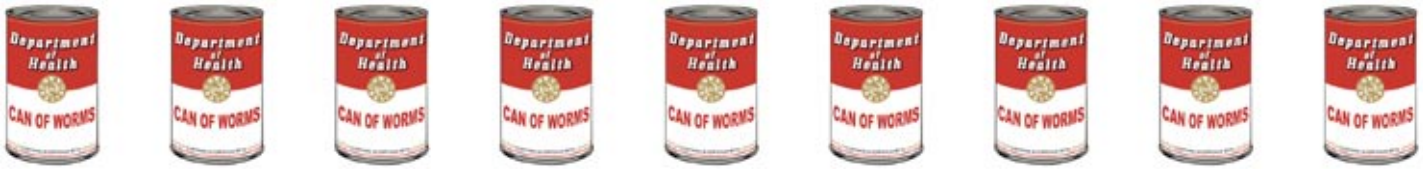

Costly failure of a risk sharing scheme

The NHS is paying for thousands of patients with multiple sclerosis to receive drugs that monitoring data suggest are not effective. **James Raftery** examines what went wrong with the access scheme that facilitated their use

The largest and most ambitious patient access scheme, the UK multiple sclerosis risk sharing scheme, was set up in 2002 after the National Institute for Health and Clinical Excellence (NICE) recommended against use of interferon beta and glatiramer acetate.[1] Under the scheme patients were closely monitored to confirm the cost effectiveness of the drugs, with an agreement that prices would be reduced if patient outcomes were worse than predicted.[2] The first report on the scheme in 2009 showed patient outcomes were much worse than predicted but judged that it was premature to reduce prices.[3] Why did this happen and what can we do to prevent it recurring?

Types of patient access schemes with UK examples

Type of scheme	Example
Financially based	
List price changes	None
List price fixed but discounts linked to:	
No of patients	Erlotinib for small cell lung cancer (cap on total costs)
No of doses	Ranibizumab for age related macular degeneration (cap on No of doses; further doses free)
Patient response	Bortezomib for multiple myeloma (NHS pays only if patient responds)
Outcome based	
Risk sharing (price can rise or fall depending on patient outcomes relative to those expected)	Multiple sclerosis risk sharing scheme

Development of patient access schemes

The high prices charged for many new drugs have led to many health systems requiring proof of cost effectiveness before they are funded. However, decisions often have to be made with limited information: licensing trials are typically short term and of little value for assessing cost effectiveness. Once licensed, drug prices are listed at prices that seldom change. Patient access schemes have developed whereby agreements are made with the manufacturer to vary drug prices according to factors such as the number of patients treated or doses used, the response of the patient, or longer term patient outcomes.

The 2009 Pharmaceutical Price Regulation Scheme, which governs drug pricing, outlined two types of access scheme: those based on finance and those based on outcomes (table).[4] Schemes based on finance involve either changes in list price or discounts linked to the number of patients or doses or to patient responses. Schemes based on responses can help identify patients who will benefit. In outcome based schemes, such as the multiple sclerosis scheme, prices are linked to longer term patient outcomes and hence to cost per quality adjusted life year (QALY). If prices can rise or fall, the risk is shared.

How the multiple sclerosis scheme works

The multiple sclerosis risk sharing scheme established by the Department of Health in 2002 "involves detailed monitoring of a cohort of patients to confirm the cost effectiveness of treatments" (box).[2] All UK patients with relapsing remitting disease were eligible, and 5000 to 7000 were expected to join, making it the biggest and longest cohort study in multiple sclerosis.[5] Prices for the drugs were set close to commercial levels (around £8000 (€9000; $12 000) a patient/year) but were to be reduced if patient outcomes were less than those required to meet a cost per QALY of £36 000.

The NHS was statutorily obliged to fund patients in the scheme. Besides the Department of Health, the scheme's steering group included the four relevant drug companies, the Association of British Neurologists, the Multiple Sclerosis Society and Trust, the Royal College of Nursing, and the Association of Multiple Sclerosis Nurses.

Failings

The first report on the scheme was published in late 2009, with details of patients' outcomes for 2005-7.[3] Disease progression was not only worse than predicted by the model used by NICE,[1] it was worse than that in the untreated control group. The primary outcome—the difference between actual and expected benefit as a percentage of expected benefit—was 113%, well above the 20% tolerance for price changes (any value above 0 indicates that benefit is less than expected). The report stated "the outcomes so far obtained in the pre-specified primary analysis suggest a lack of delay in disease progression."[3]

This dramatic finding did not, however, trigger any price reduction. Instead, the paper reports: "The scientific advisory group considered that it was premature at this stage to reach any decision about re-pricing the drugs without further follow-up and analyses." Various reasons were given, including possible underestimation in the model, that use of historical controls may miss changes in the disease, and the effects of a "no improvement" assumption. Each of these arguments has been strongly contested (convincingly to my mind) by McCabe and colleagues,[6] most of whom took part in the original modelling. However, given the terms of the scheme, such retrospective arguments should be irrelevant.

Besides failing to link prices to outcomes, the scheme proved slow to establish and was costly. It took three years rather than the planned 18 months to recruit 5000 patients. Around 120 extra multiple sclerosis nurses had to be hired

Response on bmj.com "The comment by Raftery that 'outcome based schemes should probably be avoided if at all possible' is fully unjustified by data reported in his article. In addition, this conclusion is drawn by generalising the results of a single experience"
Andrea Messori, Area Vasta Centro, Health Service of Toscana, Firenze and Prato, Italy
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to enable the scheme to operate at 73 centres. At a gross cost of £50 000 for each nurse this is £6m per year. The biggest cost was drugs, at around £40m for 5000 patients. Monitoring the scheme costs around £1m a year, making the total annual cost close to £50m. Since not all patients who are receiving drugs are included in the study the number of patients treated under the scheme is probably higher. If, as suggested by the Multiple Sclerosis Society[7] and the undersecretary for health,[8] 10 000 patients are receiving drugs through the scheme, the cost will be almost double. This may well be the most expensive publicly funded ongoing health related study in the UK, and probably anywhere, ever.

Independent decisions?

The decision not to recommend price changes was attributed to the scheme's "independent scientific advisory group."[3] No such group was mentioned in the 2002 documentation for the scheme,[2] but it seems to be the original "adjudication panel." The independence of this group is questionable. When established it had three independent members (the chair, a biostatistician, and a non-aligned industry figure) plus a representative from each of the health departments, the Multiple Sclerosis Society, the Multiple Sclerosis Trust, and the Association of British Neurologists. The last three of these had appealed against the NICE recommendation not to use these drugs. In addition, the four drug companies had the right to make written or oral representations to the committee and see the proposed price adjustments in draft.

A team from the Sheffield School of Health and Related Research (ScHARR) was originally charged with monitoring patient outcomes. However, it withdrew over concerns about the governance of the scheme. A paper on the scheme written by many of the ScHARR team states: "The commercial risks involved with the scheme led to the involvement of the companies as well as the Department of Health in the scheme's governance. The scheme was re-tendered, but the ScHARR consortium decided not to apply as they [sic] were not happy with the proposed arrangements for data access and publication rights, and the scheme is now being undertaken by a contract research organisation."[9]

The paper's acknowledgements state that the companies "were also represented on the scheme's scientific advisory group, which comments on the draft paper and gave permission for publication." This is hardly a description of an independent scientific advisory group.

No annual reports have been published on the scheme. A report by the Sheffield group to the Department of Health remains unpublished despite parliamentary questions[10] and requests from the Commons health committee.[11] My understanding is that members of the Sheffield team have had to sign confidentiality agreements. The appendix gives what has been published on the terms of reference of the scheme and the known committee members.

Governance independent of vested interests is a key principle in the design of such schemes.[12] An attempt to assess the scheme before the publication of its first results[13] found that its governance arrangements "do not appear to be designed to promote and protect the independence of the scheme." It suggested "given that the majority of the scientific advisory group appear to have a vested interest in the scheme's findings, the enforceability of the scheme is open to question."

Other aspects of the scheme must also be questioned. Firstly, designed to confirm cost effectiveness, it seems to have been unprepared for the possibility that the drugs would be ineffective, something noted in 2003.[14] The use of historical controls was an inherent part of the scheme, which was accepted and refined by the scientific advisory committee in 2002. The decision to pursue "alternative sources of data of progression in untreated patients"[3] at this stage is extraordinary. Secondly, the design of the scheme around the Sheffield cost effectiveness model used by NICE has proved difficult. Several assumptions in the model did not hold in the scheme. One was that those patients whose disease progressed would discontinue taking the drugs—many did not. Another assumption, necessitated by the way the historical control data were reported, was that treatment could at best only slow the decline in patients' disability scores. In the scheme, 38% of patients had improved scores at one year. However, the limitations of the extended disability status scales as a measure of disability were noted around the start of the scheme.[14]

None of these problems constitute compelling reasons for disregarding the terms of the scheme, which specified using the two year results to set the price. The fact that the prices would have had

KEY ELEMENTS OF UK MULTIPLE SCLEROSIS RISK SHARING SCHEME[3 5]

- *Aim of scheme*—To monitor outcomes of drug treatments in cohort of patients in order to adjust drug prices if outcomes are worse than predicted
- *Eligibility*—All UK patients who meet Association of British Neurologists criteria for relapsing remitting multiple sclerosis or secondary progressive disease in which relapses are the dominant clinical feature
- *Type of study*—Prospective observational cohort
- *Cohort study*—Subset of eligible patients
- *Outcomes*—Score on extended disability status scale (EDSS), measured annually
- *Outcome statistic*—Change relative to baseline of weighted average of proportion of patients who have progressed to disability scores of 4, 6, and 7
- *Predicted outcome*—EDSS score required to achieve £36 000/QALY based on the ScHARR model used by NICE
- *Controls*—Historical (Ontario dataset of patients followed up over 25 years)
- *No of included patients*—7500-9000 eligible; 5500–7000 likely to be included in formal comparison
- *Target dates*—Start May 2002. Recruitment to end Nov 2003 (not achieved until 2005)
- *Duration of scheme*—10 years with price setting reviews every two years
- *Stopping rule*—Discontinue when no longer effective, intolerable adverse events, or preparing for pregnancy
- *Funding*—NHS bodies to fund drug treatment. Monitoring study funded jointly by Department of Health and four drug companies
- *Governance*—Steering group with representation from four participating companies, the Multiple Sclerosis Society and Trust, Association of British Neurologists, Royal College of Nursing/Association of Multiple Sclerosis Nurses, and four UK health departments. Adjudication panel with independent chair, biostatistician, non-aligned industry figure, plus a representative from each of the health departments, Multiple Sclerosis Society, Multiple Sclerosis Trust, and Association of British Neurologists.

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Read James Raftery's recent blog on the future of NICE at http://blogs.bmj.com/bmj/

"The biggest losers are the other NHS patients who would otherwise have benefited from the money spent on the scheme"

to be cut to zero (given outcomes were less than those of the controls) is hardly a reason for not proceeding. If patients are to continue to receive drugs through the scheme, big price cuts seem necessary.

Winners and losers

Interested parties will differ on the success or failure of the scheme. The health ministers who set up the scheme may see it as having postponed a difficult confrontation with the multiple sclerosis lobby. All the health ministers at the time the scheme was set up have moved on, as predicted at the time.[5] NICE may see its decision not to recommend use of these drugs as justified. However, it has had to recommend use of a newer and even more expensive (£15 000 per patient) drug for multiple sclerosis, natalizumab, because the scheme means that interferon beta is the "current standard of practice" in the NHS.[15]

The Multiple Sclerosis Society claimed success for the scheme up to 2007 because it "improved care and support for people with MS."[7] However on publication of the results of the scheme in 2009 it withdrew its support. It states that the Department of Health has confirmed that "access to the disease modifying drugs will continue regardless of the success or failure of the research. . . . With up to 10 drug options expected to be available in 2011, action is needed now to ensure fast and equal action to latest treatments."[16] If NICE assesses the cost effectiveness of these new drugs against interferon beta, as happened with natalizumab, the scheme will have advantaged multiple sclerosis over all other diseases.

The views of patients with multiple sclerosis are not known, but, notably, although all eligible patients were assumed to want to enter, a considerable number refused. The two year review acknowledged that "it would have been desirable to have identified patients who were eligible for the scheme but chose not to participate."[3]

The scheme was a success for the drug companies, who sold at close to full price to the NHS. It has also been a success for the companies making natalizumab (Biogen Idec and Elan International), which would not have been recommended by NICE in the absence of the scheme.

For the NHS, however, the scheme can be judged only "a costly failure"[11] as suggested by the House of Commons Health Committee which has been raising concerns about the scheme for several years. The biggest losers are the other NHS patients who would otherwise have benefited from the money spent on the scheme.

The only other patient access scheme that uses outcomes—the Australian scheme for bosentan in pulmonary artery hypertension—may have been more successful. This is partly helped by a smaller patient group (528 patients), a well defined outcome measure (death), and a health system in which negotiation of drug prices is common.[17] However, it too has struggled with issues of governance, ethical permission, and data collection.[18]

What are the lessons more generally for patient access schemes? One is that financially based schemes are preferable to those based on outcomes. Outcome based schemes should probably be avoided if at all possible. For those that do go ahead, it is vital to ensure appropriate governance given the inevitable conflicts of interest. Since a robust control group is essential, policy oriented randomised clinical trials may be required. Monitoring and evaluation of outcomes must be independent of the companies involved. Transparency is essential, involving annual reports, access to data, and rights to publish. Any of these might have helped avoid the current fiasco.

James Raftery professor of health technology assessment, Wessex Institute, School of Medicine, University of Southampton, Southampton SO16 7NS
raftery@soton.ac.uk

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Contributors and sources: JR has provided health economics input to six technology assessment reports for NICE and published several reviews of NICE. He has observed the multiple sclerosis risk sharing scheme since its inception.
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1 NICE. Multiple sclerosis—beta interferon and glatiramer acetate. Technology appraisal 32. 2002. www.nice.org.uk/Guidance/TA32.
2 Health Service Circular HSC 2002/004. Cost effective provision of disease modifying therapies for people with multiple sclerosis. www.dh.gov.uk/dr_consum_dh/groups/dh_digitalassets/@dh/@en/documents/digitalasset/dh_4012214.pdf.
3 Boggild M, Palace J, Barton P, Ben-Shlomo Y, Bregenzer T, Dobson C, et al. Multiple sclerosis risk sharing scheme: two year results of clinical cohort study with historical comparator. *BMJ* 2009;339:b4677.
4 Department of Health. Pharmaceutical Pricing Regulation Scheme 2009. www.dh.gov.uk/en/Healthcare/Medicinespharmacyandindustry/Pharmaceuticalpriceregulationscheme/2009PPRS/DH_090499.
5 Warlow C. Not such a bright idea: the UK risk sharing scheme for beta interferon and glatiramer acetate in multiple sclerosis. *Pract Neurol* 2003;3:194-5.
6 McCabe C, Chilcott J, Claxton K, Tappenden P, Cooper C, Roberts J, et al. Two year results from the United Kingdom multiple sclerosis risk sharing scheme: a commentary. *BMJ* 2009;340:c1786.
7 Multiple Sclerosis Society. The risk sharing scheme for disease modifying therapies in multiple sclerosis. 2007. www.bayerscheringpharma.co.uk/html/news_documents/Risk_Sharing_Scheme_for_MS.pdf.
8 Keen A. Multiple sclerosis: drugs. House of Commons Hansard written answers 28 Oct, 2008. www.publications.parliament.uk/pa/cm200708/cmhansrd/cm081028/text/81028w0029.htm.
9 Pickin M, Cooper CL, Chater T, O'Hagan A, Abrams KR, Cooper NJ, et al. The Multiple Sclerosis Risk Sharing Scheme Monitoring Study: early results and lessons for the future. *BMC Neurology* 2009;9:1.
10 Keen A. Parliamentary written question and answers, 24 November 2008. www.theyworkforyou.com/wrans/?id=2008-11-24f.237791.h.
11 House of Commons Health Committee Top up fees. Para 118. 2009. http://www.publications.parliament.uk/pa/cm200809/cmselect/cmhealth/194i/194i02.htm
12 McCabe C, Stafinski T, Edlin R, Menon D, Banff AED summit. Access with evidence development schemes. A framework for description and evaluation. *Pharmacoeconomics* 2010;28:143-52.
13 Menon D, McCabe C, Stafinski T, Edlin R. Principles of design of access with evidence development approaches. A consensus statement from the Banff summit. *Pharmacoeconomics* 2010;28:109-11.
14 Sudlow C, Counsell CE. Problems with the UK governments's risk sharing scheme for assessing drugs for multiple sclerosis. *BMJ* 2003;326:388-92.
15 NICE. Natalizumab for the treatment of adults with highly active relapsing-remitting multiple sclerosis. Technology appraisal 27. 2007. http://guidance.nice.org.uk/TA127.
16 Multiple Sclerosis Society. Risky Department of Health scheme failing people with MS. Press release 2 Dec, 2009. www.mssociety.org.uk/news_events/news/press_releases/rss_failed.html.
17 Keogh A, McNeil K, Williams TJ, Gabbay E, Proudman S, Weintraub RG, et al. The Bosentan patient registry: long-term survival in pulmonary arterial hypertension. *Intern Med J* 2009 [Epub ahead of print].
18 Owen AJ, Spinks J Meehan A, Robb T, Hardy M, Kwasha D, et al. A new model to evaluate the long term cost effectiveness of orphan and highly specialised drugs following listing on the Australian pharmaceutical benefits scheme: the Bosentan patient registry. *J Med Econ* 2008;11:235-43.

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Continuing the scheme is unjustified

Christopher McCabe and colleagues examine the claims behind the decision not to reduce drug costs in the multiple sclerosis risk sharing scheme

Since 2002 people in England with multiple sclerosis have been able to access disease modifying drugs through a risk sharing scheme.[1] The scheme was set up after the National Institute for Health and Clinical Excellence (NICE) recommended that the drugs should not be used in the NHS because of doubts about their effectiveness and high price. It suggested instead that the Department of Health could work with the manufacturers to make the treatments available to NHS patients in a cost effective manner—that is, at a lower price.[2]

Under the terms of the scheme interferon beta (Avonex, Betaseron, and Rebif) and glatiramer acetate would be made available to NHS patients in the context of a study monitoring disease progression. The data were to be reviewed at two year intervals. If the observed benefit was less than that predicted by the model NICE had commissioned from the Sheffield School of Health and Related Research (ScHARR),[3] which four of us worked on, the drug price would be reduced to achieve a target cost effectiveness ratio of £36 000 (€40 000; $54 000) per quality adjusted life year (QALY).[1]

Since the start of the scheme, 5583 patients meeting the Association of British Neurologist criteria have received one or more treatments, costing in the region of £350m. The first report of effectiveness was not published until last December.[4] The authors of the report, which was published in the *BMJ*, concluded "we found no evidence that these treatments are cost effective."[4] They also state that "we cannot reliably determine whether the current pricing of these drugs represents value for money for the NHS."[4] Despite these findings, the NHS is still waiting for a price review. We examine the credibility of the reasons given for the delay and the implications for the NHS.

Monitoring data

The monitoring scheme compares the observed and expected disease progression using a deviation score. This score measures the difference between the expected and observed benefit from treatment expressed as a percentage of the expected benefit. It takes the value zero if the treatments perform as expected; greater than zero if the benefit is less, and less than zero if the treatment is better than predicted. Expected benefit is derived from a historical Canadian cohort followed up over 25 years, and disability was assessed with the extended disability status scale.[4]

The scheme established a tolerance range of 20% for the deviation score within which the treatments would be deemed to have performed as expected. The primary analysis reports a deviation score of 113%.[4] This means that disease progression of treated patients was greater than expected for untreated patients.[4] Patients who received the drugs are likely to have benefited from fewer relapses, but the drugs have not prevented any disability, and therefore the manufacturers would need to pay the NHS to use the drugs to make them cost effective.

Lack of action

Although the monitoring team concludes that there is no evidence these treatments are cost effective; it also argues it would be "premature, at this stage, to reach any decision about re-pricing the drugs without further follow-up and analyses." It gives three reasons for this view: the validity of the assumption that patients' disability cannot improve; that using historical controls is unsafe if the underlying epidemiology of the condition has changed over time; and that the cost and utility data used in the ScHARR model may have underestimated the impact of the disability avoided through treatment and thus underestimated the value of treatment.

All of these caveats were known at the start of the scheme. Given that they were not deemed sufficiently important to stop the scheme being launched, it is difficult to see how they can justify such an expensive divergence from the scheme rules. Perhaps more importantly, none of them supports the conclusion that the treatments are likely to be cost effective.

What if using historical controls is unsafe?

If the underlying rate of disease progression has increased since the control data were collected, the comparison used in the scheme would underestimate the effect of treatment. However, the literature on the severity of the disease suggests that although the disease is increasing in incidence, it may be less aggressive, rather than more so, in recent cohorts.[5] This may be due to ascertainment bias, and the prudent presumption would be no change. An assumption of increasingly aggressive disease cannot be supported, and continuing with the scheme will not provide additional evidence of this.

What if the costs and utilities used in the model are wrong?

The ScHARR model applies the same costs and utilities to both treated and untreated patients in the same disease state—with the exception of the drug cost.[3] The effect of inaccuracies in these data on estimated cost effectiveness depends on a divergence in the distribution of the treated and untreated cohorts across the scale used to measure disability. However, the observed treated patients do not diverge from the modelled untreated patients, so changing the costs and utility data used in the analysis cannot affect the estimates of cost effectiveness.

What if treatment really reversed progression of disability?

The *BMJ* paper reports that 32% of patients saw some improvement in their disability scores.[4] However, the primary analysis discounted such improvements. If treatment really does reverse disability, it would be wrong to exclude this benefit from the assessment.

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G C Ebers says that outcome measures were flawed

Interferons were introduced for multiple sclerosis in the early 1990s, after US-Canadian trials showed effects on clinical relapse rate and magnetic resonance imaging (MRI) spots, which were taken as surrogate outcomes for disability.[1] The drug companies who marketed the interferons, and later glatiramer acetate, were given extended patent protection under the Orphan Drug Act. Under the terms of this act surrogate markers of response to treatment can be relied on if experts certify their validity. The lack of data on hard outcomes of disability, such as the need to use a stick or wheelchair, was accepted because multiple sclerosis is a 30-40 year disease, with only half of those affected becoming moderately disabled in a decade, and keeping trials intact beyond a few years proved difficult.

Many specialists thought the visually obvious spots on MRI "were the disease." As a result MRI scanning soon became indispensable for multiple sclerosis trials and individual high profile MRI centres capitalised on lucrative contracts with industry. Over the next two decades, little effort was made to validate the suppression of MRI spots against hard disease outcomes. Amid the enthusiasm for short term MRI monitoring of the impact of interferons, their lack of impact on long term disability (despite suppression of MRI spots) in patients with secondary progressive disease was ignored.[2]

The National Institute for Health and Clinical Excellence (NICE) rejected interferons and glatiramer acetate for NHS use on the basis of a pharmacoeconomic analysis that showed, even with best case scenarios for surrogate outcomes, the price of the drugs would exceed guidelines for efficacy in terms of price per quality adjusted life year.[1 3 4] This largely circumvented any debate about whether the drugs were actually effective. Nevertheless, interested parties, including patient groups and charities, were up in arms because there seemed to be a consensus that the drugs worked but were too expensive. The government then made a political decision to make the drugs available within the risk sharing scheme.

Validity of outcome measures

At around the time the scheme was launched, my group's independent analysis of data from the placebo arms of 31 large clinical trials found that the pivotal outcomes to be used in the scheme, including short term disability scores and relapse rates, were not valid surrogates.[5] With no improvement in the treated arms within these original trials, efficacy hinged on preventing the worsening seen in those receiving placebo. The trials had defined disability progression as increases of 0.5 to 1 point on a standardised disability scale (Kurtzke) confirmed at 3-6 months, a measure that is clearly subject to—and jaw droppingly within—inter-rater variability.[6] We found that patients in the placebo group improved just as often as they worsened, by amounts equivalent to the clinical criteria for treatment failure. It was thus evident that what was being measured was random variation and measurement error in imperfectly blinded studies.[5]

So if the disability measures were not measuring disability, what about the MRI changes? Multivariate analysis of data from the placebo arms found that changes in the MRI spots made no independent contribution to end of trial outcome; the effect of the changes was accounted for by clinical features such as duration of disease—something that can be measured at no cost.[7]

Thus the only outcome measure that remained was relapse frequency—and this was unambiguously reduced in patients undergoing treatment in the risk sharing scheme. However, total relapse numbers do not predict the time to disability or death. Although relapse frequency in the first two years after onset has some association with long term outcome,[8] participants in the pivotal trials of interferon and glatiramer acetate had disease durations of several years.[1 3]

Long term data

Although the drugs have been licensed for 20 years, we still have no clear evidence on long term outcome. This is because the FDA failed to tie approval of interferon to mandatory follow-up for hard outcomes in the original trial patients, as had been suggested, and did not enforce its requirement for validation of the original surrogates.[9] The agency, beset by aggressive criticism from Congress, shifted the onus for gauging effectiveness onto practising physicians. Many US and EU physicians failed to perceive the added responsibility. A Cochrane review had conceded very short term efficacy only.[10] Evidence from more recent long term studies is not definitive and ascertainment is suboptimal.[11-13]

The sobering interim findings from the risk sharing scheme spotlight important broad issues about the importance of determining efficacy in chronic diseases, in particular, the methods required to do this. The scheme also emphasises the "fragility" of adopting surrogate outcomes of impact. Shortcuts are wanted and needed, but measures with face validity and formal validation remain essential.

The risk sharing scheme lacks randomisation, parallel control groups, and blinding of patient or examiner. It is completely reliant on data on natural course from a previous generation. That said, it may be possible to evaluate hard outcomes over time, and Boggild and colleagues are right that it is too early to make conclusions about efficacy.[14] Who could have predicted that trials exposing patients to substantial risks would continue for two decades using the same unvalidated surrogates?

More generally, the scheme's findings raise questions about industrial-academic relationships and their governance. The scheme may have been well intentioned, but perhaps the public interest would be served by an independent inquiry. As McCabe and colleagues emphasise, expenditures of £0.5bn entail opportunity costs that must now be weighed against any benefit of these therapies.

G C Ebers Action Research professor of clinical neurology , University of Oxford, John Radcliffe Hospital, Oxford OX3 9DU
George.Ebers@clneuro.ox.ac.uk

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1 INFB MS study group. Interferon beta-Ib is effective in relapsing/remitting multiple sclerosis: I. Clinical results of a multicenter randomized trial. *Neurology* 1993;43:655-61.
2 North American Study Group on Interferon beta-1b in Secondary Progressive MS. Results from a 3-year controlled study. *Neurology* 2004;63:1788-95.
3 Jacobs LD, Cookfair DL, Rudick RA, Herndon RM, Richert JR, Salazar AM, et al. Intramuscular interferon beta-1a for disease progression in relapsing multiple sclerosis. *Ann Neurol* 1996;39:285-94.
4 Johnson KP, Brooks BR, Cohen JA, Ford CC, Goldstein J, Lisak RP, et al. Copoplymer 1 reduces relapse rate and improves disability in relapsing-remitting multiple sclerosis: results of a phase III multicenter, double-blind, placebo-controlled trial. *Neurology* 1995:43:1268-76.
5 Ebers GC, Heigenhauser L, Daumer M, Lederer C, Noseworthy JH. Disability as an outcome in MS clinical trials. *Neurology* 2008;71:624-31.
6 Goodkin DE, Cookfair D, Wende K, Bourdette D, Pullicino P, Scherokman B, et al. Inter- and intrarater scoring agreement using grades 1.0 to 3.5 of the Kurtzke expanded disability status scale (EDSS). *Neurology* 1992;42:859-63.
7 Daumer M, Neuhaus A, Morrissey S, Hintzen F, Ebers GC. Magnetic resonance imaging as an outcome in MS clinical trials. *Neurology* 2009;72:705-11.
8 Weinshenker BG, Bass B, Rice GPA, Noseworthy J, Carriere W, Baskerville J, et al. The natural history of multiple sclerosis: a geographically based study. II. Predictive value of the early clinical course. *Brain* 1989;112:1419-28.
9 Ebers GC. Preventing multiple sclerosis? *Lancet* 2001;357:1547.
10 Filippini G, Munari L, Incorvaia B, Ebers G, Polman C, Amico R, et al. Interferons in relapsing remitting multiple sclerosis: a systematic review. *Lancet* 2003;361:545-52.
11 Kappos L, Traboulsee A, Constantinescu C, Erälinna J, Forrestal JF, Jongen P, et al. Long-term subcutaneous interferon beta-1a therapy in patients with relapsing-remitting MS. *Neurology* 2006;67:944-53.
12 Ford C, Goodman AD, Johnson K, Kachuck N, Lindsey JW, Lisak R. Continuous long-term immunomodulatory therapy in relapsing multiple sclerosis: results from the 15-year analysis of the US prospective open-label study of glatiramer acetate. *Multiple Sclerosis* 2010;16:342-50.
13 Ebers GC, Reder AT, Traboulsee A, Li D, Langdon D, Goodin D, et al. Long-term follow up of the original interferon-ß1b trial in multiple sclerosis: design and lessons from a 16-year observational study. *Clin Ther* 2009;31:1724-36.
14 Boggild M, Palace J, Barton P, Ben-Schlomo Y, Bregenzer T, Dobson C, et al. Multiple sclerosis risk sharing scheme: two year results of clinical cohort study with historical comparator. *BMJ* 2009;339:b4677.

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"If an assessment had been completed after the first two years, the NHS could have saved up to £250m already"

The authors suggest three reasons why recorded disability could improve between assessments—recovery from relapse, natural fluctuations, and measurement error.[4] Neither recovery from relapse nor measurement error would represent real improvements in the underlying disability state. Therefore it is appropriate for disability reversals due to either of these causes to be excluded from the assessment.

Natural fluctuation is not defined by the authors, but we interpret it to mean real changes in domains of health measured by the extended disability status scale (EDSS), which although not severe enough to be diagnosed as relapse or recovery from relapse, could move some patients across EDSS thresholds. If fluctuations are more common among treated patients, it means treatment makes the symptomatic experience of the disease less rather than more stable, which would have a negative impact on the value of the treatment.

Research on the measurement of disability in multiple sclerosis is increasingly concluding that the EDSS is a poor measure of disability. Ebers and colleagues analysed the placebo arm data of more than 30 trials and concluded that none of the measures of disability used in the pivotal trials leading to regulatory approval, including the EDSS, were fit for purpose.[6] Other authors have reported that early disease activity is a poor predictor of disease course and particularly time to major disability—that is, becoming wheelchair bound.[7] Given these problems, the observed improvements in EDSS scores are more likely to reflect the limitations of the scale as a measure of disability in multiple sclerosis than any true benefit from therapy that should be considered by the risk sharing scheme.

Lessons for the National Health Service

None of the proffered reasons for delaying the price review withstand critical assessment. So

Alastair Compston says that patients benefited

When four drugs were licensed for the treatment of relapsing-remitting multiple sclerosis in the mid-1990s, patients sensed that at last something could be done to modify the course of their illness. But the decision of the National Institute for Health and Clinical Excellence (NICE) that these drugs were not cost effective soon dashed those hopes. Behind the scenes a risk sharing scheme was designed that would provide access to the drugs but without compromising the NICE decision. This threw down a gauntlet to the drug companies: demonstrate a cost per quality adjusted life year (QALY) of £36 000 (€42 000; $53 000) or reduce your prices.[1]

The first report on 3686 patients (86% of those recruited) with relapsing-remitting multiple sclerosis in the scheme showed that patients did less well on the licensed therapies than expected from the natural course of multiple sclerosis.[2] Several reasons were given why this resoundingly negative result should be interpreted cautiously, and the scientific advisory committee decided that it would be premature to recommend re-pricing the drugs. Furthermore, as the terms of the scheme allowed, the group decided to use an alternative source of data on natural course of the disease (from Vancouver, Canada) for all further evaluations.

Criticisms

Christopher McCabe and colleagues are critical of what became of the risk sharing scheme.[3] All but one of these authors had worked on the pharmacoeconomic model used by NICE or had participated in setting up the scheme. They are derisory about the failure to recommend price reductions based on the findings and dismiss the mitigating circumstances that might have confounded the first-pass two year results. No organisations involved from the outset, other than themselves, escape reprimand. They say the scheme has already unnecessarily cost the NHS around £250m and should be closed down. James Raftery also considers that the risk sharing scheme has been a fiasco.[4] Everyone is blamed—the scientific advisory group, government ministers, NICE, the MS Society, and the drug industry.

Are these shrill cries justified? The multiple sclerosis risk sharing scheme achieved what was intended. People with multiple sclerosis in the United Kingdom were treated through the NHS; the authority of NICE was not compromised; and the principles of cost effectiveness were maintained. The scheme aimed to achieve managed entry of a product with high cost and uncertain efficacy into the prescribing arena of the NHS.

Did it function according to protocol? Not entirely. It moved slowly but reported within a reasonable time (18 months) after the first two year period of observation. Was its governance adequate? Probably not, even though the scientific advisory group has an independent chair and five members who have no conflicts of interest. Were the terms of reference delivered? Self evidently, they were not. Although drug companies reduced their prices at the start of the scheme, no changes have since been made.

Next steps

Many who once supported the scheme now do not; others remain loyal. Probably, no one expected that the first analysis would show a worse clinical course in treated patients than controls. But the result is credible. Attempts to force drug companies to repay costs would be likely to trigger complex legal arguments given the debate over methodological issues. So should the risk sharing scheme now be closed and the financial losses written off? Not until after the second analysis, due late in 2010, that uses the new control group and aims to resolve many other ambiguities identified, has reported.

Regardless of the scheme's outcome, it has advanced the situation for people with multiple sclerosis. Now that the principles of when and who to treat are better understood, more effective treatments can be developed. The culture and platform for prescribing and managing this difficult disease, and the specialist teams who support these patients, are also infinitely better in 2010 than they were in 2002. The risk sharing scheme has contributed to these welcome advances in the management of multiple sclerosis.

Alastair Compston professor of neurology, Department of Clinical Neurosciences, University of Cambridge, Cambridge
alastair.compston@medschl.cam.ac.uk

Competing interests: AC was consultant adviser in neurology to the chief medical officer in 2002 and instrumental in developing the concept of a risk sharing scheme for multiple sclerosis; he is president of the Association of British Neurologists, which spoke on behalf of patients in 2002, and coauthor of its guidelines for treating multiple sclerosis; he is principal investigator on two phase III clinical trials of alemtuzumab, for which applications for licensing and NICE approval will be submitted in 2012.

1 Cost effective provision of disease modifying therapies for people with multiple sclerosis. *Health Service Circular* 2002 Feb 4. (HSC 2002/004.)
2 Boggild M, Palace J, Barton P, Ben-Schlomo Y, Bregenzer T, Dobson C, et al. Multiple sclerosis risk sharing scheme: two year results of clinical cohort study with historical comparator. *BMJ* 2009;339:b4677.
3 McCabe C, Chilcott J, Claxton K, Tappenden P, Cooper C, Roberts J, et al. Continuing the multiple sclerosis risk sharing scheme is unjustified. *BMJ* 2010;339:c1786.
4 Raftery J. Multiple sclerosis risk sharing scheme: a costly failure. *BMJ* 2010;339:c1672.

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why does the scientific advisory group consider a price review to be premature.[4] The answer may lie in the governance arrangements of the scheme. The manufacturers, patient groups, clinicians, and the Department of Health are represented on the scientific advisory group. All these bodies have a vested interest in maintaining the status quo. The budget holders, who pay for these drugs, with responsibility for the health of populations served by the NHS, are not represented on the scientific advisory group, and as a result there is no countervailing influence on the group's decision making. To be truly independent, the scientific advisory group should resemble the data monitoring committee of a clinical trial. Without such independence, hard decisions, such as recommending a price reduction or closure of the scheme, are unlikely to be made.

The delay in the publication of these results is a further cause for concern. Depending when the majority of patients started treatment, the first analysis has reported between two and five years after the data became available. The annual drug cost of the scheme is reported to be around £50m.[8] If an assessment had been completed after the first two years, the NHS could have saved up to £250m already. Why has it taken this long? Again, the answer may lie in the governance arrangements. Day to day management of the scheme is the responsibility of the Multiple Sclerosis Trust, which campaigned for funding of these treatments and appealed against the NICE recommendation that these treatments were not cost effective.[9] There is a tension between its historical position as a proponent of the value of these treatments and its current responsibility to deliver analyses that could lead to their withdrawal from NHS practice. Good governance requires that those charged with delivering these schemes are demonstrably free of such conflicts.[9]

The final lesson we draw from the scheme is for clinicians rather than government. At the time of the NICE appraisal, many clinicians considered it unethical to undertake a randomised controlled trial of these drugs.[4] When decisions have no opportunity cost for other patients, such a position is defensible, but when treatment is funded at the expense of other patients' health care, it is questionable whether it remains so. When the key uncertainty in the evidence base for a new product relates to its effectiveness, a randomised controlled trial is likely to be the quickest, most efficient, and most ethical strategy.

Christopher McCabe professor, Academic Unit of Health Economics, Leeds Institute of Health Sciences, University of Leeds, Leeds LS2 9PL
Jim Chilcott senior research fellow, School of Health and Related Research, University of Sheffield, Sheffield
Karl Claxton professor, Centre for Health Economics, University of York, York
Paul Tappenden senior research fellow, School of Health and Related Research, University of Sheffield, Sheffield
Cindy Cooper senior research fellow, School of Health and Related Research, University of Sheffield, Sheffield
Jennifer Roberts professor, Department of Economics, University of Sheffield
Nicola Cooper senior research fellow, Department of Health Sciences, University of Leicester, Leicester
Keith Abrams professor, Department of Health Sciences, University of Leicester, Leicester
Correspondence to: C McCabe **c.mccabe@leeds.ac.uk**
Contributors and sources: CMcC, JC, PT, and KA worked on the development of the ScHARR model used in the NICE appraisal and the risk sharing scheme. JC, PT, JR, CC, and KA were members of the academic team that set up the risk sharing monitoring study between 2002 and 2005. KC was a member of the NICE appraisal committee that considered the disease modifying therapies for multiple sclerosis. He also advised on the construction of the ScHARR model.
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1 Department of Health. Health service circular HSC 2002/004. Cost effective provision of disease modifying therapies for people with multiple sclerosis. DH, 2002. February
2 National Institute for Health and Clinical Excellence. Beta interferon and glatiramer acetate for the treatment of multiple sclerosis. Technology appraisal guidance No 32. NICE, 2002.
3 Chilcott JB, McCabe C, Tappenden P, O'Hagan A, Cooper N, Abrams K, et al. Modelling the cost effectiveness of interferon beta and glatiramer acetate in the management of multiple sclerosis. *BMJ* 2003;326:522-7.
4 Boggild M, Palace J, Barton P, Ben-Shlomo Y, Bregenzer T, Dobson C, et al. Multiple sclerosis risk sharing scheme: two year results of clinical cohort with a historical comparator. *BMJ* 2009;339:b4677.
5 Tremlett H, Paty D, Devonshire V. Disability progression in multiple sclerosis is slower than previously reported. *Neurology* 2006;66:172-7.
6 Ebers GC, Heigenhauser L, Daumer M, Lederer C, Noseworthy JH. Disability as an outcome in MS clinical trials. *Neurology* 2008;71:624–31.
7 Confraveux C, Vukusic S. Age at disability milestones in multiple sclerosis. *BrainAdvanced Access* 2006;129:595-605.
8 Keen A. Multiple sclerosis: drugs. House of Commons Hansard 2008 Oct 28:col 920W. www.parliament.the-stationery-office.co.uk/pa/cm200708/cmhansrd/cm081028/text/81028w0029.htm.
9 Menon D, McCabe,C, Stafinski T, Edlin R. Principles of design of access with evidence development approaches: a consensus statement from the Banff summit. *PharmacoEconomics* 2010;28:109-11.

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FROM BMJ.COM

Domhnall MacAuley on US surgeon general Regina Benjamin

One of her ambitions is to climb Kilimanjaro. It's a tough climb even for likes of Regina Benjamin, surgeon general of the United States.

When she addressed the American College of Sports Medicine meeting I was attending in Baltimore, MD, she captivated the audience. She began with a story from everyday practice—a story of a simple mistake. In an effort to help a patient who could not afford a medication, she paid the price. In what many in the audience would have considered a kind and generous gesture, she saw on the woman's face the magnitude of her misjudgment. She had taken away her patient's dignity. It was this humanity and understanding that shone through throughout the day.

When she took off the uniform jacket she was everything you might expect of your family doctor: open, welcoming, and attentive. After 23 years working as a family physician in the Gulf Cost village of Bayou La Batre (population 2300), her commitment to family medicine is unquestionable. As America's doctor, bringing the principles of patient centred primary care to a population of 300 million is a real challenge, but she thinks of it as just a larger practice list.

Cost effectiveness in health care she considers an obvious principle. There will be objections but they will reduce with time. She intends to actively promote primary care research but doesn't, however, see primary care in isolation and emphasised the need to work with specialists. She is also acutely aware of social inequality and the needs of the less privileged. Such was her commitment to her community that she herself invested in rebuilding her practice after two hurricanes and a major fire.

As the interview progressed, she relaxed and we chatted about patients and practice. She found wearing the uniform of the surgeon general initially quite strange and, for a doctor whose patients often called her by her first name, it took time to get used to military officers saluting. She has clearly navigated successfully around medical politics, and if honesty and sincerity are the key values, I have no doubt she will succeed to make a major difference to people's health in the US.

Domhnall MacAuley is primary care editor, *BMJ*

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