Author's response to reviews

Title: Social and economic burden of walking and mobility problems in multiple sclerosis

Authors:

James Pike (james.pike@adelphigroup.com)
Edward Jones (eddie.jones@adelphigroup.com)
Krithika Rajagopalan (krithika.rajagopalan@sunovion.com)
James Piercy (james.piercy@adelphigroup.com)
Peter Anderson (peter.anderson@adelphigroup.com)

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Author's response to reviews: see over
Dear Professor Amato

Re: MS: 2077999172613700

Social and economic burden of walking and mobility problems in multiple sclerosis: results of a cross-sectional study in Europe James S Pike, Eddie C Jones, Krithika Rajagopalan, James Piercy and Peter R Anderson BMC Neurology

Further to your email dated 14 February 2012 I am pleased to attach a revised version of the above paper which we believe addresses the concerns raised by Reviewer 2. We would like to take this opportunity to thank both Reviewers for their thoughtful and considered input on the paper. We were particularly encouraged by the comments from Dr Halper who regarded the paper in an extremely positive light. While we would refute Dr Cameron’s assertion that the study cohort is small and unrepresentative (the total study population was >3500 patients and the smallest subset examined was >180) we have taken steps to clarify both the benefits and limitations of an observational study such as this as well as to explain and expand on the representativeness of the cohorts studied to the wider MS population. Please find attached a document detailing responses and amendments made to the paper in response to each of the reviewer comments, a version of the paper with all changes highlighted in bold and a clean version of the final paper. We thank you for you invitation to resubmit the paper to BMC Neurology and look forward to hearing from you.

With kind regards

James Pike
**Reviewer comments** | **Response and amendments**
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**Reviewer 1**<br>The question posed is an important one and is very relevant to MS. While not original, it is relevant to long-term management of MS. It has not been addressed recently due to the emphasis on disease modifying therapy. | No amendments requested
Data were sound but not controlled since these were obtained from chart review from physicians’ records. I do not see a problem with that method though. | No amendments requested
Conclusions and discussion were well balanced and well supported by the data. Literature review was very well done. | No amendments requested
Very well done methodology. Sufficient details were provided. | No amendments requested
This was a strong paper and very well done. | No amendments requested
I think the conclusion of the paper should include relevance to clinicians. It is vitally important to ask about mobility and walking from the first encounter with the patient and at each visit. This paper substantiates the impact of these deficits on patients’ total lifestyle. It would be helpful to include some entitled practice points or points for professional practice at the end of the work. | The conclusion section of the paper has been expanded to highlight the clinical implications of the results of the current study. While the author guidelines for BMC Neurology do not stipulate a separate section of practice points as suggested by the author, we have included a text box at the end of the paper which provides key practice points supported by the results of this analysis
**Reviewer 2**<br>The main problem with the study is that conclusions are drawn from a limited number of people who are part of a small and unrepresentative sample of people with MS. It is not possible to generalise the findings to | The reviewer correctly acknowledges a limitation of all observational studies. However, such studies provide valuable insight into the real-world clinical population of patients with a given disease or condition and are
people with multiple sclerosis because of the biased selection of the participants.

acknowledged as a valuable tool for hypothesis generation and for guiding clinical research as well as providing insight for practicing clinicians. As noted by Reviewer 1 the chart review approach applied here is ‘very well done’ and the data generated are ‘sound’.

The overall population of patients included in the study is not small, data for 3572 patients across the 5 European countries were collected. Moreover, the study is not ‘unrepresentative’ but rather represents the population of MS patients presenting for specialist neurological care. This point is acknowledged in the discussion section of the paper (paragraph 4).

Information on WMPs were available for the majority of the population (N=2111) and while the majority (64%) reported having no WMPs, 36% (N=769). This again is a large cohort of patients, larger than might be encountered in a phase III clinical trial.

The reviewer is correct in noting that the population for whom T25FW test data were available was relatively small (N=184). However, again this is acknowledged in the discussion section of the paper and is a consequence of this tool being mainly a research tool and so not routinely collected in clinical practice.

The authors therefore refute the reviewers comment that the study population was ‘small and unrepresentative’. Furthermore, there were no selection criteria applied beyond presenting MS patients. As such we feel it inappropriate to describe the sample as ‘biased’. We fully acknowledge the population examined and the limitations to the generalizability of the data in the discussion section of the paper.

The serious problem with the study is that only 61% of participants completed the patient recorded questionnaire and of these on a relatively small group reported their most bothersome symptom (about 17% of the total study participants).

The reviewer is correct in noting that 61% of patients completed a PSC to complement the PRF record. However, this represents data for 2171 patients, a considerable number. Furthermore, almost 700 patients provided information on what they considered to be their most bothersome symptom
and of these 291 (43%) specified this to be WMPs.

Given the design of the study (observational) it is inappropriate to consider the proportion of patients specifying WMPs as their most bothersome symptom within the context of the while cohort of 3572 patients as the reviewer appears to have done. The design of this (and other) observational studies places no requirement on participants to respond to every question. Consequently, responses are considered within the context of respondents as we have no data for non-responding participants.

However, to begin to address the reviewers concern regarding the representativeness of the responding vs the non-responding population within this cohort we have undertaken additional analyses in order to determine whether any baseline differences could be identified for (a) patients providing a PSC and those not, and (b) those with T25FW data and those without. These data are now included at the end of the results section and referred to in the discussion.

The percentage of participants with T25FW and caregiver requirement data is 183 ie 5% of the total sample and the percentage with T25FW and employment data is also 5% of the total sample. However, the abstract gives results without any mention of the number of participants in each analysis. The authors must address this issue and report in the abstract the number of participants included in each analysis.

The numbers have now been added to the abstract as requested.

The authors must consider how the biased sampling influences their results. Probably people with more severe mobility problems were more likely to complete the patient questionnaire. However, they are also likely to have greater education and may be more likely to be female.

This issue has now been discussed within the context of the limitations of the study and the reader has been made aware of the need to consider the results in light of the limitations of an observational study. The reviewer is correct that mobility problems were somewhat more severe among the cohort of patients who completed a PSC vss those who did not. However, such differences were not noted for the subset of patients with T25FW data and those without such that, in this way at least, the subset with T25FW data can be considered to be representative of the sampled population.