

8 Research questions

As the tables of evidence and the list of references show, there is a large volume of research relevant to the guidelines available. Despite this, the great majority of recommendations are graded D – dependent on consensus – although this is partly a consequence of the system of grading evidence (which emphasises only one research method – RCTs) and translating this to the strength of the recommendation. Although a few might become more highly graded if evidence from other neurological conditions, notably stroke, were to be included, it is nonetheless obvious that there is a great lack of evidence relevant to day-to-day clinical practice, particularly relating to the long-term effects of treatments. This section of the document puts forward some research priorities that arise from the work undertaken to develop the national clinical guidelines on MS.

Choosing research priorities is not easy. Most people, when asked, will focus on relatively specific questions that are undoubtedly important for particular patients, but do not necessarily address questions that have a large general impact. This problem has been discussed in relation to rehabilitation research priorities.⁶ Within the field of MS there are hundreds of potential specific research questions such as what dose of intramuscular botulinum toxin is effective in the biceps to control the development of contractures, do silver-coated catheters reduce morbidity if used long term, and is exercise specifically effective at reducing fatigue?

Those here have been chosen using the following criteria:

- the answer may benefit a large number of people with MS
- the process consumes significant resources.

The research priorities are given in no particular order.

8.1 Epidemiology of relapses, impairments and activity limitations

The epidemiology of multiple sclerosis has been well studied in relation to the aetiology of the disease. There are many studies on the incidence and prevalence of MS in different populations, in different parts of the world, in those who migrate, and in genetically related people. These studies have given some clues as to the cause of MS – as was the intention.

There have been some studies on the prevalence of the consequences of the disease, but these are relatively rare. They have used crude measures of impairment or disability, and they are often not fully representative. There have been no significant studies on the incidence of specific consequences of the disease, such as how many people in a given population will have a relapse each year. Indeed there is no agreed definition of a relapse, let alone studies on the reliability of its diagnosis. There are few studies investigating the mechanisms linking progressive impairments to limitations in activities and participation.

The lack of any firm data on the incidence, prevalence or severity of almost all impairments and activity limitations is one major problem in planning services, and in recommending service organisation. How many people have a relapse each year? How many people need a new wheelchair each year? How many people temporarily need a wheelchair? How many people have continuing faecal incontinence? How many people require more than four hours personal care each day?

Furthermore there is relatively little good information on the economic consequences of the disease. How many people have to stop work? How many family members have to stop work on account of the disease? How much money does the NHS spend on managing the consequences of MS?

The current cost-sharing scheme has highlighted the extreme poverty of useful information available to model the possible cost-effectiveness of expensive disease-modifying drugs. The scheme will not generate any information because it is not based on an epidemiologically sound sample.

This research recommendation does not relate specifically to any recommendation within the guidelines but without the information this recommendation should deliver, health commissioners will be unable to make estimates about the resources needed to enable any of the recommendations.

RECOMMENDATION

- R183** There should be a prospective study on an epidemiologically sound defined population to establish reasonable estimates of:
- the frequency of relapses sufficient to cause increased limitation on activities
 - the prevalence and yearly incidence of the most common impairments described in this guideline document
 - the prevalence and yearly incidence of the most common limitations on activity including work described in this document
 - the direct and indirect costs of the condition and how they relate to levels of limitation on activity, including not only NHS direct costs but all direct costs.

8.2 Diagnosing multiple sclerosis

There is much evidence that the MRI brain scan is abnormal in most people with MS. Further, it can indicate continuing disease activity in the absence of new impairments and this disease activity is dramatically reduced by disease-modifying drugs. There is also reasonable evidence that an MRI scan can predict reasonably the likelihood of MS developing in someone with an isolated first attack of optic neuritis.

However, the utility of MRI scans in clinical practice (as opposed to as part of research) is still not supported by much evidence, although major resources are involved in their use. Should MRI scans be offered to everyone, even if the diagnosis is clinically confirmed? Should second or subsequent MRI scans ever be undertaken?

Moreover the utility of other ancillary investigations is also unknown (given the predominance of MRI scanning). Is CSF examination ever helpful in confirming the diagnosis? When are visual evoked potentials useful?

This research recommendation relates primarily to recommendation R29 and may influence key recommendation 7 (Section 7).

RECOMMENDATION

- R184** There should be a prospective study on an epidemiologically sound population to investigate the most cost-effective protocols for investigating people presenting with (potential) MS to establish:
- the sensitivity and specificity of MRI scanning in people with different levels of clinical diagnostic certainty
 - the role of other investigations in confirming or positively excluding the diagnosis of MS
 - the prognostic value of MRI scan information over five years.

8.3 Rehabilitation assessment protocols

In sections 5 and 6 there is great emphasis upon initial identification of specific impairments or activity limitations. This is emphasised because specific treatments can only be given if a specific difficulty is recognised. In addition, it is important to have as good an understanding of a situation as possible before initiating interventions, if only to avoid doing harm (and usually to guide one on the best course of action). Yet, as has also been emphasised, people with MS can have one or more of a large range of problems, and both the person with MS and the clinician will rapidly become fatigued and fed up by long, detailed assessments of each potential problem.

Consequently, research is needed on the best way to approach the identification (detection) of impairments and activity limitations. This research area is *not* concerned with developing measures; it concerns the development of short, simple protocols or 'data collection tools' for identifying possible areas of need, screening for referral on to other specialist/non-specialist staff. These protocols would be designed for use by any person making contact with the person with MS, with the priority being members of the neurology and neurological rehabilitation services. The protocols should also extend possibly to monitoring people in a non-threatening and efficient way when no longer in routine contact with any service.

RECOMMENDATION

- R185** There should be a programme of research to develop and evaluate protocols, procedures or data collection tools that can be used by any profession to:
- identify the probable presence of most common impairments
 - approximately quantify activity performance in personal and household activities of daily living
 - identify areas of activity limitation that are present in people with MS.

8.4 Specialist neurological rehabilitation services

The guidelines recommend repeatedly that people with MS with any impairments or limitations on activities or social participation should be seen by a specialist neurological rehabilitation service. The recommendation is based upon some MS-specific evidence, but primarily draws upon evidence from stroke and other conditions. There are currently few specific neurological rehabilitation services in England and Wales, and certainly a completely inadequate level of services to meet even a small percentage of the needs of people with MS (let alone other neurological conditions).

Consequently this recommendation will have a major impact upon the allocation of health resources, partially through reorganisation of current resources but mainly through provision of new services. The evidence suggests that this may well be an effective and efficient use of resources – the evidence from stroke suggests that better outcomes may be achieved with similar or possibly less resources. Ultimately the cost of these services may well still be less than the cost of interferon beta. However it is notable that even strong evidence in favour of stroke units has not affected health commissioners much, and health commissioners may require more direct evidence.

Given the differing circumstances around England and Wales, with some areas being urban, others rural, and with some areas preferring outpatient and others inpatient services, it is probably best not only to investigate whether specialist services are effective but also whether one pattern of delivery is better than another. This research should certainly also investigate the health economic aspects of any service, and it would be important to consider whether there are any disbenefits for people with MS.

RECOMMENDATION

- R186** A programme of research into the relative costs (direct and indirect) and benefits (direct and indirect) should be undertaken comparing:
- current rehabilitation practice with rehabilitation given by a specialist neurological rehabilitation service
 - primarily inpatient with primarily outpatient or home-based neurological rehabilitation.

8.5 Acute relapse management: methylprednisolone and rehabilitation

Although some people with MS never have a relapse, having a progressive form from the onset (or a very benign form), it is likely that most people will have several relapses if not more. At present, treatment often involves hospital attendance if not admission, and the resources devoted simply to giving medical treatment are considerable. In addition many relapses are associated with a significant increase in activity limitation, often sufficient to require hospital admission.

Although there are many trials of many treatments for acute relapse it is still extremely difficult to give strong recommendations based on the evidence. Many questions remain unanswered, such as what dose of steroids, how long for, is oral as good as intravenous, are different types of steroids equivalent, how frequently can short courses be given, and what are the significant risks and side effects?

This lack of useful evidence needs to be set in a larger context. There is minimal evidence available on the diagnosis of a relapse and its distinction from minor progression, worsening associated with an intercurrent illness or simple normal fluctuations in a person's clinical status. In addition, the only way to access rehabilitation is often through hospital admission, and rarely can care needs be met quickly at home also often requiring hospital admission.

RECOMMENDATION

- R187** A programme of research should investigate the management of acute relapse including comparing the costs and benefits associated with policies of:
- oral methylprednisilone against intravenous methylprednisolone
 - hospital admission with early discharge once rehabilitation has started and support has been arranged against home care with rapid response care and rehabilitation input (with steroids if indicated).

8.6 Disease-modifying therapies

A recent publication has questioned the cost-effectiveness of interferon beta and glatiramer acetate and the current risk-sharing scheme.⁴⁶¹ The amount of money spent by the NHS on disease-modifying therapies (DMTs), including not only the drugs themselves but all the extra resources needed to run the scheme and to monitor the people on the scheme, is large. And this scheme only affects less than 15% of people with MS and many of those eligible withdraw due to side effects.

The guideline developers therefore agreed (by a large majority) that further well-designed research into DMT was a high priority, including impartial evaluation of their effectiveness in terms of reducing limitations on activities, the costs associated with any benefits at the level of activities, the type of side effects seen in both the short and long term, and the duration of any benefit.

RECOMMENDATION

- R188** A programme of research into disease-modifying treatments sponsored and run by an organisation independent of either health purchasers or pharmaceutical companies should be set up to investigate interferon beta, glatiramer acetate, linoleic acid and azathiaprine (and any other newly licensed medicines) in terms of:
- benefits, specifically in terms of activity performance
 - costs, including the medicines and all associated monitoring, etc
 - disbenefits, both immediate side effects and longer-term rates of withdrawal and side effects
 - effects of stopping treatment after two and four years.

8.7 Relationship between impairments and limitations in activities

The links between individual impairments and combinations of impairments and the resultant limitations on activities, and how these links may be affected by treatments including changing the environment, are unknown. If more were known, more effective interventions could be researched and undertaken. Investigations will require a prolonged programme of research based on epidemiologically sound populations of people, not only with MS but also with other neurological conditions.

RECOMMENDATIONS

- R189** A programme of research extending over many years should be instigated to investigate the nature and extent of relationships between impairments and activities and how they change over time.