



## SUMMARY



Multiple Sclerosis (MS) is a chronic, inflammatory disease of the central nervous system and it is the most common cause of neurological disability in young adults between the age of 20 and 40. MS is characterized by inflammation of the myelin sheath, i.e. the protective fiber surrounding the nerves, and which is needed for the fast electrical conduction of the action potential along the nerve. In case of MS, the body attacks its own myelin, causing inflammation of the myelin sheath. Myelin is lost in multiple areas, leaving scar tissue called sclerosis. This will lead to a disrupted conducting of impulses to and from the brain, which may subsequently lead to the multiple neurological symptoms that characterize MS. These symptoms could include motor and sensory impairments, cognitive impairment, fatigue, visual problems, sexual dysfunction, mood disturbances, and loss of bowel and bladder control.

MS has a variable but over time increasing impact on daily living and since no cure has been found yet, treatment should aim at reducing this (increase in) impact. It is therefore essential that impact of MS is measured in a reliable and valid way. These measurements can include clinical measures, such as neurological examination and MRI, which are used to quantify impairment and disability in MS. Although these measures are of interest to clinicians, they often correlate poorly with the patient's perception of his/her own well-being. Clinical outcome measures are therefore questionable as ultimate outcomes in rehabilitation and therapeutic trials.

In recent years, there has been an increasing recognition and use of self-report measurements which are based on the patient's own perspective. In order to use the outcomes of self-report measurements, the patient needs to provide reliable and valid information. Reliability and validity of outcomes generated by self-report measurements may be influenced when the patient suffers from cognitive impairment. Cognitively impaired patients may differ in the domains of functioning that they see as important, and they may differ in their outcome assessments. Also, their health and overall functioning are often difficult to assess because of the cognitive or communication problems from which they suffer.

This is described in a Health Technology Assessment (HTA) report by Riemsma et al. They performed a systematic review of all existing literature to identify the general health status measures that have been validated in patients with cognitive impairment due to acquired brain injury, explicitly including MS. It was concluded that existing self-report measurements on general health status should be used with caution in patients experiencing conditions such as cognitive impairment. Yet it might be precisely these situations when one is most interested in assessing health status. Problems may also arise when patients suffer from communication problems, depression and/or anxiety or when they experience severe symptom distress and do not want to be bothered by an interview. Exclusion of such patients, a sometimes chosen approach, may lead to biased results which are consequently difficult to generalize to the population of interest.



One of the suggestions for future research by the authors of the HTA report is the incorporation of proxy respondents (or proxies) to assess the situation of the patient. A proxy respondent is someone from the direct vicinity, for example partners, close relatives and health care providers. Proxies could provide information on the patient's health status that otherwise could be unreliable, invalid or even lost. In order to use the information provided by proxies, it should be accurate.

This lead to the following research question:

**To what extent are proxy respondents able to accurately assess the impact of MS on daily life of MS patients?**

Several studies were performed towards answering this question. In this summary, the main findings of these studies are presented.

The accuracy of proxy ratings is usually determined by examining the extent to which they are in agreement with those provided by the patients. The studies described in this thesis, focussed on patient-proxy agreement on the physical and psychological disease impact of MS on daily life of the patient.

The Multiple Sclerosis Impact Scale (MSIS-29) is the most recently developed patient-based outcome measure in MS (appendix 1), which measures the physical and psychological disease impact of MS from the patient's perspective. The MSIS-29 consists of 29 items which originated from expert opinion, literature review and patient interviews. These items can be divided into two subscales: a physical scale (20 items) and a psychological scale (9 items).

Since the MSIS-29 was originally developed for MS patients, one can not automatically use the questionnaire in a sample of proxy respondents without executing on beforehand a psychometric evaluation of the questionnaire when completed by proxy respondents. Psychometric criteria such as data quality (*were there, for example, a lot of missing data?*), scaling assumptions (*did all the items of a subscale measure the same construct?*), acceptability (*did the score distribution adequately represent the true distribution of the population?*), reliability (*were the data free of random error?*), validity (*did the questionnaire measure what it was intended to measure?*), and responsiveness (*did the questionnaire measure clinically important change over time?*), were therefore tested in a sample of 59 partners of MS patients. The partners completed a modified version of the MSIS-29 in which all items were rephrased in the third person perspective (appendix 2). They were instructed to assess the patient as they thought the patient would rate his or herself. Results, which are described in **chapter 2**, showed that the MSIS-29 was also a reliable and valid instrument when used by partners of MS patients.



This provided a solid basis for further research and the next goal was to examine whether MS patients and proxy respondents agreed on the physical and psychological impact of MS on daily life. A cross-sectional study in a sample of 59 MS patients and partners, described in **chapter 3**, demonstrated that the patient-proxy agreement on the physical and the psychological disease impact was adequate at group level. Patient-proxy agreement was good for the physical scale and slightly less, but still adequate for the psychological scale. It was concluded that partners might be useful sources when assessing impact of MS. It should be taken into account that the mean values at group level were accompanied with large standard deviations, which pointed towards large differences on individual patient-proxy level.

Although promising results were seen at cross-sectional level, the validity of these findings over time remained to be investigated. The validity of measuring changes over time in a longitudinal setting, for example in clinical trials in which the effect of treatment is assessed over time, is especially important. Therefore, patient-proxy agreement was assessed in the same sample two years after the cross-sectional study to see whether patients and proxies agreed on possible change in disease impact. Results of this study (**chapter 4**) displayed acceptable levels of patient-proxy agreement, both at baseline and follow-up, mainly on the physical scale. Conversely, the level of patient-proxy agreement on change of disease impact was low. A remarkable finding was that proxy respondents appeared to be better assessors of change over time in comparison to the patients.

Proxy respondents could also play an important role in clinical trials which are focussed on assessing treatment effect over time. Proxies should therefore be able to assess the size (*how much did the patient's experienced disease impact change as a result of the treatment?*) and direction of possible treatment effect (*did the patient's experienced disease impact deteriorate, stabilize or improve after treatment?*). Therefore, both patients and proxy respondents completed the MSIS-29 before and after intravenous steroid treatment, which the patient received due to worsening disease symptoms. This study is described in **chapter 5**. Results showed that, although large differences were seen on individual patient-proxy level, findings do point towards possible use of proxy respondents to assess patient perceived treatment change at group level.

None of these studies included data of patients who actually suffered from cognitive impairment. Nonetheless, the use of proxy respondents could be especially important in that particular group of patients. Patient-proxy agreement was therefore assessed in a sample of patients with different cognitive ability (**chapter 6**). The intuitive expectation that agreement between patients and proxy respondents was proportional to cognitive impairment was not confirmed in this study.

All the previously described studies used partners of MS patients as proxy respondents. However, health care providers could also be useful sources of information since they play a central role in the care of MS



patients. **Chapter 7** describes a study which examined whether health care providers are suitable proxy respondents and whether there was a difference with significant others. Results showed that both health care providers and significant others did not accurately assess the disease impact of MS patients in a rehabilitation setting. Health care providers indicated lower levels of physical and psychological disease impact which was in contrast with other studies in which health care providers indicated higher levels of disease impact.

Based on the findings summarized above we concluded the following:

**At group level, partners of MS patients are capable of providing reasonably accurate information, mainly on the physical impact of MS on daily life of MS patients. The use of partners of MS patients as proxy respondents at group level could therefore be a valuable method to comply with the methodological problems which may occur when using self-report measurement in MS research. However, the presence of large inter-individual patient-proxy differences requires caution when using proxy respondents to assess disease impact of MS of individual patients.**

