Health Economic Models for Relapsing-Remitting Multiple Sclerosis

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Chapter 7

Discussion

In this thesis, I developed a new modeling framework which addresses the challenges and limitations of the economic models used in existing evaluations of the cost-effectiveness of disease-modifying therapies (DMTs) for the treatment of relapsing-remitting multiple sclerosis (RRMS).

As found in the systematic literature review conducted in this thesis, the structure of the economic models used to assess the cost-effectiveness of DMTs for the treatment of RRMS has converged over time. The clinical course of the disease is characterized in terms of changes in disability measured by the Expanded Disability Status Scale (EDSS) and the occurrence of relapses over time. These models include 10 health states during RRMS (EDSS 0 – 9.5), 10 health states during secondary progressive multiple sclerosis (SPMS; EDSS 0 – 9.5), and death. A hypothetical cohort of patients, all with RRMS, starts with an initial EDSS distribution. Patients with RRMS may: 1) remain at the same EDSS level with RRMS, 2) worsen to a higher EDSS level (i.e., increased disability), 3) improve to a lesser EDSS level, 4) progress to SPMS, or 5) die. Once patients progress to SPMS, they cannot return to a lesser EDSS level or to RRMS; they can only stay at the same EDSS level, worsen to a higher EDSS level, or die. Relapses can occur at any time during RRMS and SPMS. DMTs act to delay disability worsening (i.e., transition to a higher EDSS level) and to reduce the frequency of relapses. Patients receiving treatment can experience treatment-related adverse events and can discontinue treatment because of various pre-defined reasons (e.g., progression to SPMS, reaching an EDSS level ≥7.0). Quality-adjusted life-years (QALYs) have been the primary health outcome in these models, calculated using utility weights based on EDSS during RRMS and utility decrements due to relapses and progression to SPMS. A Markov cohort modeling approach has been predominantly used in the existing economic models of DMTs for RRMS.

It is understandable that relapses and the EDSS have been used to characterize the clinical course of the disease in economic models of DMTs for RRMS. The annualized relapse rate is commonly the primary endpoint, co-primary, or key secondary endpoint in randomized clinical trials (RCTs) of RRMS. The EDSS is the most commonly used endpoint to measure disability in RCTs of RRMS,[1-4] it is well understood and is accepted by the neurology and regulatory communities.[5-8] However, the EDSS has several limitations (e.g., it cannot detect changes in people with severe disability and in various domains relevant in MS).[9-11] For this reason, alternative disability endpoints have been proposed for RCTs of MS such as the MS Functional Composite (MSFC). The MSFCS includes the Timed 25-Foot Walk (T25FW) test for ambulatory function, the 9-Hole Peg Test (9HPT) for upper-extremity function, and the Paced Auditory Serial Addition Test (PASAT) for cognition.[12, 13] Unfortunately, although the MSFC covers multiple major MS domains and has been reported to be highly reliable and correlated with the EDSS, with health-related quality of life, and with other important clinical and economic indicators, its responsiveness is not always better than EDSS and also has

several limitations.[7, 10, 12, 14-18] Thus, to address the individual limitations with the EDSS and the MSFC, endpoints combining the EDSS with the MSFC, or with individual components of the MSFC, have been proposed and used to assess the efficacy of DMTs in clinical trials of RRMS.[6, 19, 20]

Given the limitations of the EDSS and the growing interest in evaluating the efficacy of DMTs using multiple disability measures in clinical trials of MS, it may follow that additional disability measures could be more commonly included future cost-effectiveness analyses of DMTs, to supplement the EDSS and the occurrence of relapses. However, before introducing additional disability endpoints in economic models of DMTs for RRMS, it is necessary to determine whether those additional disability endpoints significantly contribute additional information on meaningful outcomes for decision makers (e.g., utility to calculate QALYs), which would otherwise not be captured by the EDSS and relapses. In this thesis, I demonstrated that there is a significant inverse relationship between the time to complete the T25FW test and utility for people with RRMS and SPMS, after accounting for the effect of the EDSS and relapses. The time to complete the 9HPT and the number of correct answers from the PASAT were not significant predictors of utility for people with RRMS and SPMS. These findings support the use of T25FW as an additional measure of disability to supplement the EDSS and the occurrence of relapses in the characterization of the clinical course of RRMS and SPMS, and the accrual of QALYs, in future economic models and cost-effectiveness analyses of DMTs for the treatment of RRMS. Not including the T25FW could lead to an incomplete assessment of the long-term clinical and economic implications of DMTs, potentially not capturing a positive (or negative) effect on patient's disability as measured by the T25FW.

Incorporating a new disability scale in economic models of DMTs for RRMS has challenges. First, the interrelated changes in the EDSS, T25FW, and the occurrence of relapses must be properly captured to avoid under- or over-estimates of the treatment effects, which would result in incorrect estimates of incremental cost-effectiveness ratios. In addition, the commonly used Markov cohort modeling approach in economic models of DMTs for RRMS may not be well equipped to model such interrelated changes because of the "no memory" property. Markov cohort models cannot efficiently track patients' relevant characteristics and past disease history over time to predict the subsequent course of disease. Furthermore, T25FW is a continuous variable which would have to be rendered as an ordinal scale in a Markov model, potentially leading to an unwieldy number of conditional health states. Lastly, the lack of long-term natural history data from population-based observational studies on T25FW poses a major challenge to use the T25FW with the EDSS and the occurrence of relapses and make reliable long-term predictions of the course of the disease.

In this thesis, I developed new disease models for RRMS and for SPMS which address the challenges that arise from the incorporation of T25FW as an additional measure of disability to supplement the EDSS and the occurrence of relapses in the characterization of the clinical course of RRMS and SPMS. First, the new disease models characterize the clinical course of RRMS and SPMS in terms of interrelated changes over time in EDSS, T25FW, and the occurrence of relapses. The interrelated changes were captured through linking variables in a set of predictive equations representing a patient's status (including confirmed improvement, confirmed worsening, and no change) in each disability scale and the occurrence of relapses over time. The linking variables capture the interrelated changes between the EDSS, T25FW, and the occurrence of relapses in the sense that changes in one trigger changes in the others, concurrently or at a later time point. Thus, when treatment effects of DMTs on EDSS, T25FW, and relapses are applied, the overall treatment effect would be proportionately accounted for by each disability scale and by the occurrence of relapses, which carry different weights when QALYs are accrued in an economic model. Second, both disease models were developed using discretely integrated condition event (DICE), a new approach developed for pharmacoeconomic analyses.[21-23] DICE allows to combine aspects from different techniques such as Markov models to determine the occurrence of confirmed disability improvements or worsening over three months as measured by the EDSS and T25FW, and discrete event simulation to model the occurrence of relapses using a time to event approach. The importance and advantages of using DICE vs. other modeling approaches became more evident when the disease models were transformed into an economic modeling framework to assess the cost-effectiveness of DMTs for RRMS, and more relevant patients' characteristics and events had to be incorporated and tracked over time. Finally, the new disease models were developed using longitudinal data from the Multiple Sclerosis Outcome Assessments Consortium (MSOAC) Placebo Database.[24, 25] The MSOAC Placebo Database data used includes 1,580 individual records of patients diagnosed with RRMS and 555 with SPMS, from the placebo arms of the five pivotal RRMS RCTs, two pivotal SPMS RCTs, and two pivotal RCTs that included patients with RRMS and SPMS. Although data from clinical trials may not be fully representative of patients in the real world and follow-up is usually relatively shorter than that in population-based observational studies, the face validity of the disease models and their predictive equations was confirmed by two clinical experts in MS. In addition, both disease models showed good internal validity closely replicating various clinical endpoints as observed in the MSOAC Placebo Database over the patients' follow-up, and good predictability of long-term disability reasonably predicting the time to progression from RRMS to SPMS as observed in the real world. Thus, the results and validations of the RRMS and SPMS disease models showed that the proposed modeling approach using data from clinical trials can be a feasible alternative to properly address the challenges of incorporating a new disability scale (T25FW) in economic models of DMTs for RRMS, and can serve as the basis for future economic models of DMTs.

Finally, I expanded upon the new disease models for RRMS and SPMS to transform them into a new economic modeling framework to assess the cost-effectiveness of DMTs for RRMS. The cost-effectiveness of two DMTs (dimethyl fumarate [DMF] and fingolimod [FGL]) for RRMS was assessed from the health care sector perspective in the United States. Two scenarios compared the results of the cost-effectiveness analysis when T25FW was accounted vs. not accounted for in the characterization of the clinical course of the disease and QALYs, to assess and illustrate whether, in addition to be a predictor of health utility in RRMS, T25FW would also impact the cost-effectiveness of DMTs. Including T25FW, treatment with both DMTs resulted in a lower change from baseline in EDSS, lower annualized relapse rate, longer time to progression to SPMS, and additional life years and QALYs vs. placebo, compared to the scenario excluding T25FW. When both DMTs were compared, the inclusion of their efficacy on T25FW had an important impact on cost-effectiveness results: FGL went from being dominated by DMF to, potentially, be cost-effective. These results confirm that clinical outcomes based solely on EDSS may not fully capture the impact of both EDSS and T25FW, and confirm the hypothesis that after accounting for the impact of EDSS, T25FW would have an additional impact in the clinical outcomes of economic models and the cost-effectiveness of DMTs.

One of the strengths and key differences of the new economic modeling framework, compared with previous economic models, is that the treatment effects of DMTs on disability are applied on the occurrence of events as measured in clinical trials of RRMS (e.g., three-month confirmed disease worsening) rather than applying them to the actual scale. Therefore, the new economic modeling framework developed in this thesis would allow to apply more accurately the treatment effects observed in clinical trials. Another strength of the model is that the treatment effects of DMTs on disability can be applied as hazard ratios or odds ratios, using the appropriate calculations as shown in Chapter 6, based on the available information. In addition, as previously noted, the underlying predictive equations of the new economic modeling framework were validated by two clinical experts in MS, and their internal validity and predictability was confirmed. Finally, the new economic modeling framework has the capability for conducting a structural sensitivity analysis in which only the EDSS and the occurrence of relapses are considered in the economic model (i.e., without accounting for T25FW in the characterization of the clinical course of the disease and QALYs), so decision makers can understand what the cost effectiveness results would be when T25FW is and is not considered.

To my knowledge, this is the first economic modeling framework developed to assess the cost-effectiveness of DMTs for RRMS that models for the interrelations of more than one disability scale (EDSS and T25FW) and the occurrence of relapses over time, and the impact of DMTs on them. A poster by Guo et al. (2013) presented at the 2013 International Society for Pharmacoeconomics and Outcomes Research (ISPOR) 18th Annual Meeting, used discrete event simulation to predict the occurrence of relapses and changes on EDSS in RRMS based

on two interrelated predictive equations.[26] In terms of disability scales, only the EDSS was considered and the predictive equations determined patient's actual EDSS level every three months. The study by Guo et al. (2013) did not expand the predictive equations into an economic model. If their predictive equations were expanded into an economic model, the effect of DMTs would have to be applied directly on the actual disability scale (i.e., EDSS level) instead of reducing the risk of the clinical event of three-month confirmed disability worsening, which is the actual disability endpoint measured in clinical trials of RRMS. A poster by Hernandez et al. (2015) presented at the 2015 ISPOR 18th European Meeting, used discrete event simulation to model interrelated changes of the six-month confirmed disability worsening events as measured by the EDSS, T25FW, and 9HPT and the occurrence of relapses in SPMS.[27] The study by Hernandez et al. (2015) did not expand the predictive equations into an economic model. One consideration of the study by Hernandez et al. (2015) is that the EDSS, T25FW, and 9HPT were considered because they were endpoints in the SPMS clinical trial (IMPACT) used to inform their predictive equations.[27, 28] As previously stated, before introducing additional disability endpoints in economic models, it is should be determined whether those additional disability endpoints significantly contribute additional information on meaningful outcomes for decision makers, which would otherwise not be captured by the EDSS and relapses. Based on the findings of this thesis, 9HPT is not a significant predictor of utility in RRMS and SPMS. Thus, if the predictive equations from the study by Hernandez et al. (2015) were to be expanded into an economic model, the exclusion of 9HPT would need to be considered. Unfortunately, only the conference abstracts of the studies by Guo et al. (2013) and Hernandez et al. (2015) were available, but not the actual posters presented at the conference. Therefore, the list of predictors included in their equations could not be compared with the final list of predictors included in the equations derived in this thesis.

A time to event approach such as in the study by Hernandez et al. (2015) was initially considered to model the occurrence of confirmed disability worsening (CDW) and confirmed disability improvement (CDI) in EDSS and T25FW for patients with RRMS and SPMS, as it was done with relapses. However, the CDW and CDI data observed in the MSOAC Placebo Database were considered immature, which could result in a high level of uncertainty when using a time to event approach fitting and extrapolating with parametric functions as in the study by Hernandez et al. (2015). In addition, the disease models for RRMS and SPMS developed in this chapter considered CDI and CDW, whereas in the study by Hernandez et al. (2015) only CDW was considered.[27] With a time to event approach, four equations would be needed for each scale in RRMS and another four in SPMS: two parametric functions and two Cox models for each scale. For these reasons, the equations derived in this thesis to model changes patients' disability status every three months used repeated-measures multinomial logistic regressions, in which the probabilities of multiple outcomes (i.e., CDW, CDI, and no change) for a given each scale could be predicted with a single equation. However, it should also be noted that calculating the probabilities of changes in patients' disability status every

three months could result in an increased the model runtime compared to a time to event approach.

The economic modeling framework developed in this thesis can be used to inform reimbursement decisions in countries where cost-effectiveness is part of the criteria to fund healthcare technologies. Reimbursement and health technology assessment agencies can use this framework to assess new DMTs and to re-assess currently approved and reimbursed DMTs to inform price adjustment decisions, considering the impact of the DMTs in EDSS, T25FW, and the occurrence of relapses. The inclusion of T25FW in the cost-effectiveness assessment of DMTs for RRMS would not only better inform decision makers regarding which DMTs would deliver better value for their money but will also incorporate in the decision-making process a scale that measures patients' walking ability and how DMTs impact it. This is important as patients with RRMS have ranked their walking ability as one of their most relevant bodily functions, right after visual function and cognition.[29] Physicians of patients with RRMS have ranked their patients' walking ability as their most relevant bodily function. [29] From the point of view of the manufacturers of DMTs for RRMS, if their DMTs have a positive effect in T25FW, the economic modeling framework developed in this thesis can help to support their value proposition, potentially improve their current cost-effectiveness vs. other DMTs, and possibly achieve a preferred status in the eyes of decision makers, including payers, prescribers and patients.

LIMITATIONS

The 1,580 individual records of patients diagnosed with RRMS and 555 with SPMS in the MSOAC Placebo Database used to derive the predictive equations that characterize the clinical course of RRMS and SPMS come from the placebo arms of the pivotal clinical trials of DMTs approved for the treatment of RRMS (including FGL, natalizumab, peginterferon, and teriflunomide) and of pivotal trials assessing the efficacy and safety of potential treatments for SPMS (including interferon beta-1a and dirucotide). However, data from other relevant pivotal clinical trials of DMTs approved for the treatment of RRMS with a placebo arm (e.g., DEFINE [DMF vs. placebo],[30] CONFIRM [DMF vs. glatiramer acetate and vs. placebo],[31] CLARITY [cladribine vs. placebo][32]) are not included in the MSOAC Placebo Database, and data from relevant RRMS pivotal trials using an active control arm (e.g., CARE-MS 1 and CARE-MS 2 [alemtuzumab vs. interferon beta-1a],[33, 34] OPERA I and II [ocrelizumab vs. interferon beta-1a][35]) are not available to the research community, to the best of my knowledge. If these data become available to the research community, they can be used to confirm the findings of this study and support their generalizability. Additional data from clinical trials of DMTs owned by pharmaceutical companies (some of which have several years of follow-up) could be used to confirm the findings from this study. Furthermore, predictive equations

derived from data of clinical trials owned by pharmaceutical companies could incorporate the efficacy of DMTs in the EDSS, T25FW, and relapses directly as predictors of the equations that model changes in disability status and level, as well as in the occurrence of relapses.
During the face validity assessment of the disease models for RRMS and SPMS, one of the clinical experts noted that most of their clinical decisions, such as which DMT to prescribe and when to switch between DMTs, are made based on imaging data (e.g., magnetic resonance imaging [MRI; gadolinium-enhancing lesions; new enlarging T2 lesions]). The clinical expert suggested lesions and MRI findings could be also studied as potential predictors of patients' disability in the disease models and the economic model. Unfortunately, the MSOAC Placebo Database does not contain imaging data. Data from clinical trials of DMTs owned by pharmaceutical companies may be the best source of imaging, disability, and relapses information to assess whether imaging data (e.g., number of T2 lesions at baseline or in the last year) are significant predictors of patients' disability and the occurrence of relapses.

Although extensive validations of the disease models for RRMS and SPME were conducted, there are additional steps that could be pursued, should the appropriate data become available, to further demonstrate the long-term predictability of the disease models for RRMS and SPMS. These include, but are not limited to: use of other external population-based data sources, examination of subgroups characterized by various demographic and disease factors, and validation on the long-term disability as measured by the T25FW using external data.

The data used to inform the efficacy of DMF and FGL vs. placebo in the cost-effectiveness analyses compared in Chapter 6 combined the results of a matching-adjusted indirect comparison (MAIC) of clinical trial data for the efficacy of both DMTs on the EDSS and relapses, with the results from two combined clinical trials of DMF vs. placebo and a retrospective real-world study of FGL vs. DMF for the efficacy on T25FW.[36] This was done due to lack of efficacy data for the DMTs on the EDSS, T25FW, and relapses reported from the same study. Ideally, the efficacy of the DMTs being compared on the relevant disability scales (EDSS and T25FW) and the occurrence of relapses would be obtained from the same study, when available.

Finally, the predictive equations that model the clinical course of RRMS and SPMS were derived from pooled data of the placebo arms of various clinical trials. Therefore, to compare DMTs using the economic modeling framework developed in this thesis, the efficacy of the DMTs on EDSS, T25FW, and the occurrence of relapses needs to be included relative to placebo, using head-to-head data or appropriate indirect treatment comparisons.

FUTURE RESEARCH

The use of these additional measures of disability in economic models of DMTs for RRMS will require that the efficacy of the DMTs on EDSS, T25FW, and the occurrence of relapses are collected in clinical trials of new DMTs,[6] and are reported, if available, for existing DMTs. In addition, appropriate indirect treatment comparisons (e.g., network meta-analysis) should be conducted for T25FW, as it has been previously done for EDSS and relapses,[37-39] to inform the relative efficacy parameters of the economic models. The availability of data is a general challenge for economic models across disease areas. However, future researchers could seek partnerships with manufacturers of DMTs to access their clinical trials' data or with groups such as MSOAC to access the data available for active treatments, and derive the efficacy of DMTs on T25FW which could then inform an appropriate indirect treatment comparison. Manufacturers of DMTs with a positive effect on T25FW may be more open to share their data to assess if the cost-effectiveness of their DMTs improves relative to that of comparators. If T25FW data are not reported or available for a specific DMT, that DMT could not be included in an economic model using T25FW, EDSS, and relapses.

In this thesis, T25FW was a significant predictor of health utility measured by the Short-Form Six-Dimension (SF-6D). With access to the clinical trial data owned by manufacturers of DMTs, researchers could also assess whether T25FW (and other measures of disability such as the 9HPT, PASAT) would be also significant predictors of health utility measured by the EuroQol-5 Dimension (EQ-5D), another commonly used measure of utility used in cost-effectiveness analyses of healthcare technologies.

T25FW was incorporated in the economic modeling framework developed in this thesis because it significantly contributes additional information on health utility in patients with RRMS and SPMS, otherwise not captured by EDSS and the occurrence of recent relapses. Other disability scales such as the 9HPT and PASAT were not significant predictors of utility in patients with RRMS and SPMS, after accounting for the effect of EDSS and relapses, and were not considered in the economic modeling framework. Costs are the other component of cost-effectiveness analyses that are relevant for decision makers. Future research could assess whether the T25FW (and other disability scales) may significantly contribute additional information on resource utilization and costs in patients with RRMS and/or SPMS, otherwise not captured by the EDSS and the occurrence of relapses, such as: direct medical costs (e.g., routine monitoring), direct non-medical costs (e.g., home health aide, support bars around the house), and indirect costs (e.g., productivity loss due to absenteeism and presenteeism). Disability scales that may be significant predictors of resource utilization and costs would be candidates for inclusion in future economic models of DMTs.

A recent multicenter three-year prospective study conducted by Heesen et al. (2018), designed to understand perceptions on the value of 13 bodily functions for 171 people with RRMS and for their physicians, found that for people with RRMS, visual function (23%) followed by cognition (17%), walking ability (16%), and lack of pain (14%) were the most relevant. For physicians, the walking ability of their patients was the most relevant (38%), followed by cognition (18%); visual function did not gain a high priority for physicians (8%). [29] In addition, visual function assessed by the Low Contrast Letter Acuity (LCLA) test has been shown to be associated with HRQoL and has been proposed to be included as part of a composite primary endpoint comprised by the T25FW, 9HPT, LCLA and the Symbol Digit Modalities Test (SDMT; to assess cognition instead of PASAT), or as a key secondary endpoint in MS clinical trials[6, 40] Future studies could conduct analyses similar to those carried out in this thesis, to investigate if visual function and cognition assessed with the SDMT significantly contributes additional information regarding the impact of disability on health utility (and/or costs), otherwise not captured by EDSS, T25FW, and relapses, and should be considered in future economic models of DMTs for RRMS.

Finally, the increase in available DMTs is likely to create a need for information regarding the cost-effectiveness of treatment sequences, as well as the cost-effectiveness of specific DMTs based on line of therapy. The economic modeling framework developed in this thesis has the capability of modeling second-line DMTs after the discontinuation of the first-line DMT for reasons other than progression to SPMS and worsening to an EDSS ≥7.0. This will allow future researchers to focus their efforts on the collection of efficacy data on the EDSS, T25FW, and relapses for DMTs in second-line, which could then be incorporated in the economic modeling framework.

CONCLUSION

The structure of the economic models used to assess the cost-effectiveness of DMTs for the treatment of RRMS has converged over time. The clinical course of the disease is characterized in terms of changes in disability measured by the EDSS and the occurrence of relapse over time, modeled predominantly with a Markov cohort approach. With the growing interest in evaluating the efficacy of DMTs using multiple disability measures in clinical trials of MS, it will become more important to appropriately model and extrapolate from the short-term results observed in clinical trials using multiple disability endpoints to assess the long-term clinical and economic implications of DMTs. An important consideration before introducing additional disability endpoints in economic models is to assess whether those additional disability endpoints significantly contribute additional information on meaningful outcomes for decision makers (such as utility and costs), which would otherwise not be captured by the EDSS and relapses. However, the addition of disability measures in economic models poses considerable

challenges, including the selection of an appropriate modeling approach to handle the correlation of changes in multiple disability scales and the occurrence of relapses over time, as well as the lack of long-term natural history data on various disability measures and relapses.

In this thesis, it was demonstrated that the time to complete the T25FW test for ambulatory function significantly contributes additional information on health utility in people with RRMS and SPMS, otherwise not captured by EDSS and the occurrence of recent relapses. These findings support the use of T25FW as an additional measure of disability to supplement the EDSS and the occurrence of relapses in the characterization of the clinical course of the disease and the accrual of QALYs in economic models of DMTs for RRMS. A new economic modeling framework was developed using DICE simulation to assess the cost-effectiveness of DMTs for RRMS, with the addition of T25FW. The new economic modeling framework appropriately models the correlation of changes between the EDSS, T25FW, and relapses. Furthermore, the validation of the underlying RRMS and SPMS disease models by clinical experts in MS and various simulations showed that the proposed approach using data from clinical trials is a feasible alternative to address the challenges of incorporating additional measures of disability in economic models of DMTs. The results of two scenarios run using the new economic modeling framework, comparing the results of the cost-effectiveness of two DMTs when T25FW was accounted vs. not accounted for in the characterization of the clinical course of the disease and QALYs, demonstrated that: clinical outcomes in economic models of DMTs for RRMS based solely on EDSS may not fully capture the impact of both EDSS and T25FW; and the addition of T25FW has an important impact on the cost-effectiveness of DMTs, moving a dominated DMT to be, potentially, cost-effective.

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