Appraisal of Beta Interferon/ Glatiram for Multiple Sclerosis
Provisional Appraisal Determination

Please note this document has been issued for consultation purposes only.

It does not constitute guidance to the NHS on the use of beta interferon or glatarimer to people with Multiple Sclerosis.

Due to media speculation about the Institute’s appraisal of beta interferon and glatarimer for multiple sclerosis, the Chairman, on the advice of two executive directors, has decided to publish this document on the Institute’s website.

When the Institute develops its guidance it follows a process that involves the national groups that represent people with the condition, the national representative professional and the manufacturers of the technology.

These groups submit information and in the case of the patient and professional groups, nominate experts to inform the appraisal. In addition all these groups are consulted on draft appraisal documents and they have the right to appeal should they wish to do so.

This document was prepared following a meeting of the Appraisal Committee held on 26 July 2001. It is a consultation document has been circulated to the consultees listed below in order that they can make comments to the Appraisal Committee. They have been asked to send their comments to NICE by 11th September 2001.

Although NICE will respond to any correspondence, comments from individuals on this document will not passed to the Appraisal Committee. If you would like to comment on the Provisional Appraisal Determination please do so through the organisation with which you feel most closely associated:

- The Association of British Neurologists
- Biogen Ltd
- Department of Health
- Faculty of Pharmaceutical Medicine
- MS Research Group of the Association of British Neurologists
- MS Research Trust
- National Assembly for Wales
- Neurological Alliance
- Royal College of General Practitioners
- Royal College of Nursing
- Royal College of Physicians
- Royal Pharmaceutical Society
- Schering Health Care Ltd
- Serono Pharmaceuticals Ltd.
- Teva Pharmaceuticals Ltd.
- The Chartered Society of Physiotherapy
- The MS Society of Great Britain and N. Ireland
- The National Hospital for Neurology and Neurosurgery
1  Guidance

1.1 On the balance of their clinical and cost effectiveness neither beta interferon nor glatiramer acetate is recommended for the treatment of Multiple Sclerosis (MS) in the NHS in England and Wales.

1.2 It is likely that patients currently receiving beta interferon or glatiramer acetate for MS would suffer loss of well being if their treatment is discontinued at a time they did not anticipate. Because of this, patients and their consultants may wish to continue therapy until they consider it is appropriate to stop, having regard to the criteria established for withdrawal from treatment in the Guidelines of the Association of British Neurologists published in January 2001.

1.3 The Department of Health and the National Assembly for Wales are invited to consider the strategy outlined in Section 7.1 with a view to acquiring any or all of the medicines appraised for this guidance in a manner which could be considered to be cost effective.

2. Clinical Need and Practice

2.1 MS is a disabling neurological disease. It is estimated that in England and Wales MS affects some 63,000 people. MS usually begins in individuals aged between 20 and 40 years, and occurs in about twice as many women as men. It is characterised by repeated episodes of inflammation of the nervous tissue in the brain and spinal cord, resulting in the removal of the insulating myelin sheath covering the nerves. Multiple areas of scar tissue (sclerosis) form along the nerve fibres, slowing or blocking the transmission of signals to and from the brain and spinal cord.

2.2 There are several forms of MS. Some 80-90% of people start with relapsing remitting MS (RRMS). In this form of the disease, recurrent attacks of loss of neurological function, termed relapses, are separated by periods of complete or incomplete recovery, described as remissions. After about 10 years (without treatment), about half of people with MS begin a continuous downward progression, which may
also include acute relapses. This form of MS is known as secondary progressive (SPMS). RRMS accounts for about 45% and SPMS for about 45% of the total population with MS. In a third type of MS, primary progressive (accounting for about 10% of cases), the disease progresses inexorably from onset. Benign MS is a fourth and relatively rare condition.

2.3 Magnetic resonance imaging (MRI) shows that lesions develop in the brain and spinal cord tissues as the disease progresses. Development of MRI lesions may not initially correlate directly with the clinical manifestations of the disease as lesions often occur in ‘silent’ areas of the brain and spinal cord. However, lesions may precede the onset of overt symptoms of MS, and MRI data have been used as a surrogate marker of disease activity and/or progression.

2.4 The course of MS is unpredictable with variations in severity and progression rate. It tends to progress faster in men and people who are older at the time of onset.

2.5 The disease has an adverse and often highly debilitating impact on the quality of life of people with MS and their families. Relapses may require admission to hospital, and be associated with a level of disability and incapacity that disrupts working, family and social life. MS, even in its early stages, undermines patients’ confidence, restricts their activity and may limit their role in society in many ways including inability to continue employment or to take part in usual family activities. Weakness, chronic fatigue, unsteady gait, speech problems and incontinence can leave people with MS feeling isolated and depressed. Substantial burdens are imposed on primary/informal carers, who are often patients’ partners. In the management of MS, emphasis is often placed on the problems of long-term disability. However, the emotional impact of relapses on patients and carers is also considerable.

2.6 Disease progression is usually measured using the Expanded Disability Status Scale (EDSS). This scale is measured in half units from 0 which represents no disability to 10 which denotes death; 7 denotes ‘essentially restricted to wheelchair’. An important feature of the EDSS scale, however, is that it is non-linear, and small incremental changes reflect a much greater effect on patients’ quality of life and dependency levels the higher they are on the EDSS scale. The full scale is set out in Appendix D.

3 The Technology
3.1 There are four general approaches to the treatment of MS, which may be undertaken separately or in combination:

i. management of symptoms and disability with speech, physio- and occupational therapy and pharmacological or other therapeutic agents;

ii. management of the emotional and social consequences of relapses and disability;

iii. treatment of acute relapses with corticosteroids;

iv. disease-modifying treatment targeted at reducing the frequency and/or severity of relapses and/or slowing the course of the disease. The beta interferons and glatiramer acetate constitute the only options presently available options.

Beta interferons

3.2 There are three beta interferon products: Avonex (manufactured by Biogen) and Rebif (Serono), are interferon beta-1a products licensed only for the treatment of RRMS. Betaferon (Schering) is interferon beta-1b and is licensed for the treatment of both RRMS and SPMS.

3.3 The beta interferons work by reducing the inflammatory process that characterises MS. Such inflammation usually precedes an MS relapse. However, the precise mode of action of these disease-modifying agents on immunological mechanisms remains uncertain.

3.4 The beta interferons commonly cause influenza-like adverse effects (in about 50% of patients), as well as injection site reactions and leucopenia. Less commonly, the use of the beta interferons is associated with symptoms of depression. The adverse effects of all three drugs are generally well tolerated, although between 3% and 12% of people with MS receiving active therapy in trials withdrew due to adverse events. In addition, these agents, by the nature of their chemical structure, have antigenic effects and therefore may induce the development of antibodies high titres of which have been observed in some patients. These antibodies may produce allergic reactions or bind to the pharmaceutical agent, neutralising its effects. The action of these antibodies on the effectiveness of the beta interferons in clinical practice is currently uncertain.

3.5 Based on a survey of health authorities in England and Wales, undertaken in January 2000, an estimated 1,750 people are currently prescribed beta interferons, which equates to 2.8% of all MS patients, or 3.3% of those with RRMS or SPMS. These
percentages vary between health authorities.

3.6 The current annual cost per patient of the beta interferons in the UK is £7,259 (Betaferon), £9,061 (Avonex) or £9,088/£12,068 (lower dose/higher dose Rebif).

Glatiramer acetate

3.7 Glatiramer acetate (Copaxone, TEVA/Aventis) works by reducing the inflammation around nerves. Such inflammation usually precedes an MS relapse. Glatiramer is an acetate salt of polypeptides formed from the synthesis of four amino acids. It resembles myelin, the basic protein which is found in the sheath surrounding nerves. In structure, therefore, glatiramer is quite distinct from the beta interferons. Its exact mode of action, as with the beta interferons, is unknown, but it is thought also to inhibit antigen presentation to white blood cells and to induce antigen-specific suppressor T cells.

3.8 Glatiramer acetate can cause flushing, chest tightness, palpitations, anxiety and breathlessness, and also injection site reactions, but these effects are generally easily managed. In addition, by the nature of its chemical structure, glatiramer acetate has antigenic effects and therefore may induce the development of antibodies in patients. Although theoretically these antibodies may produce allergic reactions or bind to the drug molecule neutralising its effects, such effects have not been observed in practice.

3.9 The annual cost per patient of glatiramer acetate is £6,650 per year.

4 Evidence

Clinical effectiveness

4.1 Clinical trials have shown that all three interferon products reduce relapse frequency in patients with RRMS. This reduction amounts to about 30% on average, and is equivalent to approximately one relapse avoided every 2.5 years in people with RRMS. This reduction has been demonstrated for the first 2 years of therapy.

4.2 Disability progression may also be delayed by treatment, but the extent of long-term effects on disability cannot be predicted reliably on the basis of the short-term evidence from randomised clinical trials seen by the Committee.
4.3 The proposition that the beta interferons have a positive effect beyond 2 years is supported by open-label studies. These longer-term studies have assessed the effectiveness of beta interferon by comparing observed with expected levels of disease activity. For people who have taken the drug in studies for between four and five years, disease activity appears to be lower than might otherwise be expected from studies of the natural history of MS.

4.4 One of the interferon products (Betaferon) has also been shown to reduce relapse frequency in SPMS). A clinical trial of another interferon product there was a difference from placebo in a similar direction but it did not reach formal statistical significance.

4.5 There is evidence on the value of MRI as a marker of disease activity in MS. MRI findings support the studies of efficacy of the beta interferons in MS from the published clinical trials. In routine clinical practice, MRI scanning has not been used as a direct measure of the progress of MS or of the response to therapeutic intervention in preference to assessment of the clinical symptoms and signs of the disease.

4.6 Clinical trials have shown that glatiramer acetate reduces relapse frequency in patients with RRMS. This reduction amounts to about 30% on average, which is equivalent to approximately one relapse avoided every 2.5 years. This reduction has been adequately demonstrated for the first 2 years of therapy.

4.7 The extent of long term effects on disability cannot be predicted accurately on the basis of this evidence. However, recent data on 73 patients with RRMS in a follow-up study show that 75% of them were unchanged or improved in terms of accumulation of disability after 8 years using glatiramer acetate. Evidence from other published data on the natural history of the condition indicates that about 25% of untreated patients would have been expected to remain stable.

4.8 The Committee considered in detail evidence taken directly from patients and two advocacy organisations (see Appendix B). The patient organisations and the patients who attended the Committee meeting spoke of the patients’ experience of this distressing disease and of the impact of the beta interferons and glatiramer on relapses and disease progression. This dialogue provided important insight into the effect of relapses on patients’ daily lives and the value that they place on the potential avoidance of relapses with the use of these drugs, as well as into the more general effects of MS on quality of life. The Committee was also provided with recently published evidence for the effect of MS on cognitive function (for example, difficulties with memory and general
alertness) which was in addition to the impact of relapses on quality of life. It was clear from the representations made to the Committee by these individuals and groups that they considered that these medicines had a positive effect.

Cost effectiveness

4.9 During 2000 the Committee initially reviewed models of the cost-effectiveness of the medicines submitted by each manufacturer and two models prepared by independent sources. All the models calculated cost-utilities - costs per quality adjusted life year (QALY) - but came to widely differing final estimates. These ranged from about £10,000 per QALY (a manufacturer's confidential estimate) to over £3 million per QALY (an American research group's findings). These estimates were very sensitive to assumptions made in the modelling process including, in particular, the impact of a relapse on quality of life and the time horizon used. In addition the committee recognised that any inaccuracies in the data or methods used were liable to magnification in the extrapolation of 2-5 years benefit to 10-20 years or more.

4.10 The Committee therefore resolved that, in the absence of further economic modelling it would be very difficult to make a confident recommendation on the issue of cost effectiveness of these medicines. In these circumstances the Institute commissioned a new cost-effectiveness analysis that was designed to address the problems associated with the existing models. In doing so the Institute sought a maximum of cooperation between the analytical team and the product sponsors. This was designed both to help reconcile views on the model design and to benefit from individual patient trial data and any other restricted access data that might inform the analysis. In the event additional data for the new analysis were provided by Schering and Biogen. Data were provided but subsequently withdrawn by TEVA. No data were provided by Serono.

4.11 The new analysis compared treated patients' experience of both relapse and progression with the natural history of the disease. It estimated that, over a 20 year time frame, costs per QALY for the beta interferons and glatiramer may be at best of the order of £40,000 to £90,000 – assuming treatment according to ABN guidelines and using the currently prescribed discount rate for future costs of 6% and for future benefits of 1.5%. The new analysis noted that an alternative approach would be to discount future costs and benefits equally over a prolonged time frame which would have the effect of increasing the estimates for the 20 year time frame to £70,000 to £200,000 per QALY. Nevertheless, using
the current Treasury approach, with discount rates at 6% for costs and 1.5% for benefits, costs per QALY are much higher over a 10 year or 5 year time frame, displaying ranges of £190,000 to £425,000 and £380,000 to £780,000 for 10 years and 5 years respectively.

4.12 Although the Committee considered that taking a long-term perspective in a disease such as MS is reasonable, it concluded that the nature of the assumptions which the modellers were required to make in order to calculate cost effectiveness ratios beyond 10 years were understandable but, in the Committee’s judgement were too optimistic. In calculating a cost per QALY using a 20 year time frame, the model had to assume that benefits accrue over a period much longer than is supported by any available evidence from clinical trials. The Committee concluded that there was insufficient basis for this assumption. In addition, the model relied on the assumption that people who ‘drop out’ of treatment maintain the benefits gained and do not gradually return to the level of disability they would have reached had they never been treated with these therapies (as per the natural history control group). Again, the Committee did not consider that this was justified. Furthermore, as noted in paragraph 4.11 the difference between cost and benefit discount rates increasingly lowers the cost per QALY gained over longer time frames. Accordingly the Committee concluded that:

(i) the lowest estimates for cost per QALY presented in the model were likely to represent an overly optimistic view of the true values for these medicines.

(ii) extrapolation of benefit beyond 20 years would give unreliable and unsupported estimates of costs per QALY.

(iii) it could not be confident of the robustness of the cost per QALY estimates over a time frame longer than 10 years.

4.13 In addition the Committee discussed the degree to which the estimates of cost per QALY in the new analysis had taken account of non NHS costs and earlier cessation of treatment with assumptions of continuing benefit. The Committee felt that the conclusions in paragraph 4.11 were not likely to be affected by these considerations or materially to effect the cost effectiveness ratios which have emerged from the new analysis.

4.14 The Committee was mindful of the various criticisms of QALYs in general and in their use in this specific context. Some of these issues are addressed in Appendix E.
4.15 The Committee, in its appraisals of health technologies, is required to consider the broad balance between benefits and costs. In doing so, it must consider not only the cost effectiveness of the particular technology under consideration, but where that cost effectiveness stands relative to treatments for other conditions. The Committee found no measures other than QALYs that could better assist in its responsibility to make a judgement about the ‘balance of costs and benefits.’ The estimates in paragraph 4.11 constitute the best available evidence. On the basis of this evidence, the Committee concluded that, on the balance of costs and benefits, the beta interferons and glatiramer are not cost-effective. In reaching this conclusion, the Committee had in mind the cost effectiveness ratios of the technologies which the Institute has previously recommended for use in the NHS in England and Wales. The cost effectiveness ratios for the beta interferons and glatiramer acetate in which the Committee can have most confidence are significantly less favourable than for any technology have so far been recommended.

4.16 In arriving at this conclusion, the Appraisal Committee took account of the Directions to the Institute laid out by the Secretary for State for Health. Those Directions require the Institute to take into account inter alia the degree of clinical need of people with the condition, the broad balance of benefits and costs and the efficient use of NHS resources. The Institute did not receive guidance from the Secretary of State or the National Assembly for Wales on the resources which may be available for these medicines.

4.17 The Committee considered the view that there was no valid basis for distinguishing in guidance between patients currently receiving treatment with one of these medicines and other patients. This would have the implication that patients currently being prescribed a beta interferon or glatiramer should have no greater access to therapy than others. The Committee felt that this view must be balanced against other considerations such as the existing, at least implicit, patient-doctor agreement to continue therapy once started and the potential loss of well being that might follow from unanticipated treatment changes. The Committee concluded that these were relevant factors, which patients currently receiving beta interferon or glatiramer acetate for MS and their consultants might bear in mind when considering this guidance. Consultants and their patients might reasonably conclude that therapy should not be withdrawn as a result of this guidance but should continue treatment until individual patients and their consultant consider it is appropriate to stop, having regard to the criteria established for withdrawal from treatment in the Guidelines of the Association of British Neurologists published in January 2001.
4.18 Other than disease modifying treatments, management strategies for MS are aimed at ameliorating symptoms, in order to allow the patient to maintain an optimal quality of life, as presently there is no cure for the disease. The Committee is aware that the Institute has commissioned a clinical guideline on the management of multiple sclerosis. It is also aware that this guideline will examine and make recommendations on the range of interventions available for people with this disease.

5 Further Research

5.1 Trusts and Health Authorities are encouraged to collect data on all people with MS who continue on beta interferon or glatiramer as indicated in paragraph 1.2. The data collected could usefully include details of the patient and the reason they are receiving treatment. It would be helpful also to record the preparation used, patient’s relapse frequency and disease progression while on treatment, the development of adverse effects and neutralising antibodies, compliance with the therapy, the reasons for discontinuing therapy and the subsequent treatment used.

6 Implications for the NHS

6.1 On the basis of the recommendations in Section 1, but subject to any developments resulting from the implementation advice in Section 7.1 below, it is not expected that this guidance will result in a material change in current expenditure on these medicines.

7 Implementation

7.1 The Committee considered that the Department of Health and the National Assembly for Wales, and manufacturers, might usefully consider what actions could be taken, jointly, to enable any of the four medicines appraised for this guidance to be secured for patients in the NHS in England and Wales, in a manner which could be considered to be cost effective. Unless further data emerges which reveals a significant improvement in their clinical effectiveness, the cost effectiveness of these medicines can only be improved if there is a significant reduction in the total cost of their acquisition by the NHS in England and Wales. The uncertainty surrounding the definition of which patients benefit and to what extent, together with the ability of the NHS to identify a total potential patient population for which these medicines might most beneficially be purchased are factors which could be considered relevant in any discussions between the Department of Health and
the National Assembly for Wales, and manufacturers on ways in which these medicines could be acquired cost effectively. The Committee noted that the results of the additional economic modelling commissioned by the Institute revealed that interferon-1b (Betaferon, Schering) is, currently, the most cost effective of the four products appraised for this guidance.

7. Further guidance on audit of the care provided to people with MS is forthcoming with the publication by the Institute of a clinical guideline on the management of MS

8 Related Guidance

8.1 The Institute has been commissioned to produce a full clinical guideline on the management of MS. The planned publication date of this guidance is January 2003.

9 Review of Guidance

9.1 This guidance will be reviewed in November 2004.

9.2 Should any significant new evidence of clinical effectiveness or any re-evaluation of published or unpublished clinical data become available, or if there were to be a substantial change in unit costs or other actions, which led to a significant change in the cost-effectiveness of the beta interferons or glatiramer, this new information will be considered by the Institute. A judgement will be made at that time as to whether such evidence should result in an earlier review of this guidance.

Professor David Barnett
Chair of Appraisal Committee

August 2001
APPENDIX A:

Appraisal Committee Members

Professor R. L. Akehurst
*Dean, School of Health Related Research*
*Sheffield University*

Professor David Barnett (Chairman)
*Professor of Clinical Pharmacology*
*University of Leicester*

Professor Sir Colin Berry
*Professor of Morbid Anatomy*
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Professor Sarah Cowley
*Professor of Community Practice Development*
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Professor Terry Feest
*Clinical Director and Consultant Nephrologist*
*Richard Bright Renal Unit and Chairman of the UK Renal Registry*
Professor Andrew Stevens (Vice-Chairman)
Professor of Public Health
University of Birmingham
APPENDIX B

Sources of Evidence

1. The following documentation and opinion were made available to the Committee:

   a) **Assessment report**
      Prepared by the Northern and Yorkshire Regional Drug & Therapeutics Centre (*Assessment of Interferon-Beta and Glatiramer for the Treatment of Multiple Sclerosis*, April 2000)

   b) **Additional Economic Modelling**
      ScHARR Consortium Final Report to the National Institute for Clinical Excellence (*Cost effectiveness of beta interferons and glatiramer acetate in the management of multiple sclerosis*), Centre for Bayesian Statistics in Health Economics, School of Health and Related Research (ScHARR), University of Sheffield

   c) **Professional/Specialist Group submissions**
      - Association of British Neurologists
      - MS Research Group of the Association of British Neurologists
      - British Medical Association
      - Chartered Society of Physiotherapy
      - RCN Institute (Clinical Nurse Specialist)
      - Royal College of Physicians

   d) **Patient Group submissions**
      - MS Research Trust
      - MS Society

   e) **Trade Associations submissions**
      - There were no submissions for this category.

   f) **Manufacturer/Sponsor submissions**
      - Biogen Limited
      - Schering Health Care Limited
      - Serono Pharmaceuticals Limited

   g) **Expert submissions**
      - Professor Alastair Compston, University Department of Neurology, Addenbrooke’s NHS Trust
      - Dr. John Zajicek, Consultant Neurologist & Honorary Senior Lecturer, Plymouth Postgraduate Medical School
h) **Patient Advocate submissions**

- Mr Peter Cardy, Chief Executive and others representing the Multiple Sclerosis Society.
- Professor Alan Thompson, Garfield Weston Professor of Clinical Rehabilitation, The National Hospital for Neurology and Rehabilitation and Medical Advisor to the MS Society
- Ms Christine Jones and others representing the MS Research Trust
APPENDIX C

Information for patients
APPENDIX D

Expanded Disability Status Scale

0.0 Normal neurological exam (all grade 0 in Functional Systems [FS]; Cerebral grade 1 acceptable).

1.0 No disability, minimal signs in one FS (i.e. grade 1 excluding Cerebral grade 1).

1.5 No disability minimal signs in more than one FS (more than one grade 1 excluding Cerebral grade 1).

2.0 Minimal disability in one FS (one FS grade 2, others 0 or 1).

2.5 Minimal disability in two FS (two FS grade 2, others 0 or 1).

3.0 Moderate disability in one FS (one FS grade 3, others 0 or 1), or mild disability in three or four FS (three/four FS grade 2, others 0 or 1) though fully ambulatory.

3.5 Fully ambulatory but with moderate disability in one FS (one grade 3) and one or two FS grade 2; or two FS grade 3; or five FS grade 2 (others 0 or 1).

4.0 Fully ambulatory without aid, self-sufficient, up and about some 12 hours a day despite relatively severe disability consisting of one FS grade 4 (others 0 or 1), or combinations of lesser grades exceeding limits of previous steps. Able to walk without aid or rest some 500 metres.

4.5 Fully ambulatory without aid, up and about much of the day, able to work a full day, may otherwise have some limitation of full activity or require minimal assistance; characterised by relatively severe disability, usually consisting of one FS grade 4 (others 0 to 1) or combinations of lesser grades exceeding limits of previous steps. Able to walk without aid or rest for some 300 metres.

5.0 Ambulatory without aid or rest for about 200 metres; disability severe enough to preclude full daily activities. (Usual FS equivalents are one grade 5 alone, others 0 or 1; or combinations of lesser grades usually exceeding specifications for step 4.0).

5.5 Ambulatory without aid or rest for about 100 metres; disability severe enough to preclude full daily activities. (Usual FS equivalents are one grade 5 alone, others 0 or 1; or combinations of lesser grades usually exceeding those for steps 4.0).
6.0 Intermittent or unilateral constant assistance (cane, crutch or braces) required to walk about 100 metres with or without resting. (Usual FS equivalents are combinations with more than two FS grade 3+).

6.5 Constant bilateral assistance (canes, crutches or braces) required to walk about 20 metres without resting. (Usual FS equivalents are combinations with more than two FS grade 3+).

7.0 Unable to walk beyond about 5 metres even with aid, essentially restricted to wheelchair; wheels self in standard wheelchair and transfers alone; up and about in wheelchair some 12 hours a day. (Usual FS equivalents are combinations with more than one FS grade 4+; very rarely, pyramidal grade 5 alone).

7.5 Unable to take more than a few steps; restricted to wheelchair; may need aid in transfer; wheels self but cannot carry on in standard wheelchair a full day; may require motorised wheelchair (Usual FS equivalents are combinations with more than one FS grade 4+).

8.0 Essentially restricted to bed or chair or perambulated in wheelchair, but may be out of bed itself much of the day; maintains many self-care functions; generally has effective use of arms. (Usual FS equivalents are combinations, generally grade 4+ in several systems).

8.5 Essentially restricted to bed much of the day; has some effective use of arm(s); retains some self care functions. (Usual FS equivalents are combinations, generally 4+ in several systems).

9.0 Helpless bed patient; can communicate and eat. (Usual FS equivalents are combinations, mostly grade 4+).

9.5 Totally helpless bed patient; unable to communicate effectively or eat/swallow. (Usual FS equivalents are combinations, almost all grade 4+).

10.0 Death due to MS.
APPENDIX E

This Appendix, taken with modifications from the Evaluation Report to the Appraisals Committee, provides some background information on the way in which health benefits are calculated. It does not form part of the guidance proper.

A 1.1 Measuring benefits

A1.1.1 Measures of the benefit of treatment used in cost-effectiveness analyses can be based on ‘natural’ units, for example years of life gained, or on value-based measures, for example Quality Adjusted Life Years (QALYs). The number of QALYs gained by using a particular treatment is a measure of its benefit in terms of improvements in the quality of life of patients (including physical performance, pain, distress and psychological improvements as well as changes in survival) summed over a period of time. It therefore incorporates the value of changes in both morbidity and mortality, where these exist.

A1.1.2 In the particular case of MS, although there are natural units which capture specific aspects of the impact of MS, such as relapses avoided and delaying progression to wheelchair dependency, there is none which captures both the impact on relapses and the full impact of progression. These measures therefore ignore some of the established benefits of the beta interferons.

A1.1.3 Although imperfect as ‘natural’ units to capture gains from delayed progression, the EDSS does provide a means to create a value-based measure of benefit. All of the studies that attempt to encompass the full effect of delayed progression have used changes in EDSS converted to changes in QALYs. This requires an estimate of utilities (adjustments for level of quality of life) applied to each of the EDSS levels, and based not on the disability itself but to include all the associated morbidity.

A1.1.4 An alternative measure is provided in the literature and in the submissions in the form of a measure based on the EDSS called variously Area Under the Curve, integrated area under the EDSS time curve or disability burden unit. This is calculated by multiplying the EDSS score by the time during which that score is observed, and summing over time. This measure is therefore very similar to the QALY, the difference being that EDSS scores are given an equal weight rather than a weight based on the relative utility of different health states.
A1.1.5 This summed EDSS measure has a number of disadvantages. The numbers used in the EDSS itself are not cardinal numbers either by construction or by behaviour. (A “cardinal” number can be added, subtracted, multiplied or divided, and the result has ready meaning.) The EDSS score is, by contrast, “ordinal”, which means that a higher score represents greater disability. But it does not imply, for example, that an EDSS score of 8 (restricted to bed or chair or perambulated in a wheelchair) is twice as disabled a state as an EDSS score of 4 (fully ambulatory and able to walk up to 500 metres without aid or rest). This means that the summed EDSS measure is also not cardinal. Its units are arbitrary, meaning that a cost per summed EDSS score avoided is equally arbitrary. The utility scores used in calculating QALYs weight the underlying EDSS scores in ways designed to produce cardinal numbers having identifiable units. The summed EDSS score therefore shares any problems that the QALY has and has a number of others besides.

A 1.2 The use of QALYs in MS.

A 1.2.1 Although all of the submissions to the Committee from the manufacturers report QALYs and cost-effectiveness ratios derived from them, some also make a number of criticisms of the approach. These include some unexplained “assertions”, but the following statements warrant further comment:

A1.2.1.1 QALYS discriminate against people with MS.

This appears to be based on two premises. The first is a mistaken belief that QALY measurement does not count transient improvements in quality of life; that is emphatically not the case. The second is a related argument that people with disabilities do not have the same potential to gain QALYs because of their lower underlying quality of life. However, this argument only applies, and then in theory only, to therapies that are life-saving. It does not apply to interventions that improve quality of life – on the contrary, lower quality of life suggests a greater capacity to gain QALYs. Since the impact of therapies for MS is dominated by improvements in quality of life, this criticism does not apply.

A1.2.1.2 QALYs do not discriminate in favour of people with MS.

The QALY approach is egalitarian in considering any particular gain in quantity or quality of life as being of equal value regardless of the
age, sex or other characteristics of the recipients. The suggestion is that QALYs should be adjusted so that they are greater for those of working age. In other words, it proposes that one should discriminate against young and old people, because they do not work or have dependants. Whilst there is some evidence that there are those who would support such discrimination, it is unclear how far it should be taken. A logical implication of the argument in favour of such discrimination is that QALYs should be weighted against individuals of working age who do not have dependants or who are unable to work. It might even imply employment of an individual weight based on the number of dependants and the size of income from employment.

A1.2.1.3 **QALY gains are estimated using a population based estimate of utility values, which are inferior to those based on patient preferences.**

The evidence provided by Parkin et al (J of Neurology, Neurosurgery and Psychiatry, 2000; 68: 144-49) suggested that despite differences in utility values for health states, estimates of QALY gains were not affected by the use of patient rather than population utilities. Moreover, there is an argument that societal-based estimates used consistently for all evaluations are more appropriate because they reflect wider values that are comparable over different therapies.

A1.2.1.4 **QALY gains include average relapses and therefore do not take account of severe relapses.**

This is not correct, since the calculation of an average includes both more severe and milder relapses as well as those of average severity. A larger sample of people with MS, thus containing more relapses than that which has been studied to date, might include a greater number of severe relapses and might plausibly raise the average severity. However, it may also include a smaller proportion of severe relapses and so lower average severity. There is no evidence either way.

A1.2.1.5 **The loss of utility due to relapses may be an underestimate because it is assessed after the event.**

This may be true; there are methodological difficulties with obtaining quality of life data during relapses that are serious enough to require hospitalisation, which mean that it is difficult to test. However, there is no evidence that the values are too high, or too low.