Original Article

MDM Medical Decision Making

Medical Decision Making
2020, Vol. 40(2) 198–211

DOI: 10.1177/0272989X19897944
journals.sagepub.com/home/mdm
SAGE

Summarizing Patient Preferences for the Competitive Landscape of Multiple Sclerosis Treatment Options

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Objective. Quantitatively summarize patient preferences for European licensed relapsing-remitting multiple sclerosis (RRMS) disease-modifying treatment (DMT) options. **Methods.** To identify and summarize the most important RRMS DMT characteristics, a literature review, exploratory physician interviews, patient focus groups, and confirmatory physician interviews were conducted in Germany, the United Kingdom, and the Netherlands. A discrete choice experiment (DCE) was developed and executed to measure patient preferences for the most important DMT characteristics. The resulting DCE data ($n = 799$ and $n = 363$ respondents in the United Kingdom and Germany, respectively) were analyzed using Bayesian mixed logit models. The estimated individual-level patient preferences were subsequently summarized using 3 additional analyses: the quality of the choice data was assessed using individual-level R^2 estimates, individual-level preferences for the available DMTs were aggregated into DMT-specific preference shares, and a principal component analysis was performed to explain the patients' choice process. **Results.** DMT usage differed between RRMS patients in Germany and the United Kingdom but aggregate patient preferences were similar. Across countries, 42% of all patients preferred oral medications, 38% infusions, 16% injections, and 4% no DMT. The most often preferred DMT was natalizumab (26%) and oral DMT cladribine tablets (22%). The least often preferred were mitoxantrone and the beta-interferon injections (1%–3%). Patient preferences were strongly correlated with patients' MS disease duration and DMT experience, and differences in patient preferences could be summarized using 8 principle components that together explain 99% of the variation in patients' DMT preferences. **Conclusion.** This study summarizes patient preferences for the included DMTs, facilitates shared decision making along the dimensions that are relevant to RRMS patients, and introduces methods in the medical DCE literature that are ideally suited to summarize the impact of DMT introductions in preexisting treatment landscapes.

Keywords
discrete choice experiment, multiple sclerosis, patient preferences

Date received: February 12, 2019; accepted: November 23, 2019

Multiple sclerosis (MS) is a chronic demyelinating disease of the central nervous system characterized by inflammation and axonal degeneration.[1] Approximately 85% of all patients are initially diagnosed with relapsing-remitting MS (RRMS), which is characterized by exacerbations and periods of disease stability after recovery.[2] Disease-modifying treatments (DMTs) that target immunological signaling proteins (e.g., interferons and cytokines) or populations of immune cells (e.g., lymphocytes) are typically used to treat RRMS.[3] DMTs are relatively successful in controlling inflammatory activity

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(i.e., relapses); however, they only reduce the rate of progression of neurodegenerative processes and do not cure the disease.[3,4]

Because no optimal DMT for RRMS exists, therapy should be tailored to individual patient preferences as well as disease progression.[5] Patient preferences are even referred to as "critical" in recently published American Academy of Neurology practice guideline recommendations.[6] Consequently, there is an intrinsic need for MS patient preference studies in the field of clinical neurology, that is, beyond the general need for patient-centered care that is respectful of and responsive to individual preferences in clinical decisions.[7,8] Appendix A in the Supplementary Material provides a structured overview of previously published MS patient preference studies.[9–23] This research has been informative regarding the general stance of MS patients on risk/benefit tradeoffs when choosing between DMTs. However, these studies have neglected one very important aspect, which is the analysis of patient preferences for actually available treatment profiles. Hence, although academically interesting, previous preference research has provided limited applicable guidance to clinicians who aim to align treatment selections with patient preferences.

The goal of the current article is to complement existing MS preference research by assessing patient preferences for entire DMT profiles. Our approach is based on discrete choice experiment (DCE) methods that are commonly used in the marketing literature and that can provide insight into patients' considerations when choosing between actual DMTs as well as aggregate information on patient preferences for different types of DMTs. Furthermore, the implemented approach facilitates an evaluation of the impact of the introduction of new DMTs, such as the recently approved cladribine tablets, into the competitive landscape of existing treatment options.[24] Unfortunately, the most recently introduced RRMS DMT (i.e., ocrelizumab) was not included in the competitive landscape because sufficiently detailed information about the side effects were unavailable during the design of the study. However, since the presented methodology is very general, new DMTs (including ocrelizumab) can easily be introduced in future extensions of the competitive landscape.

Duke Clinical Research Institute, Duke University, Durham, NC, USA (MFJ); Erasmus Choice Modelling Centre, Erasmus University Rotterdam, Rotterdam, the Netherlands (MFJ, BD, LG, RH, EdB-G); Erasmus School of Health Policy & Management, Erasmus University Rotterdam, Rotterdam, the Netherlands (MFJ, LG, RH, EdB-G, MV); Erasmus School of Economics, Erasmus University Rotterdam, Rotterdam, The Netherlands (BD); Erasmus MC–Erasmus University Medical Centre, Rotterdam, The Netherlands (LJ); Institute for Medical Technology Assessment, Erasmus University Rotterdam, Rotterdam, the Netherlands (MV); EMD Serono Inc., Billerica, MA, USA (GH, SLW). The authors declared the following potential conflicts of interest with respect to the research, authorship, and/or publication of this article: Financial support for this study was provided by a contract between EMD Serono, Inc. and the Institute of Medical Technology Assessment of the Erasmus University Rotterdam. The funding agreement ensured the authors' independence in designing the study, interpreting the data, writing, and publishing the report. The following authors are employed by the sponsor: GH and SW. The other authors have no conflicts of interests to report. The authors received no financial support for the research, authorship, and/or publication of this article.

Methods

This study used a mixed methods approach. Initially, qualitative research methods (i.e., a literature review, exploratory physician interviews, patient focus groups, and confirmatory physician interviews) were used to identify and summarize the important aspects of currently licensed RRMS DMTs. Subsequently, a DCE was developed and executed to measure patient preferences for all relevant DMT characteristics and to quantitatively summarize the patient choice process.

Theoretical Foundation

In a DCE, the preference for a medical intervention, such as an MS treatment, is established by decomposing it into separate characteristics (referred to as "attributes") and different variants of these characteristics (referred to as "levels").[25,26] For example, the attribute "mode of administration" comprises the levels "injection," "oral," and "infusion." The basic assumption in a DCE is that all interventions are a combination of levels and that individuals' preferences for interventions can be determined based on the combined evaluation of these levels.[27] The relative importance of the selected levels is empirically established by asking respondents to make tradeoffs in a series of choice tasks. Within each choice task, there are 2 or more interventions to choose from, and respondents are repeatedly asked to indicate the option that they prefer. Statistical regressions are subsequently used to derive numerical values for the relative attractiveness of all attributes and levels, using methods that have a solid foundation in random utility theory.[28]

Selection of Attributes and Levels and Summary Descriptions of the DMTs

To identify the relevant attributes and levels of the included RRMS DMTs, a literature review, exploratory

physician interviews ($n = 8$), and patient focus groups ($n = 33$ patients) were conducted in the Netherlands, Germany, and the United Kingdom. The selection of attributes and levels was based on a bottom-up approach in which a so-called "competitive landscape" of treatment options was constructed. This competitive landscape covered the most important dimensions of MS treatments (i.e., administration, efficacy, side effects, and pregnancy-related considerations). Within each dimension, a set of key attributes and levels was identified from the literature as well as patient focus groups and physician interviews. Moreover, once the initial competitive landscape had been constructed, several confirmatory sessions with physicians ($n = 8$, of which $n = 4$ were not included before) were conducted to verify the selection of attributes and levels, assess the balance and accuracy of the DMT's descriptions, and decide on the optimal classification of the included side effects. The interviews were conducted in June 2016 (Germany) and September 2016 (United Kingdom).

During these confirmatory meetings, several important decisions were made. Most importantly, side effects were classified based on their reversibility and timing of occurrence. This resulted in 3 categories: 1) immediately occurring and reversible side effects, 2) reversible side effects, and 3) irreversible side effects. In addition, it was decided to include an attribute that described the required screening intervals for potentially severe side effects, such as heart failure, liver problems, leucopenia, and macular edema. For these side effects, effective monitoring generally prevents the occurrence of irreversible side effects, although patients may be required to switch DMTs when problems are detected.

In addition to their classification, all included side effects were further described with an incidence description. For clarity and comparability, a limited set of incidence categories with a common denominator of 100 was used for all frequently occurring reversible side effects; that is, "sometimes" denoted approximately 10 of 100 patients, "often" denoted approximately 20 of 100 patients, and so forth. Similarly, a small number of incidence categories with a common numerator of 1 were used for the severe and irreversible side effects (e.g., a "very small risk" of approximately 1 of 30 000 patients or a "small risk" of approximately 1 of 10 000 patients. Although mixing risk communication strategies is generally not recommended, it was the preferred option to deal with the scale incompatibility between regularly occurring yet benign side effects versus infrequently occurring but potentially lethal adverse events. The clarity of the incidence descriptions was carefully tested in think-aloud interviews.

Considerable efforts were made to accurately describe the efficacy levels of the DMTs. Based on the literature review, almost as many formulations of the efficacy levels as DCE publications were identified. These different formulations were included and discussed in the patient focus groups and physician interviews. The consensus was that absolute descriptions (e.g., treatments resulting in exactly 2 or 3 relapses in the next 2 years) were easiest to understand for patients. However, such absolute descriptions were also deemed unrealistically simple and inaccurate from a clinical perspective. Accordingly, a relative formulation was used similar to the one used by Wicks and colleagues,[12] in which the efficacy of treatments is described as being effective, quite effective, very effective, or highly effective, which corresponds to 33%, 44%, 55%, and 66% reduction in relapse or disability risk compared with using no MS medication at all.

In terms of disease progression, most physicians did not explicitly differentiate between the reduction in the number of relapses and disability progressions in their communication with patients. The consensus was that both aspects are intrinsically linked for all currently available DMTs, meaning that in clinical decisions, no tradeoffs between both aspects of efficacy are required. In other words, if one treatment is more effective than another in terms of reducing the number of relapses, it is also equally or more effective in terms of reducing disability risk. An overview of the included DMTs, as well as a description of all important considerations constituting the final selection of attributes and levels assigned to each of the DMTs, is included in Supplementary Appendix B.

Structure and Visual Presentation of the Choice Tasks

In the choice tasks, combinations of the attributes and levels that were relevant for each mode of administration were used to construct realistic discrete choice tradeoffs. To mitigate the cognitive burden of the survey instrument, the choice tasks were separated into 4 separate sections: 1) injections, 2) infusions, 3) oral medications, and 4) an "overarching" DCE in which respondents compared all treatment types simultaneously (see Supplementary Appendix C). The fourth section was used to refine the initial preference measurements and

place them on a common utility scale. This allowed for a direct comparison of patient preferences for all DMTs without requiring choice tasks that simultaneously included all of the 16 attributes in the DCE.

To further reduce the cognitive burden of the survey (and restrict the layout of the choice tasks), the maximum number of side effects in the profiles was constrained to 5. In the choice tasks with equal modes of administration, only 3 attribute levels were allowed to be different. The differences between the choice options were highlighted, making choice tasks substantially easier for respondents.[29,30] In addition, the format of the side effects was programmed to show only the side effects that were relevant for each treatment option, instead of also showing potential adverse effects that were not associated with a particular treatment option. This again reduced the complexity of the choice tasks and was considered more realistic and congruent with how physicians describe differences between treatment options to their patients.

Carefully constructed warm-up tasks were used to gradually explain all relevant attributes and levels in the DCE. Alternating information screens and warm-up tasks were used to first introduce 1 or 2 related attributes (e.g., using a figure and/or a few sentences), followed by a choice task to clarify the tradeoff involved (see Figure 2). During the warm-up tasks, the complexity of the visual presentation was gradually increased by always including previously explained treatment attributes in the layout. This way, by the end of the warm-up questions, all respondents were fully accustomed to the choice format used in the regular DCE questions.

DCE Design

To create an efficient DCE design that adhered to the level overlap constraints and included only realistic treatment options with side effects and efficacies that are relevant for each mode of administration, a custom optimization algorithm had to be developed. This algorithm was based on the methods introduced by Sándor and Wedel[31] and was implemented in the Fortran programming language. The algorithm created 10 different versions of the DCE design, each comprising 15 fixed warm-up tasks and 28 (i.e., 4×7) regular discrete choice tasks, with DCE sample size calculations as described by de Bekker-Grob and colleagues[32] used to ensure adequate statistical power. During the data collection, the DCE design was improved several times to better reflect previously observed patient preferences and increase statistical efficiency.

Survey Development and Patient Recruitment

After the development of an initial version of the DCE design, the survey was piloted in Germany. In total, 3 German pilot studies were held with a total of 112 RRMS patients aged 18 years and older recruited via Neurotransdata. The recruitment source implied that patients were invited by their treating physicians to participate in the survey. Patients completed the questionnaire in their own clinic and under supervision of their own MS nurse. The MS nurses also actively helped to improve the survey instrument until it was considered suitable for unattended administration to MS patients.

At this point, the German survey was translated into English and piloted in an online sample of 164 respondents from the United Kingdom recruited via Opinion Health. Based on the patient satisfaction scores, cognitive debriefing questions, and DCE sample size calculations, no further changes to the survey structure were required. This allowed for the UK data collection to be completed and the initiation of the online component of the German data collection, which was conducted by Survey Sampling International alongside continued data collection via Neurotransdata. All data were collected from January to June 2017.

Survey Satisfaction and Verification of the Choice Data

After the data collection, the included survey satisfaction and cognitive debriefing questions were summarized by averaging their 7-point Likert-type scores. The survey's dropout rates were directly observed, and completion timings were calculated as the cumulative time spent on the pages of the questionnaire, maximized at 10 minutes per page to correct for respondents taking a break in between survey questions. Finally, individual-level R^2 statistics (see the next section) were calculated to assess the quality of the choice data and identify respondents with illogical response structures.

Econometric Analyses

Bayesian methods were used to estimate population and individual-level patient preferences for the German and UK samples using mixed logit (MIXL) models.[33] Such models use the observed choices as the dependent variable and the characteristics of the choice options as explanatory variables. The estimations were conducted using OpenBUGS and based on a run of 200 000 Markov Chain Monte Carlo (MCMC) draws, with the initial 100 000 discarded as burn-in iterations. Convergence was

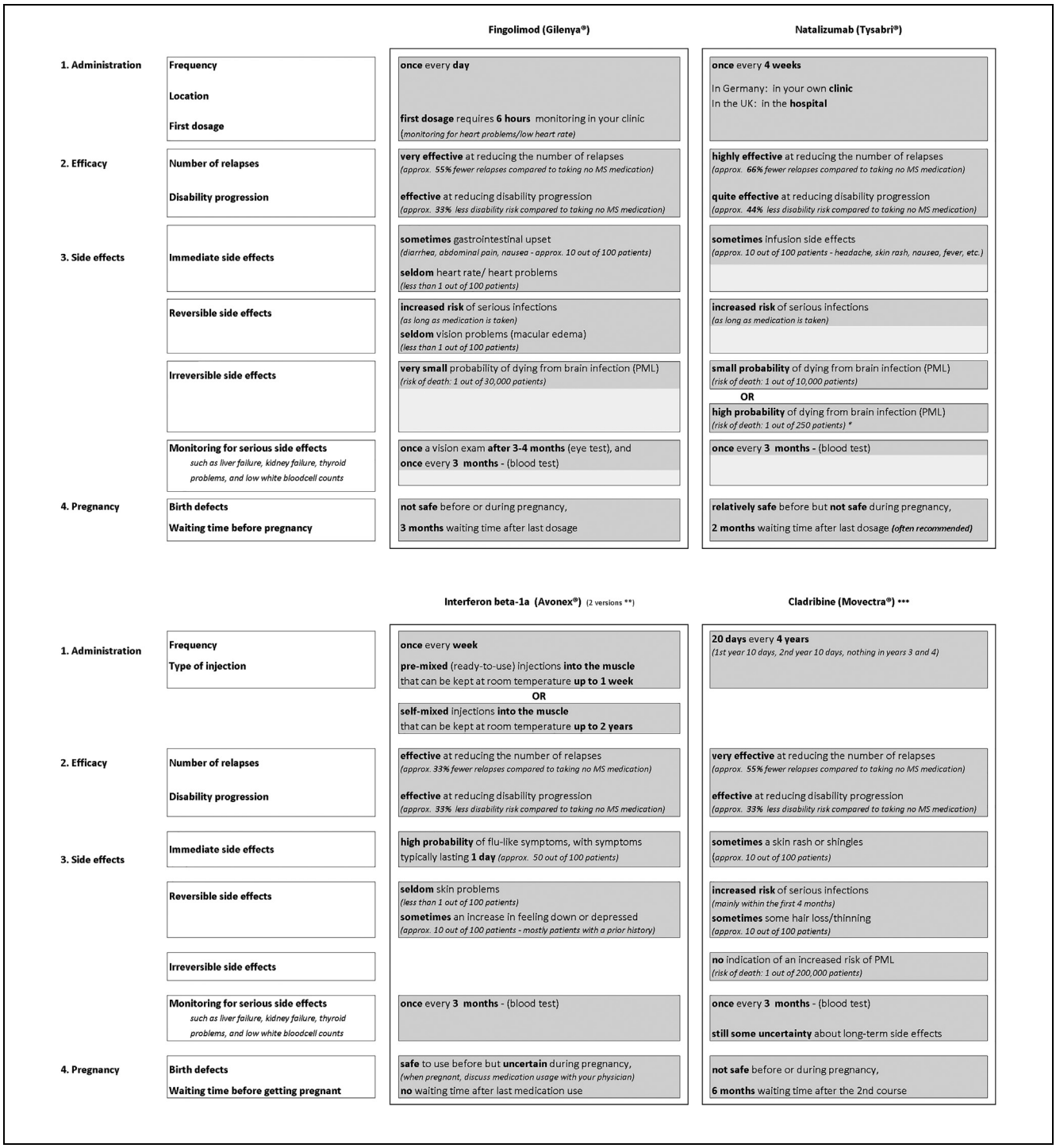

Figure 1 Example disease-modifying treatments (DMTs). The actual DMTs were not included in the survey and were not shown to respondents. Please see Supplementary Appendix B for a description of all DMTs in terms of the selected attributes and levels. *Only relevant for John Cunningham virus–positive patients. **Only the premixed version of Avonex is applicable in the United Kingdom. ***Cladribine was included with and without having still some uncertainty about its long-term side effects.

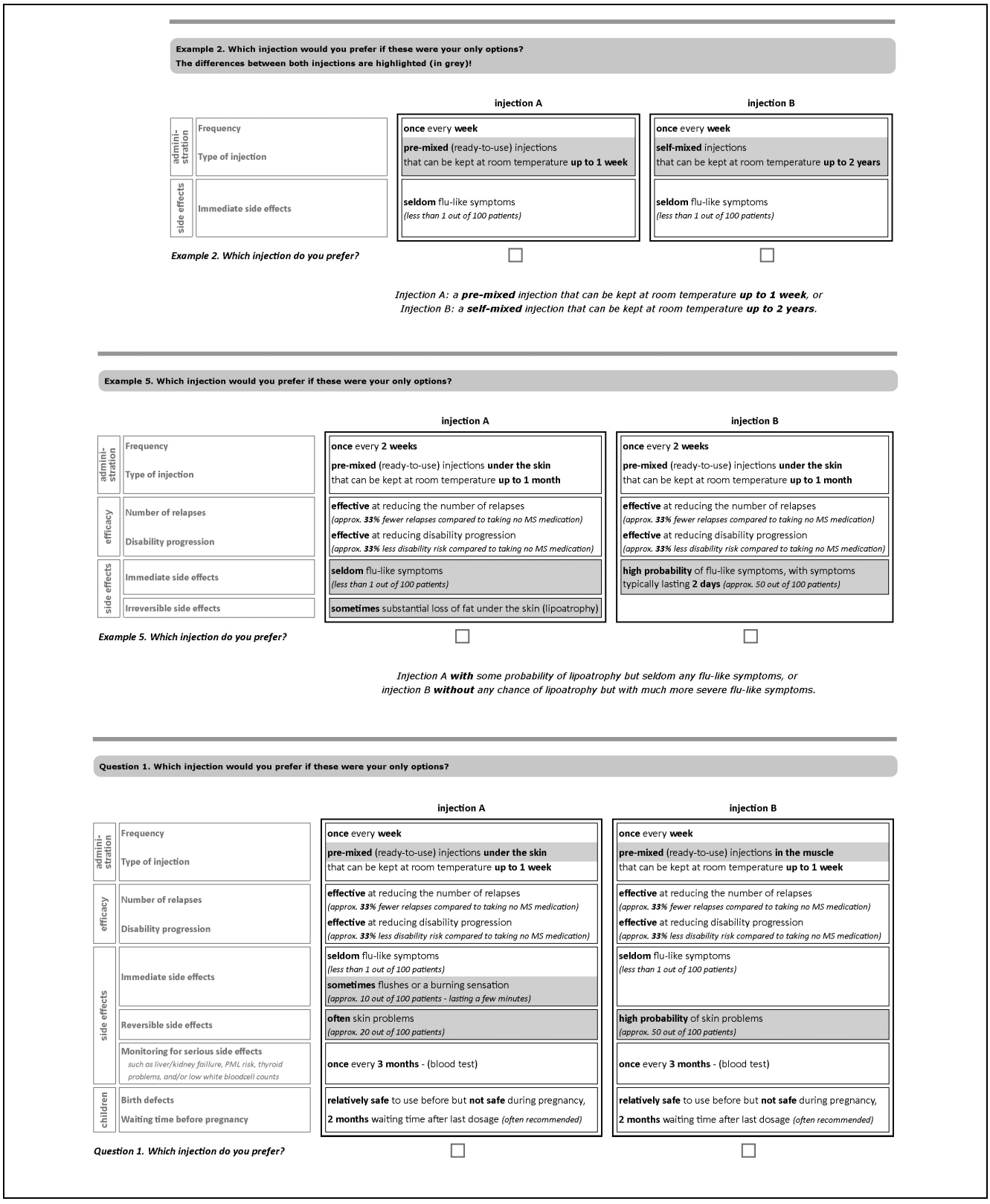

Figure 2 Two warm-up and 1 regular discrete choice experiment question.

evaluated based on a visual inspection of the chains and the diagnostics as implemented in the OpenBUGS software. The model codes with the full specification of the priors are included in Supplementary Appendix D, with detailed estimation results for the separate samples included in Supplementary Appendix E.

Obtaining the full set of preference estimates was not a goal in itself. Instead, conforming with DCE applications in the marketing literature,[34,35] our goal was to accurately summarize patient preferences for currently existing and new DMTs. This was performed using 3 additional analyses. In the first, the individual-level preference estimates as obtained from the MIXL models were used to calculate individual-level McFadden R^2 statistics. Whereas a value of zero denotes random choice behavior, McFadden[36] suggested that R^2 values between 0.2 and 0.4 represent an excellent model fit, constituting the 3-level classification of 0.0–0.1, 0.1–0.2, and >0.2 to denote poor, moderate, and excellent model fits, respectively. Hence, the first analysis was used to confirm the goodness-of-fit of the MIXL models and provide quantitative credibility of the DCE results, in addition to the qualitative information obtained from the think-aloud interviews and survey satisfaction and cognitive debriefing questions.

In the second analysis, the individual-level preference estimates as obtained from the MIXL models were used to estimate individual-level choice probabilities for all DMTs in the competitive landscape. These were subsequently aggregated, separately by country and patient characteristics, to obtain the percentage preference share for each of the included DMTs. This approach has the advantage of including all heterogeneity in patient preferences while simultaneously implying that much of the uncertainty in the individual-level estimates cancels out in the population preference shares.[35] The required calculations were performed in MATLAB and were based on the MCMC draws of the individual-level preference parameters. Accordingly, for all of the included scenarios, Bayesian 95% credible intervals of the aggregate preference shares could be reported that took the full uncertainty of the underlying individual-level preferences into account. The different scenarios that were included captured the impact of a significantly higher risk of progressive multifocal leukoencephalopathy (PML) for MS patients who are John Cunningham virus (JCV) positive, the impact of the recent introduction of cladribine tablets on patients' DMT preferences, the impact of cladribine tablets potentially still having some uncertainty about the long-term side effects, the impact of patients' experience with MS (based on the number of years since MS diagnosis), and patients' experience with DMT modes of administration based on their current and previous DMT use.

In the third analysis, a principal component analysis (PCA) was used to summarize the individual-level preference structure of all participating respondents from the United Kingdom and Germany combined. This follow-up analysis was performed using STATA15 using an orthogonal rotation to improve the interpretation of the results.[37] The PCA provided a concise description of the patient choice process using a limited set of underlying factors that were selected to jointly describe 99% of the variation in patient preferences. As such, the PCA summarizes the patient preferences as captured by the set of 48 parameters in the overarching DCE into a smaller number of dimensions that are easier to interpret and more relevant for clinical practice.

Role of the Funding Source

This study was sponsored by EMD Serono under contractual freedom to publish the results irrespective of the outcome of the study. The sponsor was kept apprised on the progress and able to provide valuable comments on the conduct of the study, while the Erasmus research team had complete contractual freedom to make independent decisions to uphold the scientific quality and integrity of the study. In addition, the funding agreement included a publication clause that guaranteed the Erasmus team to publish the outcomes of the study irrespective of the sponsor's approval.

In the exploratory interviews, participating physicians and patients were not informed about the identity of the study's sponsor, making sure that all DMT profiles would be presented and assessed in an equal and unbiased manner. In the confirmatory interviews, physicians were informed about the study's sponsor and asked to confirm that all DMTs were fairly and accurately described.

Results

In total, 1770 UK and 648 German respondents confirmed to have been diagnosed with MS and agreed with the informed consent. With many respondents excluded because of the study's RRMS inclusion criteria and with several respondents dropping out during the survey administration, this resulted in 799 and 363 completes for the UK and German samples, respectively (see Figure 3), with mean completion times of 33 and 39 min, respectively. The UK and German sample were

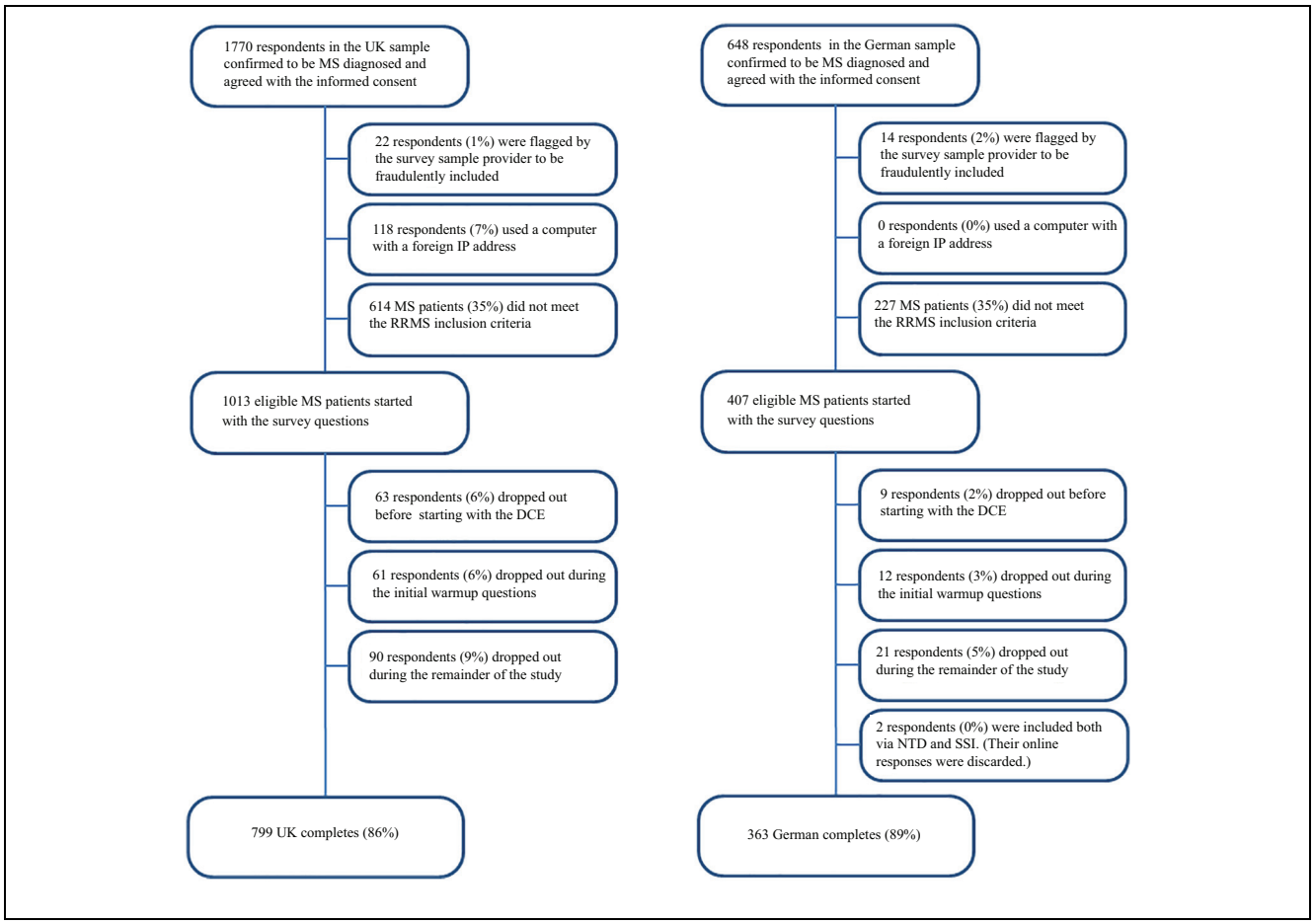

Figure 3 Flow diagram detailing the number of UK (left) and German (right) completes.

approximately equally divided in terms of educational attainment but had a different pattern of current and previous medication usage (Table 1). In Germany, participating patients were more frequently using injections (31%) than in the United Kingdom (24%) and less frequently using oral medications (38% v. 48%). A similar pattern was observed with respect to previously used DMTs.

Overall, respondents were highly satisfied with the survey, could easily identify the differences between the treatment options, and did not indicate that the number of choice tasks was too large (Table 2). Thirty-seven respondents (4.7%) in the United Kingdom and 22 respondents (6.1%) in the German sample had individual-level R^2 statistics smaller than 0.1. Vice versa, 652 respondents (82%) and 290 respondents (80%) had R^2 statistics larger than 0.2, which was indicative of a good or even excellent model fit. Excluding respondents with an R^2 smaller than 0.1 had a negligible impact on the presented results; therefore, no respondents were dropped from the sample.

Table 3 presents the aggregated DMT preferences by country and patient background characteristics. The difference in aggregated percentage preference shares between German and UK patients was small. Therefore, percentage preferences of the combined sample of UK and German respondents are reported. Starting with the historic base-case scenario, approximately 49% of all patients preferred infusions, 28% orals, 18% injections, and 5% preferred no DMT. The most often preferred DMT was natalizumab (33%), with alemtuzumab (14%) and teriflunomide (13%) ranked second and third. Mitoxantrone and beta-interferon injections were least often preferred. The introduction of cladribine tablets into the therapeutic landscape constituted our base-case scenario, in which cladribine tablets were included without uncertainty about their long-term safety profile. Here, natalizumab (26%) remained the most often

Table 1 Descriptive Statistics of the Patient Samples

	United Kingdom					Germany				
Variable	**Obs**	**Mean**	**SD**	**Min**	**Max**	**Obs**	**Mean**	**SD**	**Min**	**Max**
Female	799	0.79		0	1	363	0.74		0	1
Age	799	42.6	10.0	18	79	363	42.0	10.8	18	71
Education (low)[a]	799	0.32		0	1	211	0.33		0	1
Education (medium)[a]	799	0.33		0	1	211	0.38		0	1
Education (high)[a]	799	0.35		0	1	211	0.29		0	1
Year of diagnosis	670	2009	6.47	1977	2016	348	2006	7.2	1977	2016
Currently uses injections	799	0.24		0	1	363	0.31		0	1
Currently uses pills	799	0.48		0	1	363	0.38		0	1
Currently uses infusions	799	0.14		0	1	363	0.16		0	1
Currently uses no MS medication	799	0.14		0	1	363	0.15		0	1
Previously used injections	799	0.57		0	1	363	0.78		0	1
Previously used pills	799	0.40		0	1	363	0.30		0	1
Previously used infusions	799	0.22		0	1	363	0.24		0	1
Previously used no MS medication	799	0.23		0	1	363	0.07		0	1

[a]Low education refers to International Standard Classification of Education (2011) levels 0–2, medium education to levels 3–4, and high education to levels 5–8. MS, multiple sclerosis; Obs, observations.

Table 2 Summary of Survey Evaluation Questions[a]

	United Kingdom				Germany			
Question	**Obs**	**Mode**	**Mean**	**SD**	**Obs**	**Mode**	**Mean**	**SD**
The choice tasks were clear	799	7	6.0	1.3	363	7	5.7	1.5
The choice tasks were interesting	799	7	5.8	1.3	363	7	5.6	1.6
I could easily identify the differences between the treatment options	799	7	6.0	1.4	363	7	5.7	1.6
I could easily choose between the treatment options	799	7	5.5	1.6	363	7	5.5	1.6
I could easily have answered more choice tasks	799	4	5.0	1.6	363	7	4.7	2.2
There were too many choice tasks	799	4	3.7	1.8	363	1	3.6	2.0
The survey's topic was interesting	799	7	6.0	1.4	363	7	6.0	1.5

[a]Respondents were asked to evaluate the statements on a 7-point Likert-type scale, ranging from 1 (*I completely disagree*) to 7 (*I completely agree*). Obs, observations.

preferred DMT, with cladribine tablets (with a preference share of 22%) in second place. The introduction of cladribine tablets had little impact on the preference shares of injections (i.e., –10% on glatiramer acetate and no impact on the beta-interferons), suggesting that cladribine tablets and injections are relevant to different patient segments and not in direct competition. In the first sensitivity analysis, in which there was still some uncertainty about the long-term side effects of cladribine, cladribine tablets were considered less attractive and received a much lower preferences share (i.e., –27%). In the second sensitivity analysis, the increased risk of death due to PML made natalizumab considerably less attractive, resulting in –85% preference share and with substitution mainly occurring toward cladribine tablets (i.e., +36%), alemtuzumab (i.e., +40%), and fingolimod (i.e., +43%). The third sensitivity analysis shows that patients who were diagnosed longer ago are less likely to prefer injections (13% v. 20% preference share) and more likely to prefer more effective and less frequently administered orals and infusions (i.e., alemtuzumab and cladribine tablets). The fourth and final sensitivity analysis indicates that experience with DMTs also matters. Compared with patients who have never used a particular type of DMT, patients who have experience with injections are more likely to prefer injections (20% v. 9% preference share), patients who have experience with oral DMTs are more likely to prefer oral DMTs (51% v. 27% preference share), and patients who have experience with infusions are particularly more likely to prefer infusions (57% v. 29% preference share).

Table 3 Predicted Preferences (%) for the Competitive Landscape of Disease-Modifying Treatment Options[a]

	None	Injections					Orals				Infusions		
	No Medication	Glatiramer Acetate (Copaxone 40 mg/mL)	Interferon Beta-1a (Rebif)	Interferon Beta-1a (Avonex Premixed)	Interferon Beta-1b (Betaferon)	Peginterferon Beta-1a (Plegridy)	Dimethyl Fumarate (Tecfidera)	Teriflunomide (Aubagio)	Fingolimod (Gilenya)	Cladribine (Mavenclad)	Natalizumab (Tysabri)	Mitoxantrone (Novantrone)	Alemtuzumab (Lemtrada)
By country													
Historic base-case scenario, UK	6 [4–7]	9 [6–12]	3 [2–5]	2 [1–3]	2 [1–3]	2 [1–3]	5 [4–7]	12 [9–15]	9 [6–12]	n/a	31 [27–36]	2 [1–3]	18 [14–21]
Historic base-case scenario, DE	5 [3–7]	11 [7–15]	3 [2–5]	1 [0–1]	1 [0–1]	2 [1–4]	8 [5–11]	14 [9–18]	8 [5–12]	n/a	33 [27–38]	1 [1–2]	13 [9–18]
Cladribine without uncertainty, base-case, UK[b]	4 [3–6]	8 [5–11]	3 [2–4]	2 [1–2]	2 [1–3]	2 [1–3]	4 [3–6]	8 [6–11]	7 [5–9]	21 [16–26]	25 [21–29]	2 [1–3]	13 [10–16]
Cladribine without uncertainty, base-case, DE[b]	4 [2–5]	10 [6–13]	3 [1–4]	1 [0–1]	1 [0–1]	2 [1–3]	6 [4–9]	10 [5–14]	3 [6–9]	24 [17–31]	26 [20–32]	1 [0–1]	9 [6–13]
Cladribine with still some uncertainty, UK[c]	5 [3–6]	8 [6–11]	3 [2–4]	2 [1–2]	2 [1–3]	2 [1–3]	5 [3–6]	10 [7–13]	8 [5–10]	14 [10–19]	27 [23–32]	2 [1–3]	14 [11–17]
Cladribine with still some uncertainty, DE[c]	4 [3–6]	10 [7–14]	3 [1–4]	1 [0–1]	1 [0–1]	2 [1–3]	7 [5–9]	10 [6–14]	6 [4–10]	19 [12–26]	27 [22–33]	1 [1–1]	10 [6–14]
Natalizumab with JCV-positive risk profile, UK[d]	5 [3–6]	9 [6–11]	3 [2–5]	2 [1–3]	2 [1–3]	2 [1–3]	6 [4–7]	10 [7–13]	10 [8–14]	27 [22–33]	4 [3–5]	3 [2–4]	18 [15–22]
Natalizumab with JCV-positive risk profile, DE[d]	5 [3–6]	12 [8–16]	3 [2–5]	1 [1–1]	1 [0–1]	3 [2–4]	8 [6–11]	11 [7–16]	8 [5–12]	31 [23–39]	3 [2–5]	1 [1–2]	13 [9–17]
By background variable[e]													
Base-case, diagnosed 5 or less years ago	4 [2–5]	11 [8–15]	3 [2–4]	2 [1–2]	2 [1–3]	2 [1–3]	6 [4–7]	8 [6–11]	7 [5–10]	18 [14–23]	29 [24–35]	1 [1–2]	8 [6–11]
Base-case, diagnosed 6 or more years ago	4 [3–6]	6 [3–10]	3 [1–5]	1 [0–1]	1 [0–1]	2 [1–3]	4 [3–6]	11 [8–15]	6 [4–9]	26 [19–32]	24 [19–30]	1 [1–2]	12 [8–15]
Base-case, has experience with injections	3 [2–5]	13 [10–16]	3 [2–4]	1 [1–2]	1 [1–1]	2 [1–3]	4 [3–6]	10 [7–13]	6 [4–8]	22 [17–27]	26 [22–30]	1 [1–2]	8 [6–11]
Base-case, has experience with orals	3 [2–4]	7 [5–11]	3 [1–4]	1 [1–2]	1 [1–2]	1 [1–2]	8 [6–10]	9 [6–12]	10 [7–13]	24 [18–29]	24 [19–28]	1 [1–2]	8 [6–11]
Base-case, has experience with infusions	2 [2–4]	7 [4–11]	2 [1–3]	1 [0–2]	1 [0–2]	1 [1–2]	4 [3–6]	4 [2–7]	7 [4–11]	13 [8–18]	38 [31–44]	2 [1–4]	17 [13–22]

[a]Based on individual-level mixed logit preference estimates, taking the full uncertainty of the individual-level preference estimates into account (95% credible intervals in parentheses). Estimates were based on $n = 799$ respondents from the United Kingdom and $n = 363$ respondents from Germany.
[b]Historic base-case scenario including cladribine without uncertainty about its long-term side effects.
[c]Historic base-case scenario including cladribine with still some uncertainty about its long-term side effects.
[d]Historic base-case scenario including cladribine without uncertainty about its long-term side effects and natalizumab with progressive multifocal leukoencephalopathy risk profile for John Cunningham virus–positive patients.
[e]Based on separate analyses of the pooled data ($N = 1162$ respondents) for the current base-case scenario.

Table 4 Patient Preference Drivers[a]

1	Preferences for the most effective DMTs, irrespective of mode of administration
2	Preferences for the more effective DMT side effects (i.e., gastrointestinal problems, flushes, and increased risk of serious infections, heart problems, thyroid disorder, kidney problems, and/or blood clothing disorder/immune thrombocytopenia)
3	Preferences for risk of dying from progressive multifocal leukoencephalopathy
4	Preferences for lowest frequency of administration
5	Preferences for injections and oral DMTs v. infusions
6	Preferences for injection-related side effects (e.g., flulike symptoms, lipoatrophy)
7	Preferences for intramuscular injections with fewer skin problems
8	Preferences for pregnancy-related considerations

[a]DMT, disease-modifying treatment. Supplementary Appendix E contains the full table with component loadings for each of the attributes and levels (i.e., 48 parameters) on the principal components.

Box 1

What is already known on this topic?

- The therapeutic landscape for relapsing-remitting multiple sclerosis (RRMS) is rapidly expanding and currently comprises 13 disease-modifying treatment options (DMTs).
- Because no single optimal treatment exists, therapy should ideally be tailored to patients' preferences as well as disease progress and severity.
- Existing patient preference studies (see Supplementary Appendix A and a recent review by Webb et al.[38]) have been informative about the general stance of patients on the risk/benefit tradeoffs but have neither included nor analyzed preferences for actual DMTs. Accordingly, previous studies provided limited guidance to clinicians aiming to align treatment selections with patients' preferences.

What this study adds:

- This study is the first to provide insight into patients' considerations when choosing between entire RRMS DMT profiles and the first to present aggregate patient preference shares for all included DMTs in a competitive landscape of treatment options. In the presented RRMS application, mitoxantrone and beta-interferon injections were seldom preferred, whereas the vast majority of patients preferred either one of the oral DMTs (42%) or natalizumab/alemtuzumab infusions (36%).
- Eight principle components were identified that together explain 99% of the variation in patients' preferences for RRMS DMTs. These allow for a structured discussion of the most important differences between DMTs, precisely along the dimensions on which MS patients base their decision.
- Finally, new treatment options will continue to be introduced into the competitive landscape and older treatment options will continue to become obsolete. The presented DCE methods are ideally suited to capture these effects and, describe the substitution patterns. This is relevant for various disease areas other than MS and useful for future regulatory decisions.

Table 4 summarizes the results of the PCA analysis. As shown, patient preferences could be summarized in 8 underlying factors that together explain 99% of the between-respondent variation in DMT preferences. Based on the component loadings (see Supplementary Appendix E Table 4E), which describe how each underlying factor correlates with the estimated patient preferences in the DCE, the first 3 factors described the patients' desire for highly effective DMTs and patients' aversion for the associated side effects. Whereas preferences for many side effects were bundled into a single factor, preferences for the risk of PML were loaded on a separate factor, suggesting that risk of PML is an independent consideration. The fourth factor captured patient preferences for the lowest frequency of administration, and the next 3 factors were interpreted to describe the tradeoff between the slightly less effective oral and injectable DMTs. Apart from the general preference that patients may have for injections versus oral DMTs, this tradeoff was predominantly based on patients' relative preferences for the risk of gastrointestinal upset, flulike symptoms, skin problems, and lipoatrophy. The eighth and final factor described patient preferences for pregnancy-related considerations. In the questionnaire, 77% of the respondents indicated pregnancy-related considerations to be unimportant, but for the remaining 23%, these considerations could be decisive in their choice of DMT.

Discussion

Patient preferences in Germany and the United Kingdom for RRMS DMTs were very similar despite substantial differences in actual DMT usage. Patients in both countries predominantly preferred oral DMTs (41%) and infusions (38%). Beta-interferon injections and mitoxantrone had the smallest preference share among RRMS patients. Natalizumab was the most often preferred DMT, and cladribine tablets were the most often preferred oral DMT. Given this is the first study to calculate preference shares for the competitive landscape of RRMS DMTs, it is not possible to compare our results with previous findings, except for those pertaining to the relative attractiveness of oral and infusions over injections. With respect to the latter, our results confirm that patients generally prefer infusions and oral DMTs over injections.

Another key finding of the study is that patient choices between different DMTs can be summarized using 8 underlying factors. This finding is relevant for clinical practice, where physicians often select a "candidate set" of DMTs (2 or 3 options) that might be relevant for the patient and then discuss the pros and cons of each during the patient-physician consultation. The identification of these 8 factors allows for a structured discussion of important differences of the selected DMTs along the dimensions that MS patients base their decision upon. These findings also imply that less emphasis can be placed on aspects that are not particularly important for patients choosing between DMTs, such as the frequency of required monitoring for serious side effects.

Clearly, actual DMT usage reflects not only patient preferences for DMT characteristics but also physician preferences, prescription guidelines, reimbursement policies, and marketing efforts to increase brand awareness. Consequently, the presented preference shares can and should not be interpreted as predicted market shares. Similarly, actual market shares are not particularly informative about patient preferences, which is why a DCE is ideally suited to measuring and summarizing patient preferences for DMTs.

In terms of the strengths of this study, it is worth emphasizing that the participating patients were very satisfied with the survey, could easily identify the differences between the treatment options, and did not indicate that the number of choice tasks was too large. The MS nurses and interviewers who conducted the think-aloud survey evaluations considered the level of task complexity to be manageable for their patients. Furthermore, the quantitative assessment based on the individual-level R^2 estimates confirmed that more than 80% of the respondents had good or excellent model fit. In addition, the results have good face validity, and the included scenarios provided logically consistent results; the uncertainty about long-term side effects, a higher risk of PML for JCV-positive patients, and patients' experience with MS and modes of administration were strongly correlated with patient preferences for DMTs.

In terms of lessons learned for future studies, the feasibility of the presented methods crucially relied on the ability to keep the level of task complexity manageable for all respondents while simultaneously maximizing statistical efficiency. On one hand, the carefully constructed warm-up tasks, the adaptive visual layout that omitted irrelevant side effects and highlighted the level overlap, the maximum number of side effects per DMT and minimum amount of attribute-level overlap were all essential to reducing the level of task complexity. On the other hand, a Bayesian efficient heterogeneous DCE design algorithm that adhered to the specified design constraints, made use of informative priors, and simultaneously optimized the choice tasks for the various DCE sections had to be used to achieve adequate statistical power. Indeed, given the limited sample size and the imposed design constraints, a more traditional zero-prior DCE design would not have sufficed.

An important limitation of this study is the fact that the most recently introduced RRMS DMT (i.e., ocrelizumab) was not included in the competitive landscape because the required information was not available when the study was designed. In a future extension of this study, it would be interesting to include ocrelizumab and investigate the impact on the presented results. Of course, new treatment options will continue to be added to the competitive landscape, and older DMTs with less favorable risk-benefit tradeoffs will continue to diminish in relevance. The presented methods are ideally suited to capture these effects, describe the substitution effects, and show how patient preferences adapt to future competitive landscapes.

As with any preference study, the carefully constructed DCE profiles are an abstraction from reality and inherently based on a limited number of levels and incidence descriptions. This is a limitation in any DCE but particularly one in a study aimed at summarizing patient preferences for complex DMTs. Accordingly, maximum effort has been placed on representing all DMTs in the most realistic and balanced way possible and to allow patients to make realistic tradeoffs between a large number of important aspects of RRMS DMTs. Compared to previous preference studies, the current study was able to include considerably more detailed profiles. The presented analyses consequently supplement

previous research not merely by showing which general aspects of DMTs are important to patients but also by showing how RRMS patients make choices between actual DMTs and how this translates into preference shares of various DMTs that are either currently available or will be introduced in the near future. The latter has methodological relevance beyond the current application and will be particularly useful for regulatory decisions about future DMT introductions.

Acknowledgment

We thank Charlotte Dieteren, MSc, for valuable research assistance and the physicians and MS nurses who have contributed to this study for their helpful comments and suggestions.

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Supplemental Material

Supplementary material for this article is available on the *Medical Decision Making* Web site at http://journals.sagepub.com/home/mdm.

References

1. Compston A, Coles A. Multiple sclerosis. *Lancet*. 2008;372(9648):1502–17.
2. de Jong HJ, Kingwell E, Shirani A, et al. Evaluating the safety of β-interferons in MS: a series of nested case-control studies. *Neurology*. 2017;88(24):2310–20.
3. Motl RW, Sandroff BM, Kwakkel G, et al. Exercise in patients with multiple sclerosis. *Lancet Neurol*. 2017;16(10):848–56.
4. Way SW, Popko B. Harnessing the integrated stress response for the treatment of multiple sclerosis. *Lancet Neurol*. 2016;15(4):434–43.
5. Lugaresi A, Di Ioia M, Travaglini D, Pietrolongo E, Pucci E, Onofrj M. Risk-benefit considerations in the treatment of relapsing-remitting multiple sclerosis. *Neuropsychiatr Dis Treat*. 2013;9:893.
6. Rae-Grant A, Day GS, Marrie RA, et al. Practice guideline recommendations summary: disease-modifying therapies for adults with multiple sclerosis. Report of the Guideline Development, Dissemination, and Implementation Subcommittee of the American Academy of Neurology. *Neurology*. 2018;90:777–88.
7. Institute of Medicine. *Crossing the Quality Chasm*. Washington, DC: National Academies Press; 2001.
8. Institute of Medicine. *Best Care at Lower Cost: The Path to Continuously Learning Health Care in America*. Washington, DC: National Academies Press; 2013.
9. Johnson FR, Van Houtven G, Ozdemir S, et al. Multiple sclerosis patients' benefit-risk preferences: serious adverse event risks versus treatment efficacy. *J Neurol*. 2009;256(4):554–62.
10. Shingler SL, Swinburn P, Ali S, Perard R, Lloyd AJ. A discrete choice experiment to determine patient preferences for injection devices in multiple sclerosis. *J Med Econ*. 2013;16(8):1036–42.
11. Utz KS, Hoog J, Wentrup A, et al. Patient preferences for disease-modifying drugs in multiple sclerosis therapy: a choice-based conjoint analysis. *Ther Adv Neurol Disord*. 2014;7(6):263–75.
12. Wicks P, Brandes D, Park J, Liakhovitski D, Koudinova T, Sasane R. Preferred features of oral treatments and predictors of non-adherence: two web-based choice experiments in multiple sclerosis patients. *Interact J Med Res*. 2015;4(1):e6.
13. Poulos C, Kinter E, Yang JC, et al. A discrete-choice experiment to determine patient preferences for injectable multiple sclerosis treatments in Germany. *Ther Adv Neurol Disord*. 2016;9(2):95–104.
14. Poulos C, Kinter E, Yang JC, Bridges JF, Posner J, Reder AT. Patient preferences for injectable treatments for multiple sclerosis in the United States: a discrete-choice experiment. *Patient*. 2016;9(2):171–80.
15. Wilson LS, Loucks A, Gipson G, et al. Patient preferences for attributes of multiple sclerosis disease-modifying therapies: development and results of a ratings-based conjoint analysis. *Int J MS Care*. 2015;17(2):74–82.
16. Garcia-Dominguez JM, Munoz D, Comellas M, Gonzalbo I, Lizan L, Polanco Sanchez C. Patient preferences for treatment of multiple sclerosis with disease-modifying therapies: a discrete choice experiment. *Patient Prefer Adherence*. 2016;10:1945–56.
17. Bottomley C, Lloyd A, Bennett G, Adlard N. A discrete choice experiment to determine UK patient preference for attributes of disease modifying treatments in multiple sclerosis. *J Med Econ*. 2017;20(8):863–70.
18. Carlin CS, Higuera L, Anderson S. Improving patient-centered care by assessing patient preferences for multiple sclerosis disease-modifying agents: a stated-choice experiment. *Perm J*. 2017;21:16–102.
19. Mansfield C, Thomas N, Gebben D, Lucas M, Hauber AB. Preferences for multiple sclerosis treatments: using a discrete-choice experiment to examine differences across subgroups of US patients. *Int J MS Care*. 2017;19(4):172–83.
20. Lynd LD, Traboulsee A, Marra CA, et al. Quantitative analysis of multiple sclerosis patients' preferences for drug treatment: a best-worst scaling study. *Ther Adv Neurol Disord*. 2016;9(4):287–96.
21. Arroyo R, Sempere AP, Ruiz-Beato E, et al. Conjoint analysis to understand preferences of patients with multiple sclerosis for disease-modifying therapy attributes in Spain: a cross-sectional observational study. *BMJ Open*. 2017;7(3):e014433.

22. Hincapie AL, Penm J, Burns CF. Factors associated with patient preferences for disease-modifying therapies in multiple sclerosis. *J Manag Care Spec Pharm*. 2017;23(8):822–30.
23. Kremer IE, Evers SM, Jongen PJ, et al. Identification and prioritization of important attributes of disease-modifying drugs in decision making among patients with multiple sclerosis: a nominal group technique and best-worst scaling. *PLoS One*. 2016;11(11):e0164862.
24. Cree BA, Mares J, Hartung HP. Current therapeutic landscape in multiple sclerosis: an evolving treatment paradigm. *Curr Opin Neurol*. 2019;32(3):365–77.
25. Ryan M. *Discrete Choice Experiments in Health Care*. London: British Medical Journal Publishing Group; 2004.
26. Hensher DA, Rose JM, Greene WH. *Applied Choice Analysis: A Primer*. Cambridge, UK: Cambridge University Press; 2005.
27. Lancaster KJ. A new approach to consumer theory. *J Political Econ*. 1966;74(2):132–57.
28. McFadden D. Conditional logit analysis of qualitative choice behavior. In: Zarembka P, ed. *Frontiers in Econometrics*. New York: Wiley; 1973. p 105–142.
29. Jonker MF, Donkers B, de Bekker-Grob EW, Stolk EA. The effect of level overlap and color coding on attribute non-attendance in discrete choice experiments. *Value Health*. 2018;21:767–71.
30. Jonker MF, Donkers B, de Bekker-Grob EW, Stolk EA. Attribute level overlap (and color coding) can reduce task complexity, improve choice consistency, and decrease the drop-out rate in discrete choice experiments. *Health Econ*. In press.
31. Sandor Z, Wedel M. Heterogeneous conjoint choice designs. *J Market Res*. 2005;42(2):210–8.
32. de Bekker-Grob EW, Donkers B, Jonker MF, Stolk EA. Sample size requirements for discrete-choice experiments in healthcare: a practical guide. *Patient*. 2015;8(5):373–84.
33. Train KE. *Discrete Choice Methods with Simulation*. Cambridge, UK: Cambridge University Press; 2009.
34. Green PE, Krieger AM. *Conjoint Analysis with Product Positioning Applications, Handbooks in Operations Research and Management Sciences*. Vol. 5. Eliashberg J, Lilien GL, eds. Amsterdam, the Netherlands: Elsevier; 1993. p 467–515.
35. Sawtooth Software. *Advanced Simulation Module (ASM) for Product Optimization v1.5*. Technical paper. Provo, UT: Sawtooth Software; 2003.
36. McFadden D. *Quantitative Methods for Analyzing Travel Behavior Of Individuals: Some Recent Developments*. Cowles Foundation Discussion Papers 474. New Haven, CT: Cowles Foundation for Research in Economics, Yale University; 1977.
37. Jennrich RI. Rotation to simple loadings using component loss functions: the orthogonal case. *Psychometrika*. 2004; 69(2):257–73.
38. Webb EJD, Meads D, Eskyte I, et al. A systematic review of discrete-choice experiments and conjoint analysis studies in people with multiple sclerosis. *Patient*. 2018;11(4): 391–402.