Problems with UK government’s risk sharing scheme for assessing drugs for multiple sclerosis

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The government plans to make interferon beta and glatiramer acetate available to patients with multiple sclerosis through a risk sharing scheme, despite lack of evidence of cost effectiveness. Sudlow and colleagues argue that the money would be better spent on independent research.

The National Institute for Clinical Excellence (NICE) recently announced that interferon beta and glatiramer acetate were not cost effective treatments for multiple sclerosis and could not be recommended for NHS funding. As a result, the Department of Health and the manufacturers developed a “risk sharing scheme” aimed at providing these drugs more cost effectively. Treatment will be provided to ambulating patients with two or more disabling relapses in the past two years (about 15% of all patients with multiple sclerosis) and their progress monitored over 10 years. However, the scheme has several scientific and practical problems that we believe limit its ability to improve the care of patients in the long term. In this paper, we review the quality of the evidence on which NICE and the Department of Health reached their decisions, consider some of the problems of the risk sharing scheme, and suggest an alternative approach.

Methods

We identified randomised trials of disease modifying drugs in patients with multiple sclerosis from systematic reviews, the Cochrane controlled trials register, and the treatment guidelines of the Association of British Neurologists. We also got information from discussion with colleagues, including several international experts in multiple sclerosis. We used Cochrane RevMan software to produce summary relative risks.

What is the evidence that the drugs are effective?

NICE considered data from placebo controlled trials of interferon beta and glatiramer acetate but did not assess azathioprine, which has also been widely tested in multiple sclerosis. The three drugs produce a similar reduction (15-30%) in the relative risk of a relapse at two years (fig 1). Interferon beta and glatiramer may also reduce disability (fig 2), but appropriate data were not available for azathioprine. Although interferon beta, glatiramer, and azathioprine were all associated with more patient withdrawals than placebo, the side effects were generally mild. Azathioprine may be associated with a small increased risk of neoplasia after 10 years of treatment, but there is not enough long term experience with either interferon beta or glatiramer to exclude an increased risk of cancer.

These results, although promising, are based on limited, short term data (a few hundred patients for each drug, usually followed up for no more than two years). We therefore do not know whether the effects are sustained over the long term. Several other previously noted methodological problems also limit the interpretation of the results and may have biased them in favour of active treatment. These include uncertainty about the adequacy of randomisation, which is not always clearly described; unavoidable patient unblinding; difficulty interpreting the outcome of confirmed progression of disability, which was generally based on the widely criticised expanded disability status score; substantial losses to follow up in a few trials; publication bias (the largest randomised trial assessing interferon beta in secondary progressive multiple sclerosis showed no overall effect on progres-
sion of disability but remains unpublished); and funding of the trials by pharmaceutical companies, which own the data and were involved in the trials’ design, conduct, analysis, and reporting. Although many trials had independent data monitoring committees, it is concerning that some data from some trials have not been placed in the public domain.

Limitations of NICE’s assessment of cost effectiveness

NICE’s conclusions on cost effectiveness were based mainly on an analysis commissioned from the Sheffield University School of Health and Related Research. The researchers calculated the cost per quality adjusted life year (QALY) gained at 5, 10, and 20 years after starting treatment (table). The model suggests that the threshold of £36 000 per QALY (set by the Department of Health for the risk sharing scheme) is approached only after 20 years.

Although this economic model is probably the best available for multiple sclerosis, it has several unavoidable flaws. Firstly, it depends on the quality of the evidence for effectiveness of treatment, which, as highlighted above, has major deficiencies. Treatment effects were estimated mainly from published reports. Two companies provided some additional confidential data, one refused, and one withdrew its additional data after seeing its effects on the results. Second, because of the lack of long term placebo controlled randomised trials, the model compares the effects of treatment with the experience of a cohort of 1000 Canadian patients with multiple sclerosis recruited in the 1970s and 1980s and followed for an average of 25 years. It assumes that treatment remains effective for as long as the patient takes it and that the benefit accrued is maintained after treatment stops. NICE acknowledges that this extrapolation of treatment effects becomes increasingly unreliable as the time horizon is increased.

Thirdly, the model is heavily influenced by assumptions about future discounting of costs and benefits, the proportion of patients who stop treatment prematurely and what happens to them, and the way in which the costs of disability related to multiple sclerosis are estimated (table). Finally, it does not consider azathio-

*Data from two large trials (>1500 patients) are not included. Data were not available in the SPECTRMS paper (p=468), and the US secondary progressive trial (n=998) remains unpublished; however, the reported results for these two studies for relapse were similar to those of other interferon beta trials. The “Y” represents the uncertainty about the result for this group.

Fig 1 Risk of relapse of multiple sclerosis at about two years. Numbers were obtained from a systematic review of interferon beta in relapsing-remitting multiple sclerosis as well as individual trials. There was no statistical heterogeneity between individual trials contributing to summary statistics.

<table>
<thead>
<tr>
<th>Drug and type of disease</th>
<th>No with relapse/No randomised (%)</th>
<th>Relative risk (95% CI)</th>
<th>Relative risk (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Interferon beta</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Relapsing remitting*†‡</td>
<td>3</td>
<td>257/466 (56)</td>
<td>315/363 (70)</td>
</tr>
<tr>
<td>Secondary progressive*‡</td>
<td>1</td>
<td>194/360 (54)</td>
<td>224/358 (63)</td>
</tr>
<tr>
<td>Clinically isolated syndrome*‡</td>
<td>2</td>
<td>98/247 (28)</td>
<td>142/345 (41)</td>
</tr>
<tr>
<td><strong>Glatiramer</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Relapsing remitting*§</td>
<td>2</td>
<td>94/150 (63)</td>
<td>111/151 (74)</td>
</tr>
<tr>
<td><strong>Azathioprine</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Relapsing remitting, secondary progressive, or primary progressive*§</td>
<td>5</td>
<td>134/279 (48)</td>
<td>190/266 (66)</td>
</tr>
</tbody>
</table>

*Data from two large trials (>1500 patients) are not included. These two trials did not show any overall effect of interferon beta on disability progression. The broken arrow shows that the result is likely to be a substantial overestimate of the benefit of treatment.

Fig 2 Risk of progression of disability at about two years. Numbers were obtained from a systematic review of interferon beta in relapsing-remitting multiple sclerosis as well as individual trials. There was no statistical heterogeneity between individual trials contributing to summary statistics.
prime, which has an annual treatment cost of only about £300 a patient.

**Scientific flaws of risk sharing scheme**

The risk sharing scheme plans to use the Sheffield model as a basis for assessing and adjusting the real life cost effectiveness of interferon beta and glatiramer.

Azathioprine has been ignored. Patients meeting the Association of British Neurologists treatment criteria will be assessed annually for 10 years to determine the rate of progression from no disability (expanded disability status score < 4), through mild (4-5.5) and moderate (6-6.5), to severe disability (≥ 7). The effects of each treatment will be determined every two years by comparison with the expected progression without treatment derived from the Canadian cohort. The effects treatment experiences have been agreed with the drug companies, and if these are not achieved, the drug costs will be reduced to maintain cost effectiveness at a threshold of £36 000 per QALY over 20 years. Unfortunately, the scheme has several major problems.

**Non-randomised comparisons**

The Department of Health circular states that the scheme is not a further trial of clinical effectiveness but a study to establish long term cost effectiveness. However, a reliable estimate of long term cost effectiveness first requires a reliable estimate of long term clinical effectiveness. This will not be achieved by comparing a modern cohort of patients treated in the United Kingdom with a historical cohort of Canadian patients since non-randomised comparisons give unreliable, biased results.

**Lack of power calculations**

The scheme will include about 7000 patients in England and Wales (plus more patients from Scotland), but the circular gives no power calculations to justify this number. It recognises that the non-randomised comparison will be biased and that chance may lead to imprecise measures of treatment effect. However, rather than randomising large numbers of patients, the Department of Health proposes to incorporate a tolerance margin of 10-20% in the comparison between the treated and untreated cohorts. It does not explain how this margin was chosen; nor is it clear whether the margin represents a relative or absolute difference in outcome.

**Other biases**

The risk sharing scheme is subject to several other biases. Firstly, patients already receiving treatment at the start of the scheme will be included if they fulfilled the inclusion criteria at the start of treatment and their pre-treatment disability score and other prognostic data are available. This will bias the comparison in favour of treatment because patients who started and then stopped treatment before the scheme because of adverse effects or perceived lack of effectiveness will not be included.

Secondly, the circular states that patients who stop taking treatment during the scheme are “to be monitored as far as possible.” This is not good enough. It is essential to follow up such patients because we do not know how patients respond once they stop treatment. This information is critical to the cost effectiveness calculations.

Thirdly, the scheme does not intend to have blinded assessment of outcome. Unblinded assessment of outcome in multiple sclerosis trials can result in overestimates of the effect of treatment on progression of disease. Hence, an apparent treatment benefit may simply be due to the expectation bias of patients and their neurologists or specialist nurses. An additional competing interest bias may be introduced by unblinded assessment of outcome being done by specialist nurses whose salaries are paid for by pharmaceutical companies.

**Calculation of cost effectiveness**

The estimates of cost effectiveness depend critically on the various assumptions used in the modelling process, but the actual assumptions to be used are not mentioned in the circular. These will have to be made explicit and justified before the scheme starts.
Other issues
The circular does not state what will happen if a treat-
ment seems ineffective. Neither does it tell us which
patients will be included in the analyses or whether
these will be on a truly intention to treat basis. Ideally, a
proper intention to treat analysis would be ensured by
information on patients giving their consent being
telephoned or faxed immediately to a central site. This
would avoid the loss or non-registration of patients
who do not do well on their chosen treatment.
However, no details of this sort have been provided.

Practical problems with risk sharing scheme
The Department of Health proposed that patient
recruitment would start on 6 May 2002. However,
the national coordinating team was not appointed
until July 2002, ethical approval has had to be sought,
and many neurologists have yet to see a detailed
protocol.

The cost of the drugs (more than £50m a year) for
the scheme will have to be met from existing NHS
budgets. In addition, collecting data is likely to put fur-
ther strain on NHS resources. The circular states that
"the scheme should as far as possible build on normal
clinical practice without requiring elaborate additional
infrastructure" and that "data entry should be as simple
as possible and arise out of normal patient contacts."
However, neurological services are already extremely
stretched (median outpatient waiting times are about
26 weeks), and many potentially eligible patients do
not have regular contact with a neurologist. Many
additional consultant neurology and specialist nurse
sessions (with appropriate administrative support) will
be needed to evaluate patients who may be eligible and
to follow up those who join the scheme. Normal
patient contacts do not include assessment of the
expanded disability status score, and so appointments
will have to be longer to allow for this. It is not clear
how all these additional sessions can be provided with-
out seriously compromising the existing service,
although the pharmaceutical companies will fund
some. Local staff (probably specialist nurses) will need to
be trained to collect, store, and transfer the additional data.

Alternative proposal
We believe that the government could spend the extra
resources for patients with multiple sclerosis more
effectively. Firstly, it should commission an independ-
ent, individual patient data overview of all relevant
published and unpublished randomised trials of
disease modifying drugs for multiple sclerosis. The
overview would address unanswered questions about
the trials and may go some way towards resolving the
uncertainties about the effects of interferon beta, glat-
iramer, and azathioprine.

Secondly, the risk sharing scheme should be modi-
fied to include a concurrent, randomised control group
rather than a historical cohort. Given that the Depart-
ment of Health is committed to providing resources
for the assessment, long term follow up, and drug costs
for several thousand patients with multiple sclerosis, a
long term randomised trial, run independently of the
pharmaceutical industry, would be a far more scientific-
ly (and so ethically) justifiable use of this money.
Patients could be randomised three ways (interferon
beta or glatiramer versus azathioprine versus no treat-
ment) and followed up in the same manner and with
the same outcomes as the existing scheme. Additional
resources would be required for blinded outcome
assessment and perhaps inclusion of a quality of life
outcome, but a trial would probably be less expensive
than the present scheme because only one third of
patients would be taking an expensive drug. Careful
explanation would have to be given to patient groups
about why a randomised trial is the best way forward as
fewer patients would be receiving active treatment.
However, it is the patients who have most to gain by
reliably establishing the long term clinical effectiveness
as well as cost effectiveness of these treatments.

Conclusions
Any additional resources for patients with multiple
sclerosis are welcome. However, these should be used
to provide services that we know benefit patients and to
support further, properly designed research into inter-
ventions about which there is still uncertainty.
Uncertainty remains about the effectiveness and cost
effectiveness of interferon beta and glatiramer, and the
risk sharing scheme will neither resolve these nor
determine the possible role of promising but far less
expensive drugs such as azathioprine. All patients with
multiple sclerosis, whether eligible for treatment under
the terms of the scheme or not, deserve much better
than this. The government should consider a more
appropriate use of this large amount of public money.

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When I use a word
Wholly, holy, holy

The Greek word ὅλος (holos) means entire or whole. Now you might think that the English word whole has the same origin, but you would be wrong.

The Greek word θεός (theos) comes from an Indo-European root SOLO, meaning whole, firm, sound, or correct. A holograph is written in one's own hand, and a holocaust was originally the burning of a whole body before it came to mean the destruction of a whole nation. Catholic (from the Greek katholikos, throughout) means throughout the whole world. SOLO also gives solicitous (wholly concerned with something), solemn (wholly religious), and solid. The old Roman coin the solang is considered to be wholly reliable, and a soldier was one who was paid in solidi. Solidago is the genus of plants including goldenrod, once thought to be a panacea (making people whole), and solipeds are ungulates with unclean hooves.

Whole, on the other hand, has a different Indo-European root, KAILO, of good omen or unharmed. A celibate was originally someone who was healthy (specifically, free from sexually transmitted diseases) and later someone who lived alone. The names Helga, Olga, and Heloise come from the same root, as does holy. Someone who is hale is healthy and whole. And the greeting “Hail” is short for “Be healthy.”

The homophone hole comes from yet another Indo-European root, KEL, a hollow or to cover or hide. The goddess Calypso hid Odysseus on her island for seven years, delaying his return to Ithaca. The Eucalyptus is well covered, having caps over its buds. Odysseus on her island for seven years, delaying his return to Ithaca. The Eucalyptus is well covered, having caps over its buds.