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COST EFFECTIVE PROVISION OF DISEASE MODIFYING THERAPIES FOR PEOPLE WITH MULTIPLE SCLEROSIS

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COST EFFECTIVE PROVISION OF DISEASE MODIFYING THERAPIES FOR PEOPLE WITH MULTIPLE SCLEROSIS

Summary

1. The Department of Health, National Assembly for Wales, Scottish Executive and Northern Ireland Department of Health, Social Services & Public Safety have reached agreement with manufacturers on a risk-sharing scheme for the supply of disease modifying treatments for Multiple Sclerosis on the NHS. The scheme involves detailed monitoring of a cohort of patients to confirm the cost-effectiveness of these treatments. The arrangements will ensure that these supplies are cost-effective for the NHS. The Association of British Neurologists (ABN), the MS Society, the MS Trust, the UK MS Specialist Nurse Association and the Royal College of Nursing support the arrangements. The agreement follows on from the Guidance issued by The National Institute for Clinical Excellence (NICE). NICE has welcomed the scheme.

2. **This circular explains how patients can participate in the scheme. All patients with relapsing-remitting MS, and those with secondary progressive MS in which relapses are the dominant clinical feature, who meet the criteria developed by the ABN are eligible for treatment under the scheme**. Prescriptions under the scheme may be initiated from 6 May 2002 for those centres with appropriate infrastructure in place, and as soon as practicable after this date for those centres where such arrangements are not yet in place. It is the intention to complete the recruitment of the sub-set of patients within the scheme who will form the cohort subject to monitoring within 18 months of the scheme being initiated by the centres. Ministers have issued a statutory direction in respect of the scheme which places NHS bodies under a funding obligation equivalent to that for positive NICE guidance.

Background

3. NICE have undertaken a detailed appraisal of the clinical and cost effectiveness of beta inteferon and glatiramer acetate. Their guidance can be found at www.nice.org.uk . They considered that these treatments did not represent a cost effective use of NHS resources under the then existing arrangements for purchasing the drugs. At an earlier stage in preparing the guidance, they invited the Department of Health and the National Assembly for Wales to consider what actions could be taken to enable the medicines being appraised to be secured for patients on the NHS in a manner which could be considered to be cost effective. Discussions with interested parties including the manufacturers concerned, the Association of British Neurologists and the Multiple Sclerosis Society have resulted in the scheme. The parameters of the scheme are consistent with NICE's appraisal and the modelling by ScHARR who were commissioned by NICE to assist their appraisal. The Department and NAW consider that those drugs within the scheme are now being acquired for the NHS in a manner which will make treatment cost effective.

The Scheme

4. The full text of the scheme is included as Annex A to this guidance. The products (and relevant manufacturers) included in the scheme are:

- Avonex (Biogen Ltd)
- Betaferon (Schering Ltd)
- Copaxone (Teva/Aventis)
- Rebif, 22mg & 44mg (Serono Ltd)

5. Some key elements to note are:

- the scheme applies to patients with relapsing remitting MS and those with secondary progressive MS in which relapses are the dominant clinical feature. All patients meeting the ABN criteria are eligible to be entered into the scheme and to receive treatment. Relevant extracts from the ABN guidelines are included in Annex A;
- treatment will be initiated only by specialist MS centres determined by local agreement;
- target outcomes for patients have been agreed for each product included in the scheme. There would be an acceptable level of cost effectiveness for the NHS if the targets are achieved in full;
- outcomes for a cohort of patients in the scheme will be monitored at annual intervals. The cost to the NHS will be adjusted on a sliding scale if outcomes differ from the agreed target for a product;
- monitoring and potential price adjustments under the scheme are expected to continue over 10 years;
- a scheme co-ordinator will be appointed to liaise with specialist centres and collect and analyse the monitoring data needed for the scheme;
- there is no bar to clinicians prescribing and Health Authorities and NHS Trusts funding beta-interferon and glatiramer acetate for patients who do not fall within the ABN guidelines where they judge it clinically necessary;
- NHS bodies are expected to fund any treatment within this scheme prescribed by clinicians for eligible patients, in accordance with the directions. The choice of treatment, within those covered by the scheme, should be made on clinical grounds by the prescribing clinician in consultation with the patient taking into account expected benefit and potential side effects;
- patients currently receiving treatment who are not eligible under the scheme, should continue to be treated until such time as the consultant and patient agree that it is appropriate to stop (Paragraph 1.2 of NICE's guidance refers);
- the NHS should from the date of this circular meet the costs of disease modifying treatments currently being purchased privately by patients whose care is otherwise being provided by the NHS and the drug was not available on the NHS to the patient because of local funding or prescribing policies.

Implications for the NHS

6. NHS bodies will need to:

- assess the arrangements necessary to implement the scheme ensuring optimum use of clinical expertise and administrative support. Short term measures such as additional sessions are likely to be necessary as well as more medium term ones;

- agree funding to ensure that centres are in a position to provide the treatments prescribed by clinicians;

- agree arrangements between specialist clinics which will initiate prescribing and other neurology services;

- assess all potentially eligible new patients and collect initial monitoring data;

- initiate treatment in appropriate cases, provide continuing support for patients and undertake the annual assessments (including data collection);

- agree plans for the initial uptake of patients and provision of monitoring data with the "scheme co-ordinator" when appointed.

Action to facilitate implementation

7. The Association of British Neurologists recommends that initial assessments be undertaken by designated consultants to whom patients should be referred by other neurologists (not directly by GPs). The precise service arrangements and referral protocols will be for local agreement taking into account the current spread of specialist services.

8. The ABN and UK Multiple Sclerosis Specialist Nurse Association have developed a standard referral form to facilitate communication between neurologists and the specialist disease modifying drug clinics where prescribing will be initiated. The referral form is attached as Annex B.

9. The steering group for the scheme will issue details of minimum data set requirements to specialist centres so that treatment can start and the necessary data collected in advance of appointment of a formal co-ordinator who will then require the information to be submitted to them. The ABN is organising a meeting for neurologists involved in the initial assessment of patients to facilitate common standards and a consistent approach to EDSS assessment.

10. Early local discussion between NHS bodies is essential to gauge the extent to which their specialist MS services have the capacity for implementation and continued administration of the scheme and to determine the way in which they will work with other neurology services. Maximum use should be made of nursing support, using the experience of existing MS nurse specialists to train additional nurses. The MS Society operates an MS Nurse Fund, which provides some support for the structured expansion of NHS specialist nurse posts. The Society and participating companies may be able to provide partnership resources for MS nurses employed by the NHS within specialist multi-disciplinary teams. Further information can be obtained by contacting the MS Society at *priorityservices1@mssociety.org.uk*. Provision should be made for adequate administrative support.

11. The UKMSSNA has prepared the suggested checklist for developing a specialist clinic included as Annex C.

Drug costs & funding

12. The costs per patient per year of the drugs being supplied to the NHS for the purposes of the scheme are:

- Avonex (£8,502);
- Betaferon (£7,259);
- Copaxone (£5,823);
- Rebif (£7,513 lower dose & £8,942 higher dose).

13. Ministers have made clear their full commitment to the scheme, for which funding has been provided through normal HA allocations. There should be a clear understanding with the specialist centres about the arrangements for providing the funding to underpin the clinical decisions made under the scheme, including funding for any necessary infrastructure. Funding should be adequate to allow clinicians to prescribe any treatment in the scheme, so that they can take due account of the available evidence on clinical and cost effectiveness, which differs between products, and patient preferences. In this context cost effectiveness is defined as the net cost of treatment divided by expected clinical benefit expressed in Quality Adjusted Life Years (QALYs). Authorities and Trusts should regard funding for the scheme in the same way as positive NICE recommendations for which funds have been provided in baseline allocations. The directions, included as Annex D, place the same statutory funding requirements on NHS bodies as applies to positive NICE recommendations. The likelihood that this scheme would be put in place was taken into account in setting baseline allocations.

14. It has been estimated that the total number of patients in England and Wales who fall within the ABN guidelines might be in the range 7,500 - 9,000 [12.5% to 15% of the estimated patients with MS]. Costs of treatment in a full year could be in the order of £50 million, but is likely to be considerably less than this figure in 2002-3. Health Authorities and Primary Care Trusts should ensure that current SaFF discussions about next year's service provision should encompass the costs likely to be incurred in the operation of this scheme.

15. Commissioners, in conjunction with their designated specialist centres, should establish suitable arrangements for dealing with and funding continuing treatment. Generally, it will be appropriate for the health authority or NHS Trust to make direct payment to the supplier on submission of invoices.

Patient expectations

16. The Department is working closely with the MS Society, MS Trust and ABN to ensure that those patients who may be eligible to participate in the scheme have realistic expectations of and understand the likely time-scale for phasing in the arrangements. The MS Society will be providing information on the scheme to patients and can be contacted by patients on freephone 0808 800 8000. Some question and answer material is included at Annex E. This can be used to provide information about the scheme to patients locally.

Regional Office action

17. Regional Office Directors of Finance and Public Health have been asked to work with Chief Executives of Shadow Strategic Health Authorities to ensure that local health communities collaborate to implement the scheme, including the designation of appropriate funding streams. Specialist commissioning arrangements may provide a suitable model. The key implementation date is 6 May 2002.

This Circular has been issued by:

Hugh Taylor

Director

Annex A

DISEASE MODIFYING THERAPIES FOR MULTIPLE SCLEROSIS: RISK SHARING-SCHEME

Context and overview

1. Paragraph 7.1 of NICE's Final Appraisal Determination (FAD) on beta interferon and glatiramer invites the Department of Health (England) and National Assembly for Wales to "consider what actions could be taken .. to enable any of the four medicines appraised for this guidance to be secured for patients .. in a manner which could be considered to be cost effective." The FAD goes on to suggest discussions with the manufacturers of the four products. Subsequently, the Scottish Executive and Northern Ireland Department of Health, Social Services and Public Safety have decided to opt into these arrangements.

2. In approaching these discussions, the UK health departments[a] have taken as given

   i the judgements on clinical and cost effectiveness set out in the FAD on the basis of modelling work by the consortium led by the Sheffield School of Health and Related Research (ScHARR);

   ii the current (January 2001) guidance from the Association of British Neurologists (ABN) on the selection of patients suitable for treatment with disease modifying drugs.

   Health departments are also mindful that the companies concerned will need to be aware of the potential impact on their global business of any special arrangements made to supply patients in the United Kingdom. The scheme relates solely to the cost effectiveness of the use of these products in the NHS; it is not intended and should not be represented as a further "clinical" trial of the clinical efficacy of the products concerned which have, of course, already been licensed on the basis of their safety, quality and efficacy. Agreement to participate in the scheme will not be taken to imply that companies accept the validity of the ScHARR model, and will not prejudice their rights to take any appropriate action following from NICE's appeal process.

3. Given these preconditions, the scheme will enable

   - MS patients in the United Kingdom meeting the ABN guidelines to receive treatment with disease-modifying drugs, and

   - the NHS to acquire these drugs in a manner which could be considered to be cost effective, while addressing NICE's concerns over the uncertainty relating to the longer-term impact of these drugs.

[a] For the rest of this document we use the shorthand "UK Health Departments" to refer to the Department of Health (England), the National Assembly for Wales, the Scottish Office Department of Health and the Northern Ireland Department of Health, Social Services and Public Safety

4. The scheme has the following basic features (paragraph numbers refer to the detailed arrangements set out below):

i all patients in the United Kingdom meeting the ABN criteria will be eligible to be entered into the scheme and to receive treatment on the NHS with a disease-modifying drug (paras 6-9);

ii the companies manufacturing the four licensed products (the three interferon beta products and glatiramer) will be invited to participate and supply their products for use in the scheme. However, the scheme will continue even if not all companies agree to participate (para 10);

iii each company participating will agree with the health departments at the outset on target outcomes for patients on the respective products. These target outcomes will be selected, on the basis of the analysis over a 20-year horizon of the product's clinical and cost effectiveness in NICE's Final Appraisal Determination (FAD), in a way which if achieved in full will represent an acceptable level of cost effectiveness for the NHS (paras 10-13, 14, 15-18);

iv outcomes for all patients in the scheme will be monitored at annual intervals (paras 19-26);

v if actual outcomes for any individual product fell short of target outcomes (within a margin of tolerance to be agreed, which might be different at different review points) payments to the company concerned will from that point be reduced on a sliding scale to be agreed in advance sufficient to restore the average cost per QALY to an acceptable level of cost effectiveness[a] for the remaining period of the scheme (paras 27-31);

vi health authorities[b] and trusts will pay companies direct under the usual supply arrangements at prices which will be transparent to NHS decision makers; NHS bodies will be expected to fund all treatment eligible under this scheme (para 32-33).

[a] Ie to the DH/NAW "threshold" level which will determine eligibility to participate – see para 12 below
[b] And their equivalents in Scotland and Northern Ireland.

The scheme in detail

5. The starting point for the scheme is the final judgement[a] of NICE's appraisal committee on the clinical and cost effectiveness of the various beta interferon products[b] and of glatiramer, in their licensed indications for treating relapsing remitting and secondary progressive MS, but on the basis of the 20-year ScHARR model.

Treatment for individual patients

6. All MS patients in the United Kingdom meeting the ABN criteria[c, d] will for the duration of this scheme be eligible for treatment on the NHS and will, if they wish and there are no clinical contra-indications, enter the scheme. Choice of treatment (within those participating in the scheme) will be at the discretion of the neurologist in consultation with the patient.

7. Entry to the scheme will be taken to imply consent for certain clinical data to be stored and used, on an anonymised basis, for monitoring patient outcomes for the purposes of the scheme and (subject to the safeguards set out in para 40.iv below) for other *bona fide* research. For some patients, the monitoring data may not be used for assessing possible price adjustments (see eg paras 22-24 below) but these patients will still be eligible for treatment under the scheme.

8. Patients already on treatment at NHS expense at the beginning of the scheme will be free to continue with their existing treatment within the ABN guidelines for as long as they continue to derive clinical benefit. If their existing treatment is one of the treatments accepted for the scheme they may, in the circumstances described in para 22.i below, be asked to give their consent to be formally entered into the scheme and to have their outcomes monitored in the same way as for newly treated patients.

9. After a sufficient number of patients have been entered into the scheme for monitoring purposes (see para 37 below) it should be unnecessary to collect monitoring data on additional patients, except perhaps for specific subgroups or for research not related to the purposes of the scheme. However, even after this point any future patients meeting the ABN criteria will continue to be eligible to join the scheme and to receive treatment with any of the products accepted for the scheme.

Eligibility of products to participate in the scheme

[a] As set out in the Final Appraisal Determination and the underlying analysis by ScHARR, taking into account new estimates of the EDSS-specific utilities based on analysis by ScHARR of data from the MS Trust. Where the Appraisal Committee's views are not clear from the FAD – for instance, in relation to relatively minor adjustments which the Committee concluded will not effect their overall determination, but which may be relevant to the scheme – the Department has sought clarification from NICE.

[b] In the case of Serono's interferon beta 1a (Rebif) the two doses – 22 mg and 44mg – will need to demonstrate separately that they met the criteria for joining the scheme (ie were separately cost effective when assessed using NICE's 20-year model) but will be subsequently monitored as a single product. Evidence from actual clinical practice will be examined to determine the proportion of high to low dose Rebif which will be used on average by a clinician prescribing in line with the product's licensed indications, and this will inform the initial estimate of target outcomes. These estimates will be reviewed at each of the annual 2-year review points in the light of actual usage in the UK.

[c] The full text of the ABN treatment criteria is at Appendix IV.

[d] At present, the ABN criteria only apply to patients of age 18 and over because there is little evidence in younger patients from the original clinical trials. In practice, most neurologists are prepared to consider treatment for younger patients. Neurologists may use their clinical judgement on whether to admit patients under 18 for treatment under this scheme.

10. All the relevant companies have been invited to participate in the scheme. The central features of the agreement will be (a) a target outcome measure representing the impact of treatment on disease progression for patients within the scheme receiving the relevant product, based on the available evidence on clinical effectiveness, (b) an agreement on the price applying to all NHS patients receiving the product (whether these patients are subject to formal monitoring for the purposes of the scheme or not). Taken together these factors, over a 20-year horizon, must represent an acceptable level of cost effectiveness after taking into account those factors recognised as relevant by NICE but not explicitly quantified in the ScHARR model. The exact nature of the outcome measure is discussed below.

11. Cost effectiveness will be assessed in terms of cost per quality-adjusted life year (QALY). For the scheme to operate, a figure will need to be set under which acquisition can be considered "cost effective". This must be consistent across all products. NICE has not adopted a standard "threshold" for its judgements on cost effectiveness. However, a retrospective analysis of appraisal determinations in its first year of operation, as summarised by Sir Michael Rawlins at NICE's annual public meeting, suggests that positive recommendations were in general associated with a cost per QALY of £30,000 or less; higher cost per QALY figures were accepted only if there were special factors accepted as relevant by the Appraisal Committee and not covered by the formal modelling.

12. A number of "special factors" which might be considered to be relevant to the cost effectiveness of treatments for MS have been put to us in discussion. The FAD has specifically referred to two unquantified factors:

    i the impact of treatment on the severity (independent of the frequency) of relapses, and

    ii possible cost offsets from the avoidance of severe levels of disability requiring intervention by the Personal Social Services.

    In the light of all these considerations the threshold will be set, *for the purpose of this scheme only,* at **£36,000**.

13. Estimates of QALY gains, and of offsetting savings from delaying disability, will be taken from the ScHARR 20-year model. In general, estimates of treatment effects will be the "public domain" estimates accepted by NICE as relevant to the use of treatments for relapsing-remitting MS. Exceptions can be considered in one of two circumstances:

    i where companies have made commercial in confidence data available to ScHARR, and NICE have accepted the validity of these data as the basis of estimates of the drug's treatment effect, this can be used in place of the public domain data if it results in a more favourable cost per QALY;

    ii otherwise company data *not* presented to NICE, or not accepted by them as the basis of their estimates of treatment effect, can be used as the basis of the target outcomes in the scheme only subject to the special provisions set out in para 31 below. Any such estimates must be based on methodologically sound data and analysis (preferably from peer reviewed publications) and must relate to an area of genuine

uncertainty in relation to cost effectiveness which is capable in principle of being resolved through the scheme monitoring.

Choice of outcome statistic

14. For the purpose of the scheme, we intend to summarise the disease progression of patients in the scheme into a single (time-varying) outcome statistic. This statistic should

    i. relate closely to those aspects of the presumed treatment benefit of therapy which in NICE's view are still subject to uncertainty,

    ii. be sensitive to deviations between the intended and actual clinical effectiveness of products,

    iii. be readily estimated both from the scheme monitoring data and from the ScHARR model (based in turn on the chosen natural history dataset), and be simple to operate and readily understandable.

    It has been agreed that the statistic to be used for these purposes should be the change relative to baseline of a weighted average of the proportion of patients who have progressed to EDSS scores 4,6 and 7; the weighting factors will represent the expected utility of patients in EDSS ranges 4 to 5.5, 6 to 6.5, and 7 and over, relative to the expected utility of patients in EDSS 0 to 3.5 (see Appendix I for a precise definition)[a].

Initial prediction of scheme outcomes

15. All patients entering the scheme will be assessed for EDSS status; and information on prognostic factors such as sex, age at diagnosis, and if possible duration of disease and number of relapses in the two years before initiation of treatment, will also be collected from clinical records.

16. From the data relating to all those patients initially prescribed a given treatment – with the exception of the exclusions discussed at para 22-24 below – we will use the ScHARR model to predict the expected progress of the cohort through the EDSS states (a) without treatment and (b) with treatment on the assumption of the target reduction in the rate of disease progression. Use of the ScHARR model in this way will automatically adjust for variations in the initial distribution of patients over EDSS states. In addition we will if necessary and possible adjust for variations in the other parameters listed in the previous paragraph.

17. Subject to the completion of some validation work now underway the transition probabilities (the parameters representing the expected speed of disease progression in the absence of treatment) in the ScHARR model will as at present be derived from the Ontario dataset, which contains data on about 1,000 patients followed up for an average of 25 years. If this validation work reveals material differences in rates of disease progression between the model and the actual progress of patients in the Ontario dataset, there will be further discussion

[a] We have consider the case for using all aspects of the treatment benefit of disease-modifying drugs in some form of composite indicator. However, (a) the reduction in relapse frequency forms only a small component of the total QALY gains estimated in the ScHARR model, (b) the FAD suggests that NICE's Appraisal Committee saw no serious uncertainty over the size or long-term nature of this effect. We therefore see no practical value in including reduction in relapse frequency in the risk-sharing arrangements.

between the parties to the scheme on how the ScHARR model should be adjusted to correct for this. Companies will also have the opportunity to compare the rates of disease progression between the Ontario dataset and the placebo arms of the clinical trials of their products.

18. Estimates of the treatment effect of individual products (ie the extent to which they slow disease progression) will in general be the same as those used by DH to assess eligibility to join the scheme (see para 13 above). However, where a product at the proposed price shows better cost effectiveness than the £36K threshold, the target outcome measures will be based on the minimum treatment effect which, applied to the ScHARR 20-year model, just achieves a cost per QALY of £36K.

Monitoring and comparison of actual and predicted outcomes

19. The average predicted disease progression of the cohort receiving the given treatment, over the first t years after the start of the programme, will be summarised into a single outcome statistic D(t), as discussed above. Let $D_e(t)$ be the value of this statistic without treatment, and $D^*_e(t)$ the value with treatment. Let $B_e(t) = D^*_e(t) – D_e(t)$ be the expected benefit from treatment in terms of slowing disease progression for the cohort.

20. The actual disease progression of the cohort is then monitored at regular intervals. This will involve annual measurement of EDSS for all patients in the scheme, with formal review of the reimbursement arrangements every two years[a]. Let $D^*_a(t)$ be the actual value of the test statistic after t years, and let $B_a(t) = D^*_a(t) – D_e(t)$ be the actual benefit from treatment. The key comparison for the assessment of cost effectiveness is between the actual benefit $B_a(t)$ and expected benefit $B_e(t)$, and the difference between actual and expected benefit expressed as a percentage of expected benefit will be referred to below as the "shortfall" in actual compared to expected benefit.

21. For patients who are assessed for the first time as reaching EDSS 4 or above, the assessment will be repeated after a convenient interval (normally 6 months but between 3 and 6 months if this coincides with a visit made for clinical reasons). Only confirmed progression past the EDSS 4 milestone will be included in the calculation of the actual benefit.

Exclusions

22. Data relating to patients in the following subgroups will be excluded from the calculation of predicted outcomes and from the comparison of actual and predicted outcomes used for assessing possible price adjustments:

    i patients already on disease-modifying therapy before 6 May *2002 (the "start date" of the scheme* – see para 37), unless (a) their EDSS had been assessed before starting treatment, (b) the decision to initiate treatment was consistent with the current ABN guidelines, and (c) data on the prognostic factors used for adjusting the predicted outcomes are available;

[a] Practical implementation of these proposals will be complicated by the fact that different patients will have their initial assessment and/or enter onto active treatment at different times (see below). Ideally, the monitoring assessment for each patient should be carried out as closely as possible to the anniversary of the original assessment. However if patients are "recruited" after the target date for completion of the initial take-on their monitoring assessments should be brought forward to the anniversary of the "completion" date, ie the date which forms the basis for the 2-yearly reviews (see para 37 below). This will require some small adjustment to the predicted outcomes.

ii patients who entered the scheme after recruitment for monitoring purposes has closed (either for the scheme as a whole or for the individual product)

However, patients in these subgroups will still be fully eligible to enter the scheme and to receive treatment, and monitoring data for such patients may be collected for possible additional analyses outside the scheme.

23. Patients who are assessed at EDSS 4 or above at entry to the scheme will be monitored in the normal way. However,

    i disease progression for this subgroup will be separately analysed,

    ii the numbers of such patients will be separately calculated, as a proportion of all patients entering the scheme, for the period of the initial uptake of patients[a] – the "prevalent population" – and for subsequent 12-month periods – the "incident population".

    If (a) the treatment shortfall for the subgroup is materially different from that of the main group, and (b) the proportions of patients of EDSS 4 and above differs materially between the prevalent and incident populations, both the predicted outcomes and the monitoring data will be adjusted so that the weight given to this subgroup reflects their proportion in the incident population.

24. Patients who are already on therapy at the start of the scheme and who are included in the formal monitoring arrangements under the provisions of para 22.i will also be monitored as a separate subgroup, and if analysis suggests that the behaviour of this subgroup is very significantly different from that of the main cohort consideration will be given to whether some similar "downweighting" adjustment should be made.

Adjusting for drop-outs and product switches

25. If patients drop out of treatment altogether they should as far as possible continue to be monitored, and their EDSS scores included in the calculation of the "actual outcomes" figure, since this will help to test one of the key uncertainties in the ScHARR model. To maintain comparability, the predicted outcomes using the ScHARR model will be adjusted to use the actual proportion of patients dropping out each year in place of the assumptions originally used by ScHARR; the treatment effect assumed will also be adjusted to the minimum required to meet the £36,000 cost per QALY threshold (see para 18 above). If possible the data should be analysed to show the separate contributions of patients continuing and discontinuing treatment to any discrepancy between predicted and actual outcomes, but it is the combined effect which will be the basis of the formal mechanism for price adjustments.

26. However if patients switch from one product to another they will be excluded from further monitoring (ie the original product should not be "credited" with any subsequent treatment benefit for patients who switch to another product). To avoid possible distortions, their EDSS scores will be projected forwards from the

[a] May 2002 to November 2003 or the "completion date" if later – see para 38.

point at which they switched treatment, using the ScHARR model with the target treatment effect for the original product.

Price adjustments

27. If actual benefit is equal to or greater than expected benefit (within a tolerance margin – see below) then the NHS will continue to make payment at the price agreed at the outset of the scheme. However if actual benefit after t years was below the tolerance margin, the price for the period up to the next review point will be reduced to the extent needed to restore cost effectiveness[a] to the cost per QALY "threshold" determining entry into the scheme (para 12 above), ie £36,000.

28. We envisage that the formal monitoring process for assessing cost effectiveness and pricing adjustments will continue for up to 10 years[b]. At the end of this period payments to companies will continue at the level implied by the final review point. There will be provision for ending the monitoring process at an earlier point, for any of the individual products within the scheme, if both parties agree that the main uncertainties over longer-term outcomes had already been resolved.

29. If any company withdraws from the scheme before the 10-year point they will be required to make immediate repayment of any outstanding amount relating to shortfall in treatment benefit up to that point.

The tolerance margin

30. The "tolerance margin" reflects the fact that monitoring will not give a precise estimate of the true long-term treatment effect but will be subject to a degree of "noise" (and to any uncorrected biases between the natural history dataset used as the basis of predictions and the monitoring data). The health departments seek to achieve a fair balance between the risk borne by the NHS (ie that treatment is actually less effective than monitoring will imply) and the risk borne by companies (ie that treatment is actually more effective). The margin will be 20% at the 2-year review point and 10% at subsequent 2-yearly reviews.

Price adjustments – target outcomes based on company data

31. Special provisions will apply in the exceptional circumstances described in para 13.ii above in which the health departments agree to base the calculation of target outcomes (and the associated cost per QALY on the 20-year model) on company data *not* presented to NICE or not accepted by them. In these circumstances,

    i payments will initially be limited to the price which will just achieve the threshold cost per QALY when evaluated with the ScHARR 20-year model on the basis of the estimate of treatment effect modelled by ScHARR/NICE

    ii at each review point the price will be adjusted (in either direction) on the basis of the actual treatment benefit in such a way as to achieve

[a] This will normally require a slightly smaller percentage reduction in price than the percentage shortfall in actual compared to expected benefit. Calculations will be done using the ScHARR model, with the parameter representing the impact of treatment on disease progression reduced in the ratio of actual to expected benefit, and actual drop out rates as observed for each individual product.

[b] From the "completion date" for the individual product – see para 37 below.

the threshold value of cost effectiveness for the remaining period of the scheme, up to a maximum corresponding to the target outcomes based on the company data or the current list price, whichever is the smaller.

In other words, the "burden of proof" will be reversed – initial payments will be at a lower rate and only increased if actual outcomes were substantially better than those modelled by ScHARR/NICE.

Payments to companies and funding

32. Ministers in all four UK health departments have made clear their full commitment to this scheme, for which funding has been provided through normal HA allocations.

33. Companies participating in the scheme will invoice individual Health Authorities, Primary Care Organisations or Trusts as under current arrangements; in addition they will at regular intervals notify the health departments of the volume of product supplied to the NHS by HA/PCO/Trust. NHS bodies will be expected to fund all treatment prescribed by clinicians in accordance with the scheme, and the health departments will if necessary follow up to ensure full implementation if any difficulties are reported.

Practical implementation

34. Our overall intention is that the scheme should as far as possible build on normal clinical practice, without requiring elaborate additional infrastructure. Data entry should be as simple as possible and arise out of normal patient contacts. Any additional data collection for wider audit or research purposes will need to be discussed separately outside the remit of the risk-sharing arrangements[a].

35. Further details on implementation are given in an accompanying Health Service Circular. The paragraphs below discuss issues relevant to monitoring and price adjustments, and to the eligibility of products to participate in the scheme.

Initial take-on of additional patients

36. It will involve a major exercise to assess all potentially eligible patients and to initiate treatment in those meeting the ABN guidelines. The aim will be to complete this exercise as quickly as is consistent with adequate assessment of starting EDSS scores (and avoiding excessive distortion to other neurology services).

37. Take-on of patients is expected to start, in some centres, in May 2002 and could take up to 18 months. We have therefore taken November 2003 as the target "completion date", ie the date by which sufficient patients will have been entered into the scheme for each eligible product as the basis for monitoring scheme outcomes.

38. The total number of patients in England and Wales likely to be eligible under the ABN guidelines is estimated to be around 7,500 – 9,000 of whom about 5,500 – 7,000 are likely to be included within the formal comparison of intended and actual outcomes. The intention will be to enter the great majority of these patients within the scheme by the target completion date.

39. The completion date may however need to be put back, either for the scheme as a whole or for individual products, in the following circumstances:

    i if for any individual product the number of patients included within the formal monitoring arrangements is less than 1,000, the completion date for that product may by agreement between the company and the health departments be postponed by up to 3 months to allow further patients to be entered;

    ii if for the scheme as a whole the number of patients included within the formal monitoring arrangements is less than 5,000, the steering group (see below) will meet to consider whether postponing the general completion date, by up to 3 months, will materially increase the number of patients. If this seems unlikely, or if after a further 3 months' recruitment the number of patients still falls short of 5,000, the steering group will consider whether it will be reasonable to increase the margins of tolerance to reflect the potential increase in sampling error. Any such increase should not be more than pro rata to the estimated increase in overall sampling error (ie the overall error including that resulting from sampling error in the natural history dataset).

[a] For instance, it may be desirable to collect information relating more closely to patients' experience of the disease process, for instance using the MSIS-29 scale. This information will not however be used in the formal calculations for the scheme.

40. In each case, the "completion date" for the scheme (or for each individual product if they differ) will be the basis for calculating the dates for the 2-yearly pricing reviews.

Company funding for infrastructure support

41. All companies participating in the scheme, and the health departments collectively, will be expected to make an equal contribution to funding the administrative arrangements for the scheme (see below).

42. In addition, company funding for generic specialist MS nurses (ie nurses who provide general clinical support to MS patients not limited to the administration of individual products) will be taken into account in assessing eligibility for entry into the scheme. Any such adjustment will be based on firm proposals for spending in the financial year beginning April 2002 and estimated patient numbers for the same period assuming current market shares, subject to a overall limit (for the scheme as a whole) of £500 per patient per year[a]. The ABN, Association of MS Specialist Nurses, MS Trust and MS Society will be asked for their views on whether the proposals would represent an effective use of resources and are in patients' interests. NHS management will be asked to confirm at each 2-yearly review point that funding has actually been received in line with the proposals, and companies asked for their proposals for funding in the following two years. The allowable price adjustment for the following period will then be reassessed in the light of all information received.

Ongoing monitoring

43. Ongoing monitoring will as far as possible arise out of normal patient contact with their usual clinicians, and should be no more onerous than is essential for the purposes of the scheme. In particular:

i patients will be assessed for EDSS on entry to the scheme, and subsequently at annual intervals;

ii other than as covered by para 21 above there should be no confirmatory assessments even where a patient appears to have progressed to a higher EDSS state; however the scheme coordinator (see below) will arrange for an analysis of EDSS progression by region and centre, and if any apparent outliers are detected will investigate further to ensure that consistent standards are being applied. Where advised by the scheme coordinator, a sample of up to 10% of EDSS assessments will be validated by a second clinician.

Organisational arrangements

44. The following arrangements will apply:

i implementation of the scheme will be overseen by a steering committee with representation from all participating companies, the MS Society and MS Trust, the ABN, the RCN/Association of MS Nurses, and the four UK health departments. Once the scheme is up and running we do not envisage that the steering committee will need to meet more than annually;

[a] If the overall limit is exceeded the allowable contribution from each company will be scaled down pro rata.

ii day to day management will be through a project coordinator, chosen by competitive tender and accountable to the steering group. The project coordinator will have experience in the collection of clinical data from a large number of participating centres (eg someone with clinical trials experience, although the scheme is not a clinical trial) and will be supported by a statistician/analyst and by other supporting staff as required;

iii an adjudication group will oversee and receive the statistical analyses and, at the agreed review points, determine whether any consequential price adjustments were required. This group will be chaired by an individual independent of the direct interests of the parties participating in the scheme[a] and will include a biostatistician and one representative each of (a) the MS Society/MS Trust, (b) the ABN, (c) the health departments, and (d) a "non-aligned" senior industry figure representing the interests of the companies participating. Participating companies and health departments will have the right to make written or oral representations to the group and to see the proposed price adjustments in draft (see Appendix II for further details). They will agree to accept the determinations of the adjudication group; any company which refused to accept a particular determination will be deemed to have left the scheme (see para 29 above);

iv the monitoring data collected for the purposes of the scheme will be owned by the MS Trust and will be made available for the purposes of the scheme to (a) the scheme coordinator, (b) individual companies (in respect of their own products). The steering group will advise the MS Trust on any proposals to use the monitoring data for other *bona fide* research or to publish analyses from the data, but the presumption is that information relating to outcomes for individual products will not be published without the consent of the company concerned. Consent to publish in appropriate circumstances will not be unreasonably withheld, either by the company or by the MS Trust.

Terms of reference for the steering group and for the adjudication group are set out at Appendix III.

Revisions to the terms of the scheme

45. Any aspect of this scheme may be revised, for instance to take account of more recent information, with the mutual consent of all parties to the agreement.

46. In addition, the basis on which individual products may participate in the scheme, and calculation of any subsequent price adjustments, will automatically be reviewed if at any stage NICE revises its view of the clinical and cost effectiveness of all or any of the products. The adjudication group will be asked to carry out the necessary calculations on the basis of the principles set out above and their determination will be final, after consulting the relevant parties.

DH/NAW/Scottish Executive/DHSSPS(NI)

1 February 2002

[a] This could be a clinician from a specialty other than neurology, or a lay person eg with experience in arbitration.

Appendix I

APPENDIX I: AGREED OUTCOME MEASURE

The requirement is for a measure which is based on EDSS measurements, gives particular prominence to the proportion of patients reaching EDSS 4, 6 and 7, and can still be related back to NICE/ScHARR's estimate of the QALY gains from delaying disease progression for the various products. The agreed outcome measure is defined as follows.

Let	$P_0(t)$	be the proportion of patients in EDSS	0 to 3.5 at year t
	$P_1(t)$		4 to 5.5
	$P_2(t)$		6 and 6.5
	$P_3(t)$		7 and over

Let u_0 be the average utility averaged over all patients in EDSS 0 to 3.5 at the end of year 5 in the ScHARR "natural history" base run

u_1, u_2, u_3 be the corresponding averages for patients in EDSS 4 to 5.5, 6 to 6.5, and 7 and over respectively

then the outcome measure (measure of disease progression) is

$$D(t) = -\sum_i P_i(t)\,(u_i - u_0)$$

D should be a good approximation to the QALY loss as a result of disease progression – at year 5 for the natural history base case the approximation will be an identity. It would be possible to make the "fit" even better by allowing the utility weights u_0 etc to vary either with time or with the product being examined, but this would complicate the outcome measure more than is necessary for the purposes of the scheme.

APPENDIX II: PROCEDURE FOR THE ADJUDICATION PANEL

Although the intention is that the determinations of the adjudication panel should be final, with no further right of "appeal", there must be reasonable opportunity for interested parties (in this context companies and health departments) to submit representations, to see the basis of calculations, and to comment on draft proposals. The following arrangements will apply:

1. After each review point the scheme coordinator will arrange for the monitoring data to be collected and analysed and summary statistics sent to interested parties. ("Summary statistics" are those relevant to the possible price adjustments, plus any other contextual statistics which the steering group agrees will be helpful. Individual companies will only see data relating to their own product, health departments will see the full set.)

2. Interested parties then have 4 weeks to submit any observations to the scheme coordinator.

3. The scheme coordinator considers the data and the observations from interested parties and assesses a provisional determination of any price adjustments required. This is sent for comment to all interested parties, with details of all calculations.

4. Interested parties have a further 4 weeks to comment on the provisional determination and may also at this stage ask to make oral representations to the adjudication panel.

5. The panel meets, if needed[a], to consider the proposals from the scheme coordinator and the comments from interested parties and to hear any oral representations.

6. The panel finalises its determination and issues this to interested parties and to all members of the steering group.

[a] We suggest that if no party has commented on the provisional determination, the panel could at the chairman's discretion agree the final determination by written consultation between members.

APPENDIX III: TERMS OF REFERENCE

Steering group

1. To oversee implementation of the scheme and to advise the scheme coordinator and participants on any actions which could help to ensure the smooth and effective entry of patients into the scheme.

2. To receive regular reports from the scheme coordinator on the entry of patients and, in due course, on the results of monitoring of patient outcomes.

3. To resolve any issues of principle relating to the calculation of target outcomes.

4. To consider any proposed changes to the scheme in the light of changing circumstances, in particular those envisaged in para 39.ii of the scheme.

5. To consider any proposals for collecting additional data on patients in the scheme for wider research purposes not directly required for the price adjustment mechanism, or proposals for other research involving patients who are or could in future be entered into the scheme; and to advise the appropriate decision-making bodies.

6. To advise the Multiple Sclerosis Trust on any proposals from scheme members for publishing research based on data collected as an integral part of the scheme.

Adjudication panel

1. To agree the initial calculations of predicted outcomes for each product in the scheme, and any subsequent adjustment of these predictions in the light of changing circumstances (eg lower than expected dropouts).

2. To receive regular reports from the scheme coordinator on the results of monitoring of patient outcomes, and to agree the calculation of any quantities derived from these data.

3. To determine, on the basis of the results of (1) and (2) and of the general principles of the scheme[a], what price adjustments if any are required for products in the scheme.

[a] In the event of any uncertainty over the application of theseprinciples which cannot be resolved to the satisfaction of the panel, they should seek clarification from the Department of Health which will resolve the issue in consultation with the participating companies.

APPENDIX IV: THE ABN CRITERIA FOR STARTING AND STOPPING TREATMENT

[Excerpt from Association of British Neurologists *Guidelines for the use of beta interferons and glatiramer acetate in multiple sclerosis,* January 2001]

(B) TREATMENT CRITERIA B.1 Beta Interferon

B.1.1. Relapsing-Remitting MS

Beta interferon (using any one of the three preparations licensed for this indication) is appropriate treatment and should be offered to patients with relapsing-remitting MS who fulfill the following four criteria:

1. *Able to walk independently.* By way of illustration, the trials in relapsing remitting MS studied patients who were able to walk at least 100 metres without assistance (EDSS<_5.5). A similar 30% reduction in relapse rate was observed in the secondary progressive trials which included more disabled patients, who could walk at least 10 metres with assistance (EDSS<_6.5). We recommend treatment more strongly in the former group (EDSS<_5.5), as the potential for long term benefits, such as delaying the time until walking is no longer possible, appears greater.

2. *At least two clinically significant relapses in the last two years.* Where possible, the patient's history of relapses should have been confirmed by neurological 'examination, or from another source e.g. hospital or general practitioner's records, or by discussion with the patient's main carer.

3. *Adult age group (18 years or older).* No recommendations are possible in the paediatric age group, since trials have not been performed in this cohort.

4. *There are no contraindications* See sections C.4 & C.7.

B.1.3 Secondary Progressive MS

A **consideration of all three** trials suggests that beta interferon is not effective in slowing progression in disability in patients with a non relapsing secondary progressive course. It is therefore not recommended in such patients. In patients with relapsing secondary progressive MS, treatment should only be considered when relapses are the dominant cause of the increasing disability. Specifically, the following criteria should be fulfilled:

1. *Able to walk at least 10 metres with or without assistance.*

2. *At least two disabling relapses in the last two years*

3. *Any increase in disability due to slow progression over the last two years has been minimal.*
4. *Adult age group (18 years or older).* No recommendations are possible in the paediatric age group, since trials have not been performed in this cohort.

5. *There are no contraindications* See sections C.4 and C.7.

B.1.5 Stopping Criteria

In some patients, discontinuation of treatment may become necessary because of intolerable adverse effects, or when a pregnancy is planned. Treatment should be discontinued when it is no longer effective. The following features are likely to indicate lack of efficacy and should normally be used as stopping criteria:

(i) *Two disabling relapses*, as defined by the examining neurologist, within a 12 month period.

(ii) *Secondary progression* with an increase in disability observable over 6 months.

(iii) *Loss of ability to walk*, with or without assistance, persistent for at least 6 months (studies have excluded patients with such disability).

The stopping criteria should be made known to patients and agreed before treatment is begun. For all patients, it is recommended that a formal review of the treatment takes place at two years. If the patient and their neurologist agrees that the treatment is having a beneficial effect, it should be continued.

B.2 Glatiramer acetate

B.2.1 Relapsing-remitting MS

With the caution that clinical efficacy has been limited to reducing relapse rate but not preventing sustained increase in disability in only one substantial placebo-controlled trial to date, glatiramer acetate is an appropriate treatment to reduce relapse frequency in patients with relapsing remitting MS provided they fulfill all the following criteria:

1. *Able to walk at least 100 metres without assistance.*

2. *At least two clinically significant relapses in the last two years.* Where possible the patient's history of relapses should have been confirmed by neurological examination, or from another source, eg hospital or general practitioner's records,or by discussion with the patient's main carer.

3. *Age group 18 years or older.* No recommendations are possible for the paediatric age group, as trials have not been performed in this cohort.

B.2.3 Stopping criteria

In some patients, discontinuation of treatment may become necessary because of intolerable adverse effects, or when a pregnancy is planned. Treatment should be discontinued when it is no longer effective. The following features should normally be used as stopping criteria:

(i) Two disabling relapses, as defined by the examining neurologist, within a 12 month period.

(ii) Development of secondary progressive MS (there is currently no data on the effectiveness of glatiramer acetate in this form of MS).

(iii) Loss of ability to walk, with or without assistance, persistent for at least 6 months (studies have excluded patients with such disability).

The stopping criteria should be made know to and agreed with patients before treatment is begun. For all patients, it is recommended that a formal review of the treatment takes place at two years. If the patient and their neurologist agree that the treatment is having a beneficial effect, it should be continued.

UKMSSNA Standard referral form to MS Clinic for Disease Modifying drugs. **Annex B**

Referrals to be made by Consultant Neurologist only

Aim: Appropriate referrals will be made to the Disease Modifying Drugs Clinic.

Disease modifying drugs in MS-Referral to the Assessment Clinic:

Patient name:

Hospital number:

Date of birth

A clinical diagnosis of Multiple sclerosis was established in:

Centre:

Month:

Date (if known):

Year:

Please refer to the ABN Guidelines on the back of this form for guidance

Clinical abstract

Type of MS:

History of disease:

Relapse rate in last two years:

Mobility status:

Doctor's signature:

Contact number:

Date:

UKMSSNA checklist guide for developing a disease modifying drug clinic in MS
Annex C

Delivering Disease Modifying Drugs a recommended service framework

Disease modifying drugs should not be delivered in isolation from MS services.
This template may be used as a checklist to identify your current level service and identify gaps in service**.**

Essential components of a disease modifying drug clinic in MS

Do you have an infrastructure to deliver a specialist clinic which includes admin. support?

Yes No

Is there a named Consultant Neurologist with an interest in MS to assess patients, prescribe the drug and offer ongoing monitoring?

Yes No

Do you have access to a MS nurse employed within the NHS to commence treatment in your centre who can provide nurse led follow- up clinics?
(Maximum caseload of 100 patients on treatment per MS Nurse)

Yes No

Do you have a system in place to respond to management of MS relapses?

Yes.....No

Desirable components of a MS service

Do you have access to ?

Physiotherapy

Occupational therapy

Continence service

Community outreach teams

MDT Clinics

Rehabilitation

Counselling

Psychology

ANNEX D

NATIONAL HEALTH SERVICE ACT 1977

Directions to Health Authorities and Primary Care Trusts in England

The Secretary of State for Health, in exercise of the powers conferred upon him by sections 17, 97(6) and 126(4) of the National Health Service Act 1977[(a)] and of all other powers enabling him in that behalf, hereby gives the following directions:

Application, commencement and interpretation

1.—(1a) These Directions shall come into force on 4 February 2002 and shall apply to every Health Authority and Primary Care Trust in England.

(2) In these Directions

"the Act" means the National Health Service Act 1977;

"NHS treatment" means treatment provided to a patient under the Act;

"patient" means any person who is receiving NHS treatment;

"the scheme" means the arrangement made between the Department of Health (England), the National Assembly for Wales, the Scottish Office Department of Health, the Northern Ireland Department of Health, Social Security and Public Safety and Biogen Limited, Schering Health Care Limited, Serono Pharmaceuticals Limited, Teva Pharmaceuticals Limited together with and Aventis Pharma Limited dated 1 February 2002([b]) which is annexed hereto as Annex A for the supply and administration of products for the treatment of multiple sclerosis;

"scheme patient" means a patient with multiple sclerosis who is eligible to receive treatment under the scheme on or after 6 May 2002;

"a scheme product" means any of the following products for the treatment of multiple sclerosis manufactured by a company that is a party to the scheme:

Interferon beta-1a: Avonex and Rebif (22mg and 44mg),

Interferon beta – ib: Betaferon,

Glatiramer acetate: Copaxone ;

"treatment" includes prevention, examination and diagnosis.

[(a)] 1977 c. 49. Section 17 was substituted by section 12(1) of the Health Act 1999 (c.8) ("the 1999Act") and was amended by Schedule 5, Part 1, paragraph 5(1) and (3), to the Health and Social Care Act 2001 (c.15). Section 97(6) was amended by the National Health Service (Primary Care) Act 1997 (c.46, section 41(10 and Schedule 2,paragraph 22; the 1999 Act, section 65, Schedule 4 paragraphs 4, and 31(1) and (2), and Schedule 5. The function of the Secretary of State under sections 17 (except in some cases not relevant to these directions), 97(6) and 126(4) are, so far as exercisable in relation to Wales, transferred to the National Assembly for Wales by article 2(a) of the National Assembly for Wales (Transfer of Functions) Order 1999, S.I. 1999/672 as amended by section 66(4) to (6) of the Health Act 1999 (c.8).
([b]) Disease Modifying Therapies for Multiple Sclerosis: Risk Sharing Scheme dated 1 February 2002.

Application of sums paid to Health Authorities and Primary Care Trusts

2. A Health Authority shall, in exercising those functions that it has been directed to exercise by the Secretary of State([a]), apply such amounts of the sums paid to it under section 97(3) of the Act([b])as may be required so as to ensure that:

(a) a scheme product can be supplied or administered under the scheme to a scheme patient;

(b) a scheme product can be supplied or administered to a patient with multiple sclerosis who is not a scheme patient for the purpose of his NHS treatment and who was on 4 February 2002 receiving a course of treatment for this condition with the same product and for the purposes of this direction such course of treatment includes a course of treatment otherwise than under the NHS.

3. A sum paid to a Primary Care Trust by a Health Authority under section 97C(1)(b)([c]) of the Act shall, for the purpose of section 97C(5) of the Act be subject to these Directions to the extent that such sum relates to the exercise by a Primary Care Trust of its functions ([d]).

Signed by authority of the Secretary of State

4 February 2002

A .J. McKeon
Member of the Senior Civil Service
Department of Health

Annex E

Disease Modifying Therapies for Multiple Sclerosis

([a]) S.I.2001/747.
([b]) Section 97(3) was amended by the Health Act 1999 (c.8) ("the 1999 Act"), section 4(2)(b) and (4), sub-section (3AA) was inserted by the Health and Social Care Act 2001(c.15) ("the 2001 Act"), sections 1(1) and (2); subsections (3A) and 3(B) were substituted by subsequent sub-sections (3BB) in relation to the financial year 1999-2000 and subsequent financial years by the 1999Act, section 4(2)(c) and (4), sub-sections (3C)-(3F) were inserted by the 1999 Act sections 8(1) and (2); (although not yet brought into force) sub-section (3C) was substituted by the 2001 Act, sections 2(1) and(2); sub-section (3D) was amended by the 2001 Act, sections 2(1) and (3).
([c]) Section 97(1) was inserted by the Health Act 1999 (c.8), section 3.
([d]) S.I. 2000/695.

Q1 What are the key elements of the risk sharing scheme?

The scheme allows disease-modifying drugs for MS to be prescribed on the NHS to patients who meet criteria set out by the Association of British Neurologists (ABN). Groups of patients will be specially monitored over the lifetime of the scheme. Prices paid by the NHS will be adjusted according to whether expected patient benefits are realised over the long-term.

Q2 Who is eligible for treatment?

All patients with relapsing-remitting MS and those with secondary progressive MS in which relapses are the dominant feature are eligible under the scheme for treatment on the NHS if they meet the ABN criteria.

Q3 What are the criteria for patients with relapsing-remitting MS?

Patients should:

- be able to walk independently (beta interferons) or at least 100 metres without assistance (glatiramer acetate);
- have had at least two clinically significant relapses in the last 2 years;
- be aged 18 or over.

Q4 What are the criteria for patients with secondary progressive MS?

Patients should:

- be able to walk at least 10 metres with or without assistance;
- have had at least two disabling relapses in the last 2 years;
- have had minimal increase in disability due to gradual progression over the last 2 years;
- be aged 18 or over.

Q5 What about patients aged less than 18 years?

The criteria do not cover patients less than 18 years old because there is little evidence about the use of these drugs in younger people. However, specialist neurologists can exercise their judgement and, if it is considered clinically appropriate, prescribe for younger patients.

Q6 What are the ABN guidelines for stopping treatment?

The guidelines say that treatment should continue until it is no longer effective. Two disabling relapses within a twelve-month period, an observable increase of disability due to secondary progression over 6 months, or loss of ability to walk are likely indications that treatment does not have, or ceases to have, the desired beneficial effect and will normally be used as stopping criteria. The specialist will discuss this and agree with patients before treatment starts.

Q7 Who takes the decision to prescribe?

The decision will be taken by specialist neurologists.

Q8 What is the process for getting prescriptions?

Patients will have to be assessed by the neurologist to confirm that the criteria are met and there is likely to be benefit from using the drugs. Many patients eligible under the scheme will already be under the care of a specialist neurologist who should arrange a call up for examination. Non-specialist neurologists should make arrangements to refer likely patients to specialist neurologists for assessment. All clinics should make arrangements for handling referrals from GPs of patients currently not under the care of a neurologist. It may take some time for all patients to be seen and we expect priority to be given to patients according to clinical need.

Q9 When does the scheme start?

The scheme starts to operate on 6 May 2002. This is to give the specialist centres sufficient time to set up the arrangements. Some centres will start later depending on the work that has to be undertaken to set up specialist clinics.

Q10 What is the significance of the 18 month period referred to in the HSC?

The 18 month period is the time that it should take to initiate those patients on the scheme who will be subject to more detailed monitoring over the duration of the scheme.

Q11 What does the monitoring mean for patients?

All patients meeting the criteria will be thoroughly assessed to establish the state of their disability. This is necessary to provide a baseline to monitor the patient's progress with the treatment. Patients will then be followed up at periodic intervals by their neurologist and/or MS nurse, and once a year will have a further assessment of their condition. Information from the initial and subsequent assessments will be sent on an anonymous basis to the co-ordinator responsible for analysing the data needed for the scheme. Patients will be asked to consent to their inclusion in the arrangements to monitor the scheme.

Q12 What happens after 18 months?

New patients will continue to be assessed for eligibility under the scheme using the ABN criteria and those eligible will receive treatment on the NHS.

Q13 Which products are included in the scheme?

Avonex, Betaferon, Copaxone and Rebif (both 22mg and 44mg doses) are all included in the scheme.

Q14 What happens to patients already receiving treatment on 6 May 2002?

All patients receiving treatment on 6 May 2002 may continue with that treatment until the specialist and patient agree that the treatment is no longer effective (see Q6).

Q15 What happens to those patients paying privately for treatment?

Patients receiving private prescriptions for treatment because of local funding or prescribing policies should be treated the same as patients treated on the NHS. This means that the treatment will be funded by the NHS until it is deemed to be no longer effective for the patient. Health Authorities and Primary Care Trusts will make arrangements to fund such treatment from the date of this circular.

Q17 How many patients will be eligible to participate in the scheme?

It has been estimated that up to 9,000 patients may be eligible to receive treatment, but we have no precise estimates of the number that will actually receive treatment because of uncertainties about the profile of the MS population.

Q18 Does the scheme apply to MS patients in Wales, Scotland & Northern Ireland?

Yes, the scheme applies across the UK. The National Assembly for Wales, the Scottish Executive and Northern Ireland Department of Health, Social Services & Public Safety are preparing similar guidance for their NHS bodies.

Q19 What is the status of NICE's guidance on these therapies?

NICE guidance stands. They considered that on the basis of the evidence the treatments were not cost effective unless there was a different approach to acquiring them for the NHS. The scheme brings about that different approach. It ensures that supply of those treatments included in the scheme is cost-effective for the NHS.