & adherence/compliance will be high among patients if approved by the NHS. Section_5: The annual cost of existing MS therapies AND supportive care are MORE expensive to ineffectively treat disabling and accruing relapses, than preventing them with the ultimately low costs of Tysabri which results are higly effective and improve the MS patient''s Quality of Life, per the THREE YEAR NATALIZUMAB DATA FOUND AT: http://www.elan.com/News/full.asp?ID=913012. Section_6: Enough research already, TIME IS BRAIN. To not have Tysabri available by the NHS would leave persons with MS, who have highly active relapsing disease, only hopelessness and dispair, further debilitating relapses with accumulating disabilities, and a rapid decline in their health and well-being, with increased suffering. Section_7: Failure of the NHS to authorize Tysabri will result in untreated highly active relapsing-remitting MS leading to repeated hospital admissions for eventual ineffective steroid treatments and increased costs to be borne by the NHS (due to the lesser effective older generation treatments), with an ultimate	

	showing by NICE and the NHS of a wanton disregard for the complete destruction of a suffering patient"s life that they will condemed to PERMANENTLY. Section_8: Mr. Barnett, and the members of the NICE Appraisal Committee: TIME IS BRAIN - Approval of Tysabri is needed NOW...Show the entire World your collective wisdom, compassion and economic good sense by approving Tysabri (Natalizumab) for MS, and lead the World as you once did by giving the MS patient hope and a fighting chance to live a fulfilling life and substantially contribute to society. Do the right thing, recommend Tysabri (Natalizumab) to the NHS for the treatment of highly active relapsing-remitting forms of Multiple Sclerosis.	
NHS professional	Section_3: Although the SENTINEL data was not submitted, this was due to safety, not efficacy concerns: reading the paper, it seems clear that the interferon was contributing little, if anything, to the treatment effect in the combination arm. The magnitude of the treatment effect in this, and the other nataluzimab studies, would strongly support the use of nataluzimab (or mitoxantrone, unlicensed) in these "treatment failure" patients. Section_4: The choice of "appropriate comparator" seems bizarre. Experts would probably agree that current DMT such as interferon are inadequate, and poorly effective, in this patient group (RES) but that is very different from saying they are "ineffective", and therefore "not indicated for long term treatment". This patient group would almost always be started on DMT, because there is no other (licensed) option. If a potential new therapy for this patient group (nataluzimab) were available, selecting "supportive care" (ie no treatment at all) as the comparator is a nonsense. It should at least be compared to current DMT (interferon, glatiramer). It would make more sense to compare it to mitoxantrone, which has similar efficacy and is used in the same patient groups (RES and SOT), though is unlicensed in the UK.	Comments noted. Following the consultation on the ACD, the Committee agreed that the appropriate comparator for determining the cost effectiveness of natalizumab in the RES group is beta interferon and that natalizumab should be recommended for this group.
Patient	Section_1: i think that nice should give natalizumab its license as it is to be used for a small group of ms sufferers and surely if these people can enjoy a better quality of life it is worth it.said people could work again and continue to pay into the system also the need of care for these people would be less .the uk is failing ms sufferers and writing them off without giving them a chance at living and only existing shame on nice Section_2: the cost of this drug is only a couple of grand over the cost of beta	Comments noted.

	interferons and the cost would still be lower than someone being in hospital for long periods at a time Section_4: why can"t peoples quality of life be considered who would look after my children if i became too ill? have these costs been added to your equations Section_6: all well and good but what if it proves effective will it still boil down to money like other treatments for other conditions? Section_8: 2010 is too far away when usa and other eu countries have given it the go ahead its like living in a third world country as we appear to be europes poor relation	
Patient	Section_1: Presently, I am undertaking Mitoxantrone chemotherapy treatment to try to stabilise my condition. Previously, my consultant was very concerned how my M.S. was progressing. As I am sure you are aware, this is only a short term measure as there is a limit as to how many doses of Mitoxantrone can be given. Previous to the Mitoxantrone treatment, my consultant prescribed both Rebif and Copaxone which are the standard treatments at present. Unfortunately, I could not continue with either of these due to some extremely upleasant side effects. After discussion with my consultant, he felt that the most likely cause of these side effects was some kind of allergic reaction. I am now reaching the point where I cannot continue with Mitoxantrone treatment much longer as I am close to my lifetime limit. Obviously, being only 33 years of age I am extremely concerned about my future prospects without effective treatment, especially as the Mitoxantrone treatment appeared to have no adverse effects. Whilst I understand that any new treatment is likely to be expensive, I fail to understand why this treatment cannot be prescribed in rare cases where standard treatments are unsuitable. Section_2: As mentioned previously, I cannot take either Rebif or Copaxone, and my consultant is in full agreement that this is the case. Whilst I fully understand the risks which could be associated with Tysabri, this does not compare with the certainty that without treatment, my condition will worsen. The only uncertainty with my condition is how quickly I will deteriorate once the Mitoxantrone has to finish. Section_4: Based on the evidence, I feel that the following issues are relevant:- a) most new treatments are expensive as the drug companies spend millions of pounds bringing a new drug to the marketplace b)MS sufferers who cannot tolerate either of the only two current treatments could return to work, and thus	Comments noted.

	produce tax revenue, less reliance on benefits and the need for, and expense of providing care. Section_5: Further research - where is the incentive for the drug companies to spend time and money on research only to have the treatment declined due to cost. Future new treatments for any disease need time and money, and it is my belief that the authorities have a moral obligation to provide these treatments - it is the only way to reduce the cost of the treatment over the longer and provide the incentive to allow the drug companies to continue their work Section_6: USA, Eire and most other EU countries have concluded that Tysabri needs no further trials before being licensed - why is the UK different? is this an excuse not to spend the money? Section_8: One last point, I understand that the closing date for the consultation period coincides closely with the end of the Parliamentary recess. Is this a co-incidence or was there an underlying reason. 15 days also appears to conflict with the standard 4 week consultation period which is normally the case. With regards to your proposed review date of 2010, that is an awfully long time to wait for the only effective treatment for myself and many others in my situation. Please note that I intend to raise this matter with my M.P., and I would suggest that the media would also be interested in this as this situation appears to laymen like myself to be remarkably similar to recent licensing of Herceptin for Breast Cancer patients.	Parliament has never formally scrutinised NICE guidance and has not indicated to the Institute that it wishes to. Therefore, the Institute does not limit consultations to the periods when Parliament is sitting. MPs are not constrained by the formal Parliamentary calendar from commenting on NICE guidance.
Patient	Section_1: recommending against the use of tysabri is a purely accounting point a view of medical treatment. Section_2: Why not at least let t patients consider using it after all they do pay even if only indirectly Section_3: money it's a crime a well know song Section_6: That's evident Section_7: The two references both say that there not cost effective and date from 2004 this is not the opinion of other countries. Section_8: So why not start now and be sure of the data you collect	Comments noted.
Carer	With regard to Tysabri being stopped just like Beta Interferon was, is this an infingment of my Wife,s human rights by the Goverment body NICE.	Comment noted.
Patient	Section_1: Recommendation for natalizumab to include use with monitoring Could NICE consider permitting the use of natalizumab in patients with Highly Active RRMS with conditions which require that outcomes are closely monitored	Comments noted.

	and treatment discontinued after one or two years, should the response be less than a predefined limit (eg occurrence of >1 disabling relapse within a 12-month period) or tolerability unacceptable? Such stipulations have been issued by NICE in the past. For example, in TA 103 issued last year, NICE recommended prescription of etanercept to adult patients with moderate to severe plaque psoriasis, with the direction to monitor outcomes carefully & discontinue treatment if there was an inadequate response. Similarly, the -interferon & glatiramer acetate risk-sharing scheme has established stopping criteria which are agreed with the patient before starting treatment. Section_2: Until this century, there were no treatments available which could modify the course of the disease for people with multiple sclerosis (MS). However during the last few years, clinical advances have been made in the treatment of people with relapsing remitting MS (RRMS) with the approval & usage of -interferons & glatiramer acetate, leading to an approximately one-third reduction in the relapse rate compared to best supportive care. Recently monoclonal antibodies in clinical development for RRMS have demonstrated further improvements in reducing relapse rate, with natalizumab showing an approximately two-thirds reduction and being approved for use in Highly Active RRMS patients. This has provided hope for MS patients, especially people diagnosed with RRMS in the last few years. However, none of these advances will be of any clinical value nor will the results of their use in patients be a spur to further research, if patients are not given the possibility to receive these new treatments. It is unjust if the only ones who benefit are those who can afford to pay privately or have the good fortune to be treated in a clinical trial. Section_3: Scientific and medical advances are made incrementally, with the knowledge obtained used to gain insights into the disease mechanism and thus design treatments with further improvements to currently available medicines. Each step may be relatively small and thus not appear to be particularly ""cost-effective"". Yet if all the steps are not taken, the eventual aggregated benefit to patients and society cannot be achieved. The assessment of cost effectiveness for natalizumab does not consider indirect costs from two very important areas and may thus undervalue this medicine. 1. increasing carer costs which MS patients need when they continue to experience regular relapses & acquire increasing disability. In addition, without effective support, those carers can become the patients of tomorrow & users of NHS resources 2. loss of or decline	

	in income & the resulting fall in their tax contribution to society as regular relapses gradually lead to reduction in working hours or loss of employment. I acknowledge that these are not the remit of NICE which has as its aim to apportion NHS costs equitably, but they are relevant for the overall cost burden of the disease. Section_4: The size of the HARRMS patient population in the UK who would be eligible for natalizumab is small, considered to be approximately 2,500 by the 5th year after its introduction, according to the manufacturers submission. With an annual cost of the drug and its administration of approximately 15802/patient, this amounts to 39.5 million nationally, which is a 53% increment on the current costs estimated in the manufacturers submission to treat the same group of patients with beta-interferons or glatiramer acetate (18.6 million). Such revenues are small in the context of the overall NHS budget. Section_5: Let me give you my personal experience to explain the potential impact of both MS and the availability of new treatments to individual patients. In 2001 I was diagnosed with RRMS and although it was not called Highly Active, since this category was not recognised then, its likely that I fell into this group, with 2 relapses in the space of 6 months which reduced me from an active life including skiing and hiking at weekends to walking 1-200 yards at a snails pace leaning on a friend or shopping trolley. This was accompanied by other symptoms including visual blurring & chronic fatigue, which led to a reduction in my working hours as a clinical development director at an international pharmaceutical company from 5 days to 3 days/week. Section_6: I was referred to Addenbrookes Hospital in Cambridge & offered the chance under the compassionate use scheme to receive another monoclonal antibody in clinical development for RRMS, alemtuzumab (Campath-1H) in 2002 & 2003. Since then, I have not had a single relapse & my fatigue has slowly diminished such that my working hours are now increased to 4 days/week & I"ve re-established my career as a clinical scientist at an international level. Ive been skiing again & have resumed walking regularly at home & on holiday, often doing 6-8 miles and climbing 1000m. For me, my family & friends, this has been little short of a miracle and without the intervention of a new monoclonal antibody treatment, there is a good chance I would have been wheelchair-bound & unemployed at this stage more than five years later. Instead I am an effective tax-paying member of society. Please do not deny others the opportunity to	

	receive the option of treatment which may be life-changing for them and, in view of the small number of eligible patients, relatively inexpensive for the NHS. Section_7: The format of this draft guidance does not readily lend itself to adding personal experience. I trust that it will be considered, although split between the previous two spaces for comment.	
NHS professional	Biogen Idec are one of the four companies funding the risk-sharing scheme via the DH/MS trust, i am seconded 1 day per week to the scheme (which involves the beta interferons and glatiramer) though have had no direct involvement with the development of Tysabri or the Biogen submissions Section_4: Though overall I concur with many of the appraisals provisional conclusions - primarily on the basis that the drug has not been truly trialled as monotherapy in either of the licenced indications - I would strongly disagree with the contention that the best comparator for treatment of patients with very active RRMS is "best supportive care". Patients with very active disease will generally now be offered treatment with an Interferon (often ineffective) or in centres like ours more aggressive treatment strategies such as Mitoxantrone (used in Liverpool, Manchester, Glasgow, Nottingham, Oxford and Sheffield to name a few) or CAMPATH-1H (Cambridge, Cardiff, Plymouth, Bristol). Both drugs, though unlicenced in the UK for MS (mitox has a US licence) have shown clear evidence of effect in active RRMS and are an order of magnitude cheaper than Tysabri. Both drugs should be considered in this setting as their use reflects current "best practice" in "rapidly evolving severe" MS (of which i am sure incidentally there were very few such patients in the Tysabri studies given the availability of other licenced therapies at the time or randomisation). Section_5:	Following the consultation on the ACD, the Appraisal Committee was persuaded that the appropriate comparator for determining cost effectiveness in the RES group is beta interferon.
Representative of MS Society	The MS Society challenges the Committee"s recommendation that natalizumab should not be used in the NHS. We believe the recommendation to be damaging to the care available to people with multiple sclerosis (MS) and to be based on clinically inaccurate assumptions. The Committee has stated that for those with RES, the most appropriate comparator is best supportive care, not other currently licensed disease-modifying drugs (4.6), which is significant to the resulting recommendations. We strongly dispute this analysis. We refer the Committee to the Association of British Neurologists" assessment that treatment with beta interferon is the recommended first-line standard of practice for people	Following the consultation on the ACD, the Appraisal Committee was persuaded that the appropriate comparator for determining cost effectiveness in the RES group is beta interferon.

	with RES MS and that offering best supportive care only is not acceptable clinical practice. We are surprised and concerned to read that clinical experts informed the Committee that, for people with highly active disease, beta interferon is not generally considered to be effective and is consequently not used as a long-term treatment (4.6) This is neither the Association of British Neurologists" opinion nor our own understanding of current best clinical practice. Section_4: As above, we strongly dispute the analysis that the most appropriate comparator is best supportive care. The fair and appropriate comparators are the current licensed drug therapies which people with RES MS would inevitably be taking. People with RES MS have frequent disabling relapses and an active MRI scan. Treatment with beta interferon has proven efficacy in reducing frequency of relapses by a mean of 1/3 and is shown to reduce MRI lesions by up to 50-70%. Natalizumab has been shown to reduce clinical relapse rate by a mean of 2/3, a significant improvement on beta interferons. The analysis of the economic case is also based on comparison with best supportive care; comparing natalizumab with the therapies would lead to a different cost effectiveness conclusion. It also fails to consider the small size of the UK MS population who would meet the current prescribing criteria for natalizumab, an estimated 2,500. Cost to the NHS would be relatively low compared with potential individual and societal savings. People would be more able to remain employed and require fewer supportive services if they were to experience fewer relapses and a reduced risk of disability progression. Section_6: We support the recommendation by the Committee for further research into the clinical effectiveness of natalizumab for the treatment of highly active relapsing remitting MS (6.1). However, given the known benefits of the treatment and the lack of alternatives currently available, we do not think that additional research should be required before natalizumab receives approval. Over 10,000 people with MS in Ireland, Germany, the USA and elsewhere are already benefiting from natalizumab. England has one of the highest prevalence rates of MS in the world. It is therefore particularly important that people with RES MS who meet the eligibility criteria have access to natalizumab under the NHS. Additionally, it should be added that people with MS would stand to benefit from the earliest possible intervention with treatments that might reduce disability progression. Longer-term safety data should be used to reconsider the	Comments noted. The Appraisal Committee revised its recommendations for the RES group following the consultation on the ACD.

	possible use of natalizumab in early relapsing-remitting MS once this data is available.	