Author’s response to reviews

Title: Impact on healthcare resource utilization of multiple sclerosis in Spain

Authors:

Antoni Sicras-Mainar (asicras@bsa.cat)
Elena Ruiz-Beato (elena.ruiz-beato@roche.com)
Ruth Navarro-Artieda (rnavarro.germanstrias@gencat.cat)
Jorge Maurino (jorge.maurino@roche.com)

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Author’s response to reviews:

Dear Editor-in-Chief:

We submit our revised manuscript "Impact on healthcare resource utilization of multiple sclerosis in Spain" (BHSR-D-17-00961) incorporating all the suggestions and comments made by the reviewers.

Below you can find a point-by-point response to each of the issues. In addition, we highlighted the changes within the manuscript using colored text.

Sincerely yours,

The authors

Reviewer #1

1. In methods, specifically in page 7 (columns 31 and 32) you write "this study did not include any non-healthcare direct costs, classified as "out-of-pocket" costs paid by the patient, family, as they were not recorded in the database". I think that these data should be shown in "limitations of the study".

Following the reviewer’s suggestion, we included this sentence in the Limitations section (pages 10 and 11).
2. Related to methods, I would like to know how the work productivity losses were calculated through the days off work due to sick leave? In affirmative case, how did you get this information? Through primary attention?

Indirect costs are those related to work productivity loss (days off work due to sick leave).

The days absent from work were quantified from primary care according to the official minimum wage salary (source: Instituto Nacional de Estadística-INE, Spanish National Statistics Institute).

This information was clarified in the Methods section (page 6).

3. In limitations of the study should be included the absence of the informal caregivers in the study to calculate informal cost.

Following the reviewer’s suggestion, we included this issue in the Limitations section (page 10).

Reviewer #2

1. Inclusion criteria deserve to be fully clarified. First of all, it is not clear whether the population was selected from existing records for general medical purposes, or from specific multiple sclerosis datasets. Indeed, on the one hand authors use quite general diagnostic criteria (e.g. in the ICD-9 clinically isolated syndrome is considered as multiple sclerosis). On the other hand, authors included rather specific clinical features, such as EDSS and the diagnosis of CIS (which is then not analysed).

This study analysed patients from 19 primary care centres covering a population of 315,658 inhabitants. Population was selected from existing medical records for general medical purposes (national health system). (Methods section, page 4).

This study included patients with a diagnosis of MS according to the International Classification of Primary Care (IPC-2, code N86) and the International Statistical Classification of Diseases (ICD-9, ninth revision, code 340). Our National Health System in the primary care setting collects diagnosis in its databases according to both international classifications. Anyway, the distribution among different clinical MS types in our sample is aligned with classical epidemiologic series following Mc Donald criteria.

However, we included this issue in the Limitations section (page 10).
2. In addition, what is a long-term prescription program? Does it specifically involve disease modifying treatments? If so, authors likely only included relapsing remitting multiple sclerosis. Otherwise, I would assume authors were treating progressive multiple sclerosis (what eligibility criteria does the local regulatory body apply?). Also, the inclusion of the treated population might depict a non-representative multiple sclerosis population. Accordingly, prevalence they found is relatively low.

The long-term prescription program is a specific software designed for the management of medical prescriptions at hospital and primary care levels.

Our study included patients with a diagnosis of MS according to the IPC-2 and the ICD-9 classifications regardless if they were receiving disease-modifying therapies (DMTs) or not. A total of 23.9% of the patients included were not receiving any DMT.

Only MS DMTs were analysed in the study. Concomitant medications were not evaluated. This issue was also included in the Limitations section (page 10).

3. Overall, statistics need a revision. Analyses are based on the classification EDSS 0-3.5 or >4.0, which is not completely reliable, as the 2 groups differ in size (150 vs 70) and do not depict specifically different multiple sclerosis populations. I would suggest authors to use regression models to assess associations between EDSS (as a continuous variable) and different costs/variables of healthcare resource utilization. Also, models should be adjusted for a subset of covariates such as age, gender, disease duration, EDSS, disease course.

We thank very much the reviewer’s feedback. However, in our study, statistical analysis stratifying subgroups of patients according to the EDSS score (“no to moderate disability” vs “severe disability” [0.0-3.5 vs 4.0-9.5, respectively] were based on a similar approach already applied in different prior publications at national and international settings (Casado et al, 2006; Kobelt et al, 2006; Karampampa K et al-Tribune study, 2012). Indeed, using this approach we found a significantly correlation between costs and disability progression similar that was showed in those publications mentioned before (Fernández O, et al. Estimate of the cost of multiple sclerosis in Spain by literature review. Expert Rev Pharmacoecon Outcomes Res. 2017;17:321-33).

On the other hand, the multiple linear regression model included age, gender, RUBs, Charlson Comorbidity Index, time since MS diagnosis, and EDSS score (Methods section, pages 6 and 7).

4. For the EDSS, can you please provide median and range?
We included the median EDSS score and its range in the text (page 7)

5. Results of regression models have to be completed by reporting 95% confidence intervals.
We included the reviewer’s suggestion in the text (page 8)

6. Associations not including costs (e.g. between EDSS and age, time since diagnosis, relapses etc) are out of the objectives of this paper and can be removed.
We agree with the reviewer removing this information from the text

7. Among limitations, authors should consider the use of standard cost for sick leave, rather than the specific costs depending on patients' income.
We agree with the reviewer including this issue in the Limitations section (page 11)

7. In the abstract, the ANCOVA is mentioned as main statistical analysis. However, results from regression models are reported. Please, consider revising with more complete statistical methods.
Following the reviewer’s suggestion, we modified the statistical methodology description in the abstract (page 2).