CHAPTER 1

General Introduction
Multiple Sclerosis (MS) is a progressive disease of the central nervous system that is characterized by lesions in the brain and spinal cord. These lesions affect the myelin sheath which causes inhibition of axonal transmission and axonal loss. MS is the most common chronic disabling neurological disease in young adults and results in a broad range of symptoms which including motor, sensory, visual and cognitive problems. Although the exact etiology of MS remains to be elucidated, it involves environmental exposure and genetic susceptibility. Approximately 2.3 million individuals worldwide are affected with MS.\(^1-3\) Globally, the prevalence of MS is 33 per 100,000, whereas the highest prevalence was found in North America and Europe, being more than 100 per 100,000.\(^4,5\) MS is more common among women than men and symptoms occur at around 30 years of age, when people are economically most active and when they would be most likely to start or support a family.

**DIAGNOSIS AND DISEASE COURSE**

The disease typically presents with an acute episode of neurological dysfunction (relapse) with symptoms as loss of vision, sensory and motor disturbances, cognitive problems, mood disorders, loss of bladder and bowel control, sexual dysfunction and others like pain and fatigue. The diagnosis of MS is based on clinical findings and magnetic resonance imaging (MRI) of the central nervous system. The diagnostic criteria for MS have been revised over the years.\(^6-9\) The disease may start with a single clinically evident episode caused by demyelination in the brain or spinal cord without any preceding episodes. This is called a clinically isolated syndrome (CIS). In these cases dissemination in time (and often also in space) is lacking and therefore CIS patients are not yet diagnosed with MS.\(^1\) The majority of these patients will eventually develop MS and show a relapsing remitting (RR) disease course characterized by relapses (i.e. episodes of neurological dysfunction) from which they usually recover. With time, recovery from relapses can be incomplete, and persistent symptoms may accumulate. In due time the majority of RRMS patients enters the secondary progressive phase (SP),\(^3\) characterized by steady progression of disability, with or without superimposed relapses. In around 20% of the MS patients the disease course is characterized by slow progression from the onset of the disease, without relapses, but with continuous
accumulation of neurological disability, called primary progressive (PP). The clinical courses of the disease types are shown in Figure 1.1.

![Figure 1.1 Schematic overview of the disease courses of MS subtypes](image)
The X-axis represents time, the Y-axis represents neurological disability

**CLINICAL ASSESSMENT IN MS**

For the evaluation of disease activity and disease progression, various methods can be applied to assess disability, impairment and impact of MS. These assessments can be physician based, for instance neurological examination, neuropsychological evaluation and functional tests, or patient derived, by using patient reported outcome scales or interviews. Quantification of MS symptoms is difficult due to the variety of neurological symptoms and the lack of one outcome parameter that covers the full range of MS symptoms. Therefore a combination of physician based and patient based measures can be useful. The physician based outcome measures that are often used in MS research are described below.

**EDSS**
The Expanded Disability Status Scale (EDSS)\textsuperscript{10} uses information from neurological examination to evaluate several functional systems: visual, brainstem, pyramidal, sensory, cerebellar, bladder/bowel and cerebral function. The ordinal scale ranges from 0 to 10, in which a high score refers to more severe disability. The EDSS is internationally the most common used outcome measure of disability in MS, despite its limited reliability, the limited ability to reflect change and the psychometric disadvantage of an ordinal scale with non-linear steps.\textsuperscript{11-13}
MSFC
The Multiple Sclerosis Functional Composite (MSFC)\textsuperscript{14} is a functional measure combining three quantitative tests assessing dimensions that are possibly affected by MS. The Timed 25-Foot Walk (T25FW) evaluates ambulation, the 9-Hole Peg Test (9HPT) evaluates arm dexterity and cognition is assessed by the Paced Auditory Serial Addition Test (PASAT). Although the tests are often used separately, the designed composite, a combination of three tests, has not gained wide acceptance.

BRB-N
The Brief Repeatable Battery for Neuropsychological Tests (BRB-N)\textsuperscript{15-17} is widely used to evaluate cognitive impairment. A recent study comparing neuropsychological test batteries concluded that the BRB-N is reliable and sensitive to use in MS patients.\textsuperscript{18} The BRB-N was developed as a short observational instrument to identify disturbances of cognitive domains in MS patients and consists of five subtests: The Selective Reminding Test (SRT);\textsuperscript{19} The Spatial Recall Test (SPART);\textsuperscript{20} The Symbol Digit Modalities Test (SDMT);\textsuperscript{17,21} The Paced Auditory Serial Addition Test (PASAT);\textsuperscript{16,22} and the Word List Generation (WLG) test.\textsuperscript{16} The indication of possible cognitive impairment of patients in this thesis was based on normative values of a Dutch sample of healthy controls.\textsuperscript{23}

PATIENT REPORTED OUTCOMES

Patient reported outcome scales (PROs) are increasingly used as measures of disease impact, physical functioning, psychological functioning, cognition and quality of life in MS.\textsuperscript{24-28} The advantages of PROs, compared to more former clinical tests, are that they are time efficient and easy to complete. Using PROs the patients’ disease can be monitored during routine clinical care or responses can be evaluated at group level in cohort studies, evaluating the short and long term effects of MS. The quality of PROs can be determined by the evaluation of psychometric criteria: The reliability (consistent performance on test items), validity (measure of the intended underlying construct), interpretability (sensitivity and specificity of the scale) and responsiveness (ability to detect change).\textsuperscript{13} The PROs used in this thesis are described in the following sections and presented in the Appendix.
**General Introduction**

**MSIS-29**
The Multiple Sclerosis Impact Scale (MSIS-29)\(^{29}\) evaluates disease impact of MS on daily life and can be divided into two subscales; a physical scale which consists of 20 items and a psychological scale with 9 items. The range of item scores is 1 (no impact on daily life) to 5 (extremely influencing daily life). Two separate scores for the subscales can be calculated. The MSIS-29 satisfied the psychometric criteria for patient and informant use.\(^{30}\)

**MSWS-12**
The Multiple Sclerosis Walking Scale (MSWS-12)\(^{31}\) is a patient-based measure of walking ability in MS with a 12-item scale, ranging from 1 (no problems with walking at all) to 5 (extremely difficult). The scale is restricted to patients who can walk and can also be completed by an informant. The MSWS-12 satisfies the standard criteria as a reliable and valid patient-based measure of the impact of MS on walking ability.

**MSNQ**
The Multiple Sclerosis Neuropsychological Screening Questionnaire (MSNQ)\(^{32}\) is a brief self-administered questionnaire with 15 items that reflects neuropsychological competence in patients with MS during activities of daily living. The questionnaire can be completed by the patient or an informant. Every item has 5 response options, 0 (does not occur) to 4 (very often, very disruptive), a higher score indicates more cognitive problems. The psychometric properties of the MSNQ are evaluated in one of the studies in this thesis.\(^{33}\)

**GNDS**
Guy’s Neurological Disability Scale (GNDS)\(^{34}\) is an interview-based questionnaire measuring neurological disability. The GNDS contains 12 items in which an interviewer comes to a score with one or more questions to the patient or informant. The items include cognition, mood, vision, speech, swallowing, upper limb function, lower limb function, bladder function, bowel function, sexual function, fatigue and 'others'. All items are scored on a 0 (no problems) to 5 (disabled) scale. The GNDS was found to be a reliable, responsive and valid measure of neurological disability.
PROXY MEASUREMENTS

Research projects are often driven by information obtained directly from patients. Unfortunately, when the patients’ response is less reliable or missing due to disease status, age, cognitive functioning or mood disorders, it can be useful to obtain data from another perspective, for instance a proxy respondent. A proxy respondent can be a partner, close family member or healthcare provider of the MS patient. Proxy measurements have recently been evaluated in several patient populations such as elderly, children, stroke, cancer and patients with Alzheimer’s disease. These studies report different results according to the agreement between patient and proxy. In most studies proxies rated patients as more severely affected than patients themselves and agreement was better on physical scales compared to evaluation of (neuro)psychological and cognitive status. According to these studies, proxy responses cannot be used as a direct substitute for missing patient data without considering other patient and proxy related variables.

PATIENT-PROXY AGREEMENT IN MS

In order to explore the use of proxy measurements in MS, the accuracy of proxies (i.e. partners of MS patients) rating the impact of MS and treatment induced change was evaluated in groups with small sample sizes. The accuracy was determined by the extent to which proxy ratings agree with responses provided by the patients on the MSIS-29. On the MSIS physical scale good to perfect agreement was found between patients and proxies, but larger differences were seen on the MSIS psychological scale. There was a tendency for proxies to overestimate, to report more disease impact of MS than patients themselves did. The advise out of these studies was to extend the number of patients and proxies and focus on factors that may cause discrepancies in proxy versus self-report measurements, for example cognition and mood disorders.

THE ACCURACY OF PATIENT REPORTS

Cognitive deficits are present in 40-70% of the MS patients. Disturbances in the domains of attention, information processing speed, memory and executive skills are major features of
the cognitive profile and can often be detected early in the course of the disease. These deficits affect many aspects of daily life, such as social and emotional functioning, ability to run a household, employment status and the overall quality of life. Patients fatigue, anxiety and depression have been identified as important contributors to cognitive performance and the accuracy of patient reports. As cognitive dysfunction, fatigue and mood may cause methodological problems, such as loss to follow-up or reduction of the reliability of patient scores, the use of proxy reports could be beneficial.

THE ACCURACY OF PROXY REPORTS

Researchers aiming to explain the differences between patients' and proxies' assessments have focused on patient related factors, such as cognition and mood, which can reduce the reliability of MS patients' self-assessment. However, coping with MS symptoms is not only challenging for patients. A range of psychological, physical and financial changes may also affect the MS patient's partner (proxy respondent) and family. Thereby the disease can change relationships and caregiving roles. These factors can cause long-term stress in proxies and influence their physical health, mental health and quality of life. Hence, it is important for researchers to consider both the patients' disease status and their proxies' physical health, mental health, mood and caregiver strain when examining the agreement between the patient and proxy rating on MS PROs.

AIMS AND OUTLINE OF THIS THESIS

Researchers in MS often have to deal with loss of information and loss to follow up as a result of disease burden. The time points of this methodological problem are not random, but are often critical stages in the disease of the patient in which important information about the health status and disease progression should be collected. Moreover, a full understanding of self-report forms and the ability of the patient to respond adequately can be influenced by disease worsening, fatigue, mood disturbances and cognitive problems due to MS. Therefore including proxy respondents (i.e. partners of patients) to evaluate the disease state of the patient might be useful to continue reliable follow-up research. In earlier studies the
use of proxy responses on the MSIS-29 was evaluated. The goal in this thesis was to explore whether other types of MS PROs are also suitable to be used by proxy respondents of MS patients.

The aim of this thesis was to estimate patients’ long term outcomes using proxy responses. Therefore we evaluated patient and proxy responses on several patient reported outcome scales that are often used in MS research. We analyzed different patient and proxy related variables that could be of influence on (dis)agreement between patient and proxy scores to establish the most accurate prediction of long term patient outcomes.

When using proxy responses, one should be able to rely on the measurement scales to yield the same results for patients and proxies. Since earlier studies comparing MS patients’ and informants’ responses on the MSNQ showed opposing results the validity and interpretability of the MSNQ patient and informant form were evaluated for the Dutch population of MS patients and proxies in chapter 2.

In chapter 3 the exploration of patient-proxy agreement is described on five PROs that are frequently used in MS research, the MSIS-29 physical and psychological scale, the MSWS-12, the GNDS and the MSNQ. In chapter 3.1 the mean differences between patients and proxies on these five scales were analyzed. The agreement between patients and proxies on scale level and item level was evaluated for all PROs. Following these results the patient and proxy related factors that could be of influence on the (dis)agreement were analyzed and described in chapter 3.2. The difference between patient and proxy was used as outcome variable and several patient and proxy related variables such as age, gender, education, health status, type of MS, cognitive status, mood and caregiver burden were used as independent variables in linear regression analyses. This resulted in a model explaining a part of the differences between patients and proxies for each PRO separately.

The study so far did not include patient-proxy measurements over time. In chapter 4 the responses of patients and proxies in a longitudinal setting are described. Data of both patient and proxy were collected at a 6 months and a 2 year follow up. Because results in the previous sections has shown that physical MS scales acquire more agreement between
patient and proxy, the focus in chapter 4.1 is on longitudinal changes in patient and proxy responses and explanation of agreement and disagreement over 2 years on the MSIS physical scale and the MSWS. Demographic, disease related and proxy related variables that could potentially explain (dis)agreement between patients and proxies were investigated using linear regression analyses. Finally, in chapter 4.2 the search for the most accurate prediction of the patient follow up score on the MSIS physical scale is described using proxy follow up scores and potential other contributing patient and proxy related scores or variables.
REFERENCES


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