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Decision-making about disease modifying treatments for relapsing-remitting multiple sclerosis: stated preferences and real-world choices

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Abstract

Background People with relapsing-remitting multiple sclerosis (PwRRMS) can benefit from disease modifying treatments (DMTs). Several DMTs are available which vary in efficacy, side effect profile and mode of administration.

Aim To measure PwRRMS' preferences for DMTs using a discrete choice experiment and to assess which stated preference attributes correlate with the attributes of the DMTs they take in the real world.

Methods DCE attributes were developed from literature reviews, interviews and focus groups. In a DCE, participants were shown two hypothetical DMTs, then chose whether they preferred one of the DMTs or no treatment. A mixed logit model was estimated from responses and individual-level estimates of participants' preferences conditional on their DCE choices

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calculated. Logit models were estimated with stated preferences predicting current real-world on-treatment status, DMT mode of administration and current DMT.

Results A stated intrinsic preference for taking a DMT was correlated with currently taking a DMT, and stated preferences for mode of administration were correlated with the modes of administration of the DMTs participants were currently taking. Stated preferences for treatment effectiveness and adverse effects were not correlated with real-world behaviour.

Conclusion There was variation in which DCE attributes correlated participants' real-world DMT choices. This may indicate patient preferences for treatment efficacy/risk are not adequately taken account of in prescribing. Treatment guidelines must ensure they take into consideration patients' preferences and to improve communication around treatment efficacy/risk.

Keywords: multiple sclerosis; disease modifying treatments; discrete choice experiments; stated preference; external validity

Key points for decision makers

- We use a discrete choice experiment to measure people with relapsing-remitting multiple sclerosis' preferences for DMTs
- We examine how well stated preferences correlate with real-world treatment decisions
- Stated preferences for mode of administration and intrinsic preferences for DMTs correlated with real-world decisions, but stated preferences for treatment benefits/risks did not

1. Introduction

Relapsing-remitting multiple sclerosis (RRMS) is a long-term condition of the central nervous system leading to chronic disability in most cases [1-3]. People with RRMS (PwRRMS)

experience periods of function loss (for example impaired mobility or vision) termed relapses, followed by full or partial recovery [2]. PwRRMS may experience permanent loss of function and disability over a longer period of time.

There is no cure, but a range of disease modifying treatments (DMTs) exist which can reduce the frequency with which PwRRMS experience relapses and slow the rate at which long-term disability is accumulated [4, 5]. DMTs vary in their effectiveness at reducing the frequency of relapses and the accrual of disability [6, 7], and in terms of possible adverse effects [8] ranging from mild (e.g. nausea) to life-threatening [9, 10]. DMTs also vary in their mode of administration including pills taken regularly [11, 12], injections [13, 14], and infusions given either at regular intervals [15] or as two clusters of infusions lasting 3-5 days, separated by 12 months [16].

The treatment landscape PwRRMS face is complex, involving risk/benefit trade-offs. The current study examines PwRRMS' decision-making about DMTs, including whether to take one at all, and their preferences for different aspects of treatment. The results can be used to help improve services and guide development of new treatments to be better reflective of PwRRMS' preferences.

We measure PwRRMS' stated preferences for DMTs using a discrete choice experiment (DCE) [17, 18]. In a DCE, participants make a series of choices between two or more hypothetical options. Each option is decomposed into a set of attributes [19], for example in the current study attributes include reduced risk of relapse, risk of side effects, and mode of administration. Analysing responses reveals participants' relative preferences for each attribute and the trade-offs they make between them.

Some concerns have been raised about DCEs' external validity, and the correlation between people's stated intentions and their choices in the real world [20-25]. To address such concerns,

we also examined how well participants' stated preferences correlated with what DMT (if any) they were taking in real life. Just as the hypothetical options in a DCE are described in terms of a set of attributes, real world treatments can also be decomposed into attributes such as reduction in relapse risk, risk of side effects, mode of administration, etc. We examined the correlations between stated preferences for individual attributes of hypothetical treatments and the corresponding attributes of real-world DMTs. For example, whether participants' stated preferences for mode of administration are correlated with how they take DMTs in real life: Those who state they prefer pills take pills; those who state they prefer infusions take infusions, etc.

This approach allowed us to investigate whether the association between participants' stated preferences and real-world choices varied by attribute type. For example, in many healthcare systems DMTs are categorised as first line and second line, with access to the more effective but higher risk second line treatments being restricted to patients with more active disease. This might mean a poor correlation between participants' stated preferences for risk of adverse events and the risk profile of the DMTs taken in real life. Yet if this were the case, participants' stated and observed preferences for DMT mode of administration could still be strongly correlated. Several previous DCE studies have examined preferences for DMTs [26-30]. However, we are not aware of any previous study which has examined whether stated preferences correlate with real-world DMT decisions. We aimed to address this knowledge gap while adhering to best practice guidelines, both when developing the survey instrument using qualitative work [31], and in communicating probabilistic treatment attributes [32-35].

The current study was part of a research project called Considering RIsk and benefits in Multiple Sclerosis treatment selectiON (CRIMSON), which aimed to develop a patient decision aid [36] to help PwRRMS make more informed decisions about DMTs [37]. At the outset we gathered evidence to inform the content and structure of a patient decision aid by

examining preferences for DMTs using diverse approaches. This included literature reviews [30, 38], qualitative studies [39, 40], the current DCE and a linked DCE looking specifically at women with RRMS' preferences for reproduction specific attributes of DMTs [41].

2. Methods

Ethical approval was obtained from the NHS Health Research Authority (IRAS: 199646)

2.1. Design and sample

An online survey using discrete choice methods was employed to elicit the stated preferences of PwRRMS for DMTs. Participants were recruited from the UK MS Register (https://ukmsregister.org/), a research portal and data repository supported by the MS Society of Great Britain & Northern Ireland which links people with MS, researchers and MS service providers. The register has over 25,000 members compared to an estimated 130,000 PwMS in the UK [42], and the cohort has been shown to be representative of the clinical population [43]. Register participants are regularly asked to complete health/quality of life measures and research surveys which can be linked to routinely collected data to minimise respondent burden.

2.2. Questionnaire development

The DCE was developed in line with recommendations for good practice [44, 45], using an extensive development process [31, 46]. This included literature reviews [30, 38], interviews (*N*=30) with PwRRMS [39, 40], and three focus groups (*N*=17) with PwRRMS, neurologists and MS nurses. This resulted in a set of potential attributes which was reduced in number via ranking exercises conducted in four workshops (*N*=33) with PwRRMS.

A draft survey was iteratively refined during a series of think-aloud interviews with PwRRMS (*N*=28). This process aimed to ensure the survey did not over-burden participants, was understandable, and that participants interpreted attribute levels in the intended way. Survey

refinement also aimed to create choices that appropriately reflected PwRRMS' real-world decision-making situations.

Table 1 gives the final list of attributes/levels, with an example question in Figure 1(a). The DCE had a dual response design: participants first made a choice between two treatments, then made a further binary choice between their preferred DMT and no treatment.

Probabilistic attributes were presented to participants using evidence-based principles to aid their understanding [33, 47]. This included using icon arrays to aid participants' understanding of risk [35, 48] (see Figure 1(b)). Two different icon array types were used, one with grouped dots and one with randomly scattered dots, with participants randomly allocated to seeing one of the two styles throughout the survey. The different styles were used to explore the effect of risk presentation. No difference was seen between participants' choices in the two treatments (details available on request to the corresponding author), and the results are not discussed further in this manuscript.

The survey's statistical design, i.e. what levels each attribute takes in each task, was created using NGene (© ChoiceMetrics), software commonly used in DCE design [17]. The design maximised D-efficiency, a measure of how much information it is possible to get from resources. The design had 80 tasks, too many for a single participant to complete. It was thus split into 10 blocks of eight questions each, with participants randomly allocated to a block. The order of presenting treatment benefits (relapse frequency/relapse severity/improved future functioning), adverse effects (side effects/chances of additional long-term/life-threatening conditions) and mode of administration was randomised between participants, but consistent across tasks for a given participant. Randomisations to survey block, icon array type, and attribute order were independent.

2.3. Data

PwRRMS enrolled in the MS Register and consented to being asked to complete external surveys were contacted via email. Consent was obtained, then participants completed the DCE tasks. A subset of participants who indicated they were considering having a child were asked to complete a second DCE with DMT attributes specific to reproduction (results reported elsewhere [41]).

Participants answered questions about themselves and their MS, including whether they were currently taking a DMT, if so which one, and any DMTs taken previously. They also answered questions assessing their time and risk preference. Full survey materials are provided as supplementary online material. The MS Register provided matched data for study participants from previous responses to the Multiple Sclerosis Impact Scale (MSIS-29) [49], EQ-5D-3L [50], the Hospital Anxiety Depression Scale (HADS) [51] and the Fatigue Severity Scale (FSS) [52].

Missing values in MS Register data were imputed using random forest methods [53]. Cases where participants' latest available measure of MSIS-29, HADS, EQ-5D-3L or FSS was more than one year prior to completing the survey were treated as missing. The proportion of missing data is shown in Summary statistics for participants' health status

Table A 1. Birth year, gender, whether currently employed, whether has degree, whether has dependent children were used in imputation.

2.4. Analysis

The analysis strategy can be summarised as follows. First, DCE responses are analysed using a model which allows for preference heterogeneity. The results are used to construct individual-level measures of how much each respondent prefers each attribute. To assess the correlations between stated preferences and real-world treatment decisions, we then estimate models with

real-world DMT choices as a dependent variable and individual-level preferences for each attribute as independent variables.

2.4.1. Discrete choice experiment model

DCE responses were analysed using a random utility framework. Let $u_{ijt} = \boldsymbol{\beta}_i \boldsymbol{x}_{jt} + \varepsilon_{ijt}$ be the utility of treatment option j to individual i in choice task t. Here $\boldsymbol{x}_{jt}$ is a vector of j's characteristics in task t (possibly including an alternative specific constant (ASC)) and ε_{ijt} is an error term. The vector $\boldsymbol{\beta}_i$ represents i's preferences and is assumed to follow a distribution $f(\boldsymbol{\beta}|\boldsymbol{\Omega})$, where $\boldsymbol{\Omega}$ is a vector of distributional parameters (means/standard deviations).

The no treatment option was qualitatively different from the two treatment options, and it was likely that preferences for it were not wholly captured by the DCE attributes. In such circumstances, it is common to use an alternative specific constant (ASC) which measures preferences between alternatives which are not due to differences in their attributes. Here an ASC was used for the no treatment option which captured participants' intrinsic preference for avoiding treatment over and above what attributes the treatments had.

It was assumed that all participants would prefer fewer and less severe relapses, a lower chance of worse future functioning, less severe side effects and less risk of additional long term/life threatening side effects. Thus, these parameters were modelled as log-normally distributed, constraining them to be negative. Parameters for mode of administration and the no treatment ASC capturing intrinsic preference for not taking a DMT were modelled as following a normal distribution, as it was assumed that some participants would have a positive and some a negative preference for those attributes. As it is common in health DCE studies [17], we did not model correlations between attributes, as this facilitated the post-estimation analysis described below. Whether the means of normally distributed parameters were significantly different from 0 was assessed using t-tests. Tests were not performed for whether negative log-

normally distributed parameter means or standard deviations were different from 0, there are all positive by definition.

2.4.2. Measures of individual stated preferences

The mixed logit model produced a distribution of preferences for each attribute. We constructed measures of individual-level preferences for attributes by estimating where each participant was most likely to be positioned on the distribution. Following Hess [54], the position of participants' preferences in the distribution may be estimated by conditioning on their choices. If $\boldsymbol{Y}_i$ is a vector representing individual i's treatment choices, the likelihood of preferences conditional on choices is $L(\boldsymbol{\beta}|\boldsymbol{Y}_i) = L(\boldsymbol{Y}_i|\boldsymbol{\beta})f(\boldsymbol{\beta}|\boldsymbol{\Omega})/\int_{\boldsymbol{\beta}} L(\boldsymbol{Y}_i|\boldsymbol{\beta})f(\boldsymbol{\beta}|\boldsymbol{\Omega})d\boldsymbol{\beta}$. The most probable value for i's preferences is found by taking the mean: $\overline{\boldsymbol{\beta}}_i = E(\boldsymbol{\beta}|\boldsymbol{Y}_i) = \int_{\boldsymbol{\beta}} \boldsymbol{\beta}L(\boldsymbol{Y}_i|\boldsymbol{\beta})f(\boldsymbol{\beta}|\boldsymbol{\Omega})d\boldsymbol{\beta}/\int_{\boldsymbol{\beta}} L(\boldsymbol{Y}_i|\boldsymbol{\beta})f(\boldsymbol{\beta}|\boldsymbol{\Omega})d\boldsymbol{\beta}$.

The mean conditional estimate $\overline{\boldsymbol{\beta}}_i$ is the closest possible estimate of i's preferences. These estimates were then normalised to aid their interpretation and facilitate comparisons across different parameters. Denote by $\overline{\boldsymbol{\beta}}'_i$ the conditional estimates transformed such that for every parameter the distributions of conditional estimates across all individuals have mean 0 and standard deviation 1. Now $\bar{\beta}'_{i\ell}$ is positive, i's preference for attribute ℓ is above the population average and vice versa. Also, if $\bar{\beta}'_{i\ell} = 1$, this indicates i's preference for ℓ is one standard deviation above the population average.

Now let i choose between real-world treatment options. We assumed that i's choice utility for option k could be modelled as

$$w_{ik} = \delta_k + \boldsymbol{\gamma}_{ik}\overline{\boldsymbol{\beta}}'_i + \eta_{ik} \qquad (2)$$

where δ_k is an ASC, η_{ik} is an error term, and $\boldsymbol{\gamma}_{ik}$ is a vector of parameters to be estimated. The greater a parameter $\gamma_{ik\ell}$, the greater the variation in revealed preference for k is

explained by variance in stated preferences for attribute ℓ. It may be that the researcher believes only certain attributes in the stated choice survey are relevant to real-world choices, in which case $\overline{\boldsymbol{\beta}}'_i$ may be replaced with only some of its elements.

2.4.3. Choice of disease modifying treatment vs. no treatment

Several models of the form of equation (2) were constructed to assess correlations between stated preferences and observed behaviour. In the first model we looked at individuals' decisions about whether to take a DMT or not. The binary logit model had a dependent variable equal to 1 if a participant was currently taking a DMT and 0 otherwise, with stated preferences for all DCE attributes as dependent variables.

2.4.4. Mode of administration choice

A multinomial logit (MNL) model was estimated with the dependent variable of whether participants were taking a DMT via pill, injection, monthly infusion or two infusions a year apart, and including only stated preferences for modes of administration as independent variables. Other stated preference conditional estimates were excluded as they were felt to have little relevance for choosing mode of administration. Pill was selected as the baseline category.

2.4.5. Disease modifying treatment choice

In the final model, for participants currently taking a DMT not classified as "other", we looked at what DMT they were taking. An MNL model was run with a dependent variable of taking alemtuzumab, dimethyl furmurate, fingolimod, glatiramer acetate, interferon beta, natalizumab or teriflunomide. Stated preferences for all attributes were included as independent variables, with the exception of the no treatment ASC as that was not relevant for choices between different DMTs. It was necessary to have a pill as the baseline outcome, since stated preferences for mode of administration in the DCE are measured relative to a pill, and dimethyl

fumurate was chosen since it wasthe most common pill DMT in the sample. Stated preferences for modes of administration were restricted to appear only in the utility equations for treatments delivered via that mode, and were also restricted to be the same for all treatments delivered via a given mode. Formal equations defining utility for the choice objects in each model are not included in the supplementary online material.

2.4.6. Robustness tests

Several robustness tests were run. To check whether stated and revealed preferences were only correlated for people who had chosen a DMT recently, models for DMT mode of administration and current DMT were re-estimated with stated preference parameters interacted with the length of time participants had been taking their current DMT. It was possible that correlations between revealed choice and stated preferences were both being driven by participant demographics and/or health status. To examine this possibility, models of on-treatment status, DMT mode of administration and current DMT were run with only demographic and health variables included as independent variables, with no estimates of stated preference.

Statistical significance was judged at the 5% level after adjustment for multiple testing using Holm's sequential Bonferroni correction [55]. All models were estimated using the Apollo choice modelling package for R [56].

3. Results

Responses were collected from May 2018- March 2019. About 1,500 MS Register participants with RRMS were invited via email.[1] A total of 600 PwRRMS completed the survey online and were included in the analysis.

[1] It is not possible to give a precise number, as due to an error an unknown number of people with progressive MS were also invited. The MS Register has over 25,000 members, however due to changes to data protection

Table 2 summarises participants' demographics (data from DCE survey). Participants' average age was 47.3, with a range from 20 to 77. A majority of the sample, 80.2%, were women, which is higher than the fraction of PwRRMS who are women, estimated at 65-75%. The sample was well educated, with 46.7% having a degree or equivalent qualification. Summaries of participants' health measures are given in Summary statistics for participants' health status

Table A 1 of the supplementary online material (data from MS Register).

Table 3 summarises the DMTs participants were taking. Almost three-quarters were currently taking a DMT, with 17% treatment naive. Dimethyl fumarate was the most common current DMT.

3.1. Discrete choice experiment model

Table 4 gives the results of the mixed logit model of DCE choices. Participants preferred treatments reducing number or severity of relapses, that reduced the chance of worse future functioning, and which had less severe side effects. While participants preferred treatments with lower risks of both an additional long-term condition and a life-threatening condition, the latter was more important than the former. Pill was the most preferred mode of administration, followed by two infusions a year apart, then monthly infusions, then injections. The size of the standard deviation parameter indicates preference heterogeneity. For example, although injections were the least preferred option on average, the distribution of its parameter implies that 18% of respondents preferred it to pills. The no treatment ASC measured participants' intrinsic preference for receiving no treatment, over and above preferences captured by the DCE attributes. It was significantly negative, indicating an intrinsic aversion to no treatment, or in other words, a preference for treatment over and above the benefits explicitly stated by

laws shortly before survey launch, we could only invite those who explicitly consented to being contacted to complete external surveys.

the attributes. The standard deviation also indicated preference heterogeneity: About 14% of participants had a positive no treatment ASC, suggesting an intrinsic preference for avoiding taking a DMT, regardless of the DMT's properties. Figure 2 illustrates distributions of individual-level preference estimates after normalisation, i.e. it shows how the measures of stated preference for each DCE attribute used as independent variables in subsequent models were distributed.

3.2. Choice of disease modifying treatment vs. no treatment

Table 5 gives the results of the logit model with whether participants were currently taking a DMT as the dependent variable and stated preferences for DCE attributes as independent variables. Model coefficients are expressed as odds ratios and stated preferences were normalised to have mean 0 and standard deviation 1. This means a coefficient of, for example, 2 should be interpreted as the odds of taking a DMT being twice as high if a respondent's preference for an attribute increases by one standard deviation. Only the no treatment ASC is significant, with an odds ratio below one. The odds of participants being on a DMT almost halve if their stated intrinsic preference for avoiding DMTs is one standard deviation higher.

3.3. Mode of administration choice

Table 6 gives the results of the MNL model with how participants' current DMT was administered as the dependent variable and stated preferences for DMT mode of administration as independent variables. Again, coefficients can be interpreted as odds ratios, e.g.. the coefficient of 1.59 for injections means that if a participant's stated preference for injections increases by one standard deviation, the odds of the participant taking a DMT via injection are 1.59 times greater. Stated preferences for injection and two infusions a year apart were both statistically significant. Those for monthly infusion were not significant, although the point

estimate of the odds ratio was greater than one, consistent with a positive association between stated preference for monthly infusions and taking a DMT with that mode of administration.

3.4. Disease modifying treatment choice

Table 7 shows the results of the MNL model with current DMT as the dependent variable and stated preferences for DCE attributes as the independent variables (excluding the no treatment ASC). Only the coefficients for injection and two infusions a year apart are significant.

3.5. Robustness tests

Detailed results of robustness models are contained in the supplementary online material. For models with interactions between stated preferences and length of time on current treatment (Tables A1 and A2), no interaction terms were statistically significant, indicating the strength of association between stated and revealed preferences did not depend on the time since the revealed preference decision was made. For models of real-world choices with only demographic and health characteristics as independent variables (Tables A3-A15), most coefficients were insignificant. There were indications that age slightly reduced the odds of being on treatment, and on being on a treatment administered as two infusions a year apart, and that a more positive attitude to risk reduced the odds of an individual taking an injection DMT.

4. Discussion

The stated preference results were largely in line with expectations: Participants preferred DMTs with greater benefits (reduced number and severity of relapses, a better chance of lesser future disability) and with fewer drawbacks (milder side effects, lower risk of additional long-term and life-threatening conditions).

There were significant correlations between participants' DMT choices and their stated preferences. However, there was variation in which DCE attributes were associated with real-world choices. The no treatment ASC was strongly correlated with on treatment status:

participants whose stated preference for the no treatment parameter was one standard deviation greater than the mean were about half as likely to be taking a DMT. An intrinsic preference for treatment regardless of its properties is consistent with previous findings that some PwRRMS express that taking a DMT is a way of re-gaining control over their lives [38, 57, 58]. Our study contributes by demonstrating that such preferences are reflected in the likelihood of taking a DMT in the real world. No other stated preference parameters were statistically significant, so that, for example, a greater tolerance for adverse events, or a greater desire to avoid relapses, was not associated with a greater probability of taking a DMT.

Participants' preferences for mode of administration were similar to previous results [30] and were also correlated with the mode of administration of the DMTs participants were taking in real life. The stated preference parameters for injection and two infusions a year apart were statistically significant in the MNL model of DMT mode of administration, and the parameter for monthly injections was positive, although not significant. A similar pattern was seen in the general MNL model of DMT choice. Our results provide external validity to this study's (and other similar DCEs) stated preference findings regarding mode of administration. Our previous qualitative investigations [39, 40] revealed heterogeneous preference for mode of administration, partly due to differences in daily routines and how conveniently each mode is to fit around them. It is encouraging that such differences were reflected in participants' stated and revealed preferences.

DCE attributes for treatment efficacy and risk of side effects were not correlated with what DMTs participants were taking in real life. One interpretation is that, while PwRRMS have meaningful influence over whether they take DMTs or not, and mode of administration, they have less influence over access to riskier, but more effective treatments. Individual attitudes towards treatment efficacy/risk not influencing decision-making is consistent with National

Institute for Health and Care Excellence (NICE) guidelines restricting such second-line DMTs to patients with greater disease activity [59-61].

Our findings are also consistent with previous qualitative findings that PwRRMS struggle to process the information given about DMT efficacy and risk [39, 40], and may not even agree about what efficacy means [38]. In particular, Manzano et al. [40] found that many PwRRMS, when presented with a list of possible treatments, tended to group and decide based on mode of administration, since this was the only DMT attribute they could relate to.

Under either of the interpretations outlined above, that stated preferences for efficacy and risk are not correlated with real-world decision-making cannot be attributed to the DCE instrument failing to measure participants' preferences accurately. Either participants' real-world choices were restricted, or they were not profited with information in an appropriate way so they could incorporate it into their decision-making (or a mixture of the two). In the first scenario, a recommendation from this study is to re-visit prescribing guidelines and clinical practice to examine if they are in line with PwRRMS' preferences for treatment efficacy and tolerance for risk. In the second scenario the recommendation is to improve communication around DMT properties.

To help improve communication around DMTs, the results of this project were used to inform the creation of a patient decision aid for PwRRMS [37]. DMTs were categorised according to method of action (immune modulation/immune reconstitution/immune blocking) to avoid an undue focus on mode of administration as the only familiar attribute. Also, care was taken to present efficacy and risks according to the best available clinical evidence, but also in ways that were easily interpreted [32-35]. It is hoped that this decision aid will help PwRRMS make better informed decisions in future.

The DCE results suggest that four mild relapses over a course of four years is roughly as preferable as experiencing three severe relapses. However, there is a lack of evidence as to DMTs' effect on relapse severity, independent of relapse frequency, with a typical trial including relapse frequency and long-term physical functioning as primary endpoints [55, 56]. A recommendation for future clinical studies is to investigate whether and to what extent DMTs reduce relapse severity. Treweek et al. [57] found that clinical trial endpoints often failed to reflect patient and clinician priorities, and this recommendation may help DMT research better align with PwRRMS' preferences.

In the robustness tests, few variables were significant in the models including only demographic/health status variables. There is thus little evidence that participants' characteristics were driving both stated and revealed DMT preferences. We also found that the associations between stated preference and real-world DMT choices were not influenced by how long participants had been taking their current DMT.

4.1. Strengths and weaknesses

This study has several strengths, including being the first of which we are aware to compare PwRRMS' stated and revealed preferences for DMTs. Studying the correlations of stated preferences and real-world choices has given additional insight into PwRRMS' decision-making, and how their preferences interact with a complex real-world decision-making environment. We also used an innovative approach to combining stated and revealed preferences which was suitable for the topic of DMT choice by PwRRMS: A wide range of treatment options with varied characteristics exist, and within RRMS there is a heterogeneity in patient experience. The DCE instrument was also developed following recommendations for good practice [31, 46, 62], including an extensive qualitative process. Another strength of the

study was that it included relapse severity as an attribute, while many DCE studies of DMT choice in RRMS focus only on the reduction in the number of relapses due to treatment.

This study also has some limitations. First, it analysed association, not causation, which can provide insight into people's decision-making processes and patterns of reasoning but cannot unpack which attributes predict future choices. So, for example, we cannot say whether a favourable attitude towards injections predicted preference for a DMT delivered by injectionor having a DMT delivered by injection impacted people's attitudes towards injections. To what extent treatment decisions as measured by a DCE drive treatment choices or DCE responses are influenced by real-world decisions is a topic for future research.

Attributes were presented in random order, with the aim of minimising any potential ordering effects [63], but no treatment was always the right-most alternative. It may be that the presentation order affected individuals' choices. Given the importance of the no treatment ASC for our results, it is a limitation that we are unable to disentangle it from a potential left-right bias [64]. However, the extensive pre-survey interviews revealed that such a decision feature was important for participants' understanding of the DCE instrument.

Another limitation is that our sample volunteered to be a part of the MS Register and take part in this research and were able to complete a DCE. It is likely that people with different needs/lifestyles will trade-off these attributes in different ways, to suit what is important in their lives. What is important to our sample's lifestyle may not be representative of the wider population of PwRRMS.

5. Conclusion

This study has given insight into PwRRMS' stated preferences for DMTs. The results highlighted heterogeneity in preferences for mode of administration and intrinsic preferences for treatment. It also revealed that relapse severity matters to PwRRMS as well as frequency,

and a recommendation for future research is to gather clinical evidence on DMTs effects on relapse severity.

There were differences in how much stated preferences for various treatment attributes correlated with the treatments participants took in real life. In particular, there was little association between stated preferences for DMT efficacy or risk tolerance for side effects and participants' real-life treatments. Future research could usefully investigate whether PwRRMS' preferences for those aspects of treatment are adequately taken account of in the prescribing process. In particular, a recommendation is to reassess whether guidelines restricting access to second-line treatments take sufficient accounts of patient preferences. A further recommendation is to improve communication around DMT efficacy/risks.

This is the first study of which we are aware to examine the correlations between revealed preference and individual stated preference attributes. Future DCE studies may find such an approach useful, as it gives additional insight while requiring minimal extra information to be collected.

Statements and Declarations

Author contributions

All authors conceived the study, defined the study aims and contributed to the survey design. EW and DM collected the data. EW conducted the statistical analysis and wrote the first draft of the manuscript, and all authors contributed to and approved the final version.

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The funders have had no input on the study design, collection and analysis of data, the writing of the manuscript or the decision to submit it for publication.

Ethics approval

Approval for this study was given by a National Health Service (NHS) Research Ethics Committee. The MS Register has been approved by the South West Central Bristol National Research Ethics Service (16/SW/0194).

Consent to participate

All participants gave informed consent before completing the survey, as well as consent to merge their responses with data from the UK MS Register.

Data availability

Discrete choice experiment data is not publicly available as consent was not obtained for this. It may be shared on a case by case basis if an application is made to Leeds Institute of Health Sciences and a formal data sharing agreement is entered into. For access to UK MS Register data see https://ukmsregister.org/.

Competing interests

Jeremy Chataway has received support from the Efficacy and Mechanism Evaluation Programme and Health Technology Assessment Programme (NIHR); UK Multiple Sclerosis Society and National Multiple Sclerosis Society; and the Rosetrees Trust. In the last 3 years, he has been a local principal investigator for trials in MS funded by Receptos, Novartis and Biogen Idec, and has received an investigator grant from Novartis outside this work. He has taken part in Advisory Boards/consultancy for Roche, Merck, MedDay, Biogen and Celgene.

Klaus Schmierer has received support from the Efficacy and Mechanism Evaluation Programme and Health Technology Assessment Programme (NIHR); UK Multiple Sclerosis Society and National Multiple Sclerosis Society; consulting fees from Biogen, Merck, Novartis and Roche, and payments for lecturing activities from Biogen, Merck, Novartis, Roche, Teva, Neurology Academy and Medscape. Hilary L. Bekker provides guidance, based on her academic expertise in medical decision-making, to health policy organisations, patient advocacy groups, health professionals and health scientists on research methods and techniques to develop and evaluate patient decision aids and shared decision-making interventions. Her time and expenses in attending meetings, carrying out evaluations and collaborating with other projects are remunerated. She does not gain financially from the outcomes or outputs of these collaborations. Helen Ford has received support from the Health Technology Assessment Programme (NIHR) and the UK MS Society. In the past 3 years, Helen Ford has been a local principal investigator for trials in MS funded by Biogen Idec, Novartis and Roche and has taken part in advisory boards and consultancy for Biogen, Merck, Novartis, Roche, Sanofi-Genzyme and Teva. Edward Webb, David Meads, Ieva Eskytė, George Pepper, Joachim Marti, Yasmina Okan, Sue Pavitt, and Ana Manzano have no conflicts of interest to declare.

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Table 1: Attributes and levels

Attribute	Level 1	Level 2	Level 3	Level 4	No treatment level
Average number of relapses over 4 years	1 relapse	2 relapses	3 relapses		4 relapses
Relapse severity	Requires no steroids	Requires oral steroids	Requires intravenous steroids		Requires intravenous steroids
Average number of people whose functioning is significantly worse after 10 years	650 out of 1000 (65%)	700 out of 1000 (70%)	750 out of 1000 (75%)		800 out of 1000 (80%)
Typical side effects of treatment	Mild – no additional medication	Moderate – manage with over the counter medication	Severe – manage with MS clinic visit		-
Chance of additional long-term and/or life-threatening medical condition over 4 years	100 in 1000 (10%) chance of long-term condition 2 in 1000 (0.2%) chance of life-threatening condition	200 in 1000 (20%) chance of long-term condition 10 in 1000 (1%) chance of life-threatening condition	300 in 1000 (30%) chance of long-term condition 20 in 1000 (2%) chance of life-threatening condition		-
How you take the treatment	Pill taken daily, takes less than a minute at a convenient location	Self-injection every two days, takes 10-15 mins at a convenient location	Infusion (drip) once a month, takes several hours at a hospital	Two infusion (drip) treatments, 1 year apart, takes several days at a hospital	-

Table 2: Participants' characteristics

Variable	N	(%)
Age - *mean (standard deviation)*	47.3	(10.3)
Female	481	(80.2)
Employed/self-employed	309	(51.5)
Degree level qualification	280	(46.7)
One or more dependent children in household	193	(32.2)

Table 3: Which disease modifying treatments participants' took

Treatment	Mode of administration	First/second line treatment	Currently taking		Previously taken	
			N	(%)	N	(%)
No treatment	-	-	165	(27.5)	-	-
Any DMT	-	-	435	(72.5)	500	(83.3)
Dimethyl Fumarate	Pill	First line	112	(18.7)	66	(11)
Glatiramer Acetate	Injection	First line	53	(8.8)	97	(16.2)
Interferon beta	Injection	First line	70	(11.7)	30	(5)
Teriflunomide	Pill	First line	26	(4.3)	8	(1.3)
Alemtuzumab	Two sets of infusions one year apart	Second line	44	(7.3)	11	(1.8)
Fingolimod	Pill	Second line	54	(9)	23	(3.8)
Natalizumab	Monthly infusion	RES-MS	55	(9.2)	24	(4)
Other	-	-	21	(3.5)	11	(1.8)

N=600; DMT = disease modifying treatment; s.c. subcutaneous; i.m. intramuscular; RES-MS Rapidly evolving severe MS, i.e., two disabling relapses in the past 12 months and magnetic resonance imaging evidence of active disease

Table 4: Results of mixed logit estimation

Attribute	Mean (μ)	Standard deviation (σ)
Number of relapses†	-0.79	0.753
	(-0.936 ,-0.644)	(-0.143 ,1.65)
Relapse severity		
Mild	Baseline	
Moderate†	-0.39	0.683
	(-0.530 ,-0.249)	(-1.57 ,2.93)
Severe†	-0.739	0.112
	(-0.893 ,-0.586)	(-0.287 ,0.512)
% chance worse future functioning†	-0.1	2.17
	(-0.121 ,-0.0804)	(-0.941 ,5.28)
Side effects		
Mild	Baseline	
Moderate†	-0.192	0.0296
	(-0.324 ,-0.0613)	(-0.176 ,0.235)
Severe†	-1.88	2.78
	(-2.18 ,-1.58)	(1.26 ,4.30)
% chance additional long-term condition†	-0.0619	0.154
	(-0.0708 ,-0.0531)	(-0.0119 ,0.320)
% chance life-threatening condition†	-0.407	1.8
	(-0.509 ,-0.306)	(-1.50 ,5.09)
Mode of administration		
Pill	Baseline	
Injection‡	-1.33*	2.17
	(-1.57 ,-1.09)	(1.31 ,3.03)
Monthly infusion‡	-1.03*	0.491
	(-1.22 ,-0.828)	(0.0253 ,0.957)
Two infusions a year apart‡	-0.571*	0.58
	(-0.751 ,-0.392)	(0.177 ,0.984)
No treatment ASC‡	-3.80*	12.2
	(-4.34 ,-3.26)	(6.80 ,17.5)

Note. N=600; Bayesian information criterion=7498.94; 95% confidence intervals in parentheses; * = statistical significance at 5% level after Holm's sequential Bonferroni correction (normal distribution means only); † = follows negative log-normal distribution – means/standard deviations are for underlying normals, so negative log-normal means and standard deviations are $-exp(\mu + 0.5\sigma^2)$ and $\sqrt{(exp(\sigma^2) - 1)exp(2\mu + \sigma^2)}$; ‡ = follows normal distribution; ASC = alternative specific constant

Table 5: Binary logit model with real-world on-disease modifying treatment status as dependent variable and stated preferences for discrete choice experiment attributes as independent variables

Stated preference	Odds ratio
Number of relapses	1.02
	(0.821, 1.26)
Relapse severity	
Mild	Baseline
Moderate	0.936
	(0.788, 1.11)
Severe	1.06
	(0.872, 1.28)
% chance worse future functioning	0.886
	(0.713, 1.10)
Side effects	
Mild	Baseline
Moderate	0.942
	(0.777, 1.14)
Severe	0.938
	(0.769, 1.14)
% chance additional long-term condition	1.11
	(0.930, 1.33)
% chance life-threatening condition	0.768
	(0.600, 0.983)
Mode of administration	
Pill	Baseline
Injection	1.21
	(0.978, 1.49)
Monthly infusion	1.02
	(0.838, 1.23)
Two infusions a year apart	0.945
	(0.769, 1.16)
No treatment ASC	0.568*
	(0.466, 0.693)
Constant	2.89*
	(2.38, 3.51)

Note. Dependent variable baseline was no treatment; *N*=600*;* Bayesian information criterion=733.79; 95% confidence intervals in parentheses; * = statistical significance at 5% level after Holm's sequential Bonferroni correction; ASC = alternative specific constant

Table 6: Multinomial logit with mode of administration for current real-world disease modifying treatment as dependent variable and stated preferences for mode of administration as independent variables

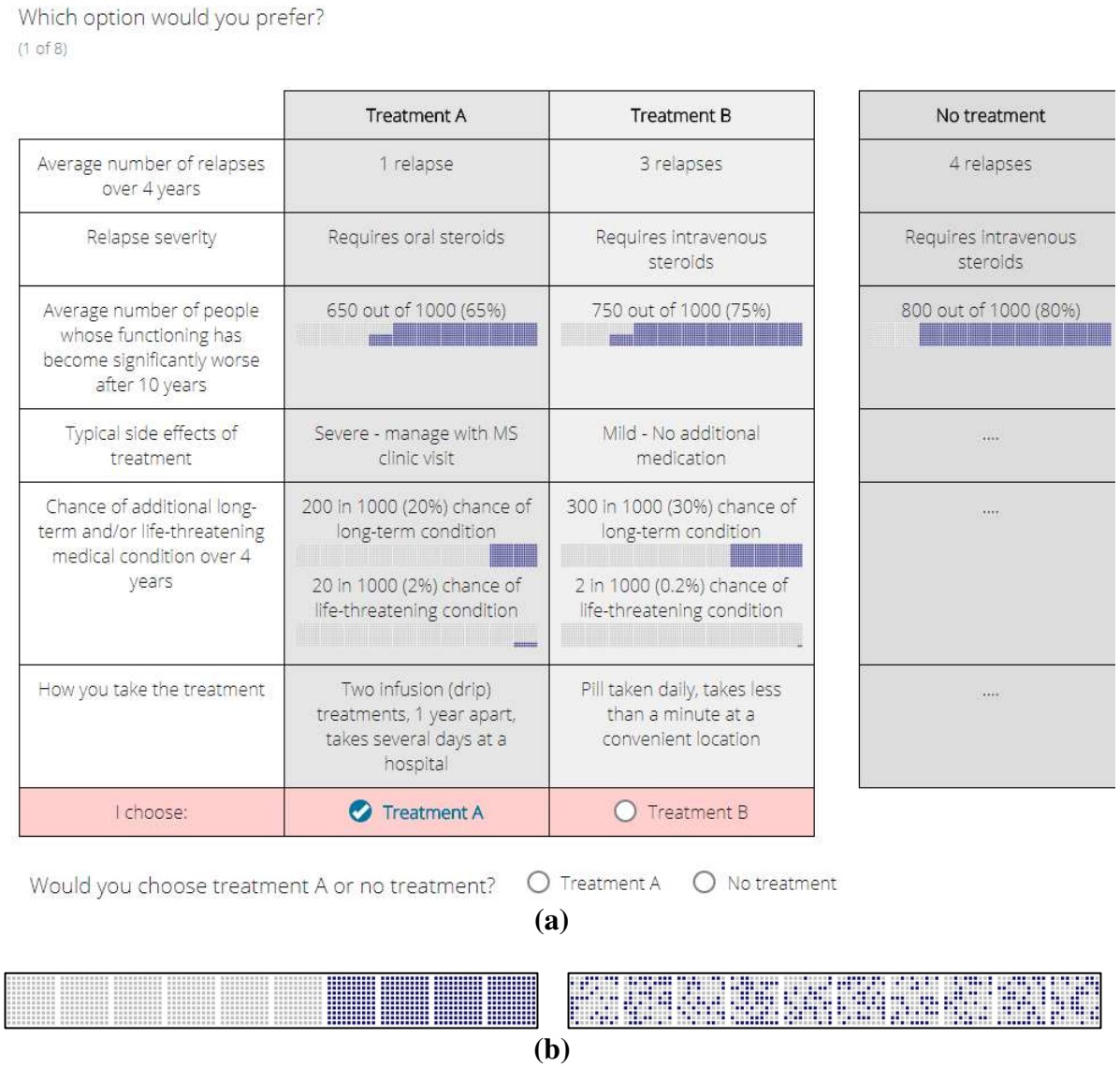
Stated preference	Current DMT mode of administration		
	Injection	Monthly infusion	Two infusions a year apart
Mode of administration			
Pill		Baseline	
Injection	1.59* (1.27, 1.98)		
Monthly infusion		1.36 (0.997, 1.86)	
Two infusions a year apart			2.27* (1.61, 3.20)
Constant	0.589* (0.464, 0.748)	0.274* (0.200, 0.374)	0.178* (0.121, 0.263)

Note. Dependent variable baseline pill; coefficients are odds ratios; *N*=414*;* Bayesian information criterion=1001.43; 95% confidence intervals in parentheses; * = statistical significance at 5% level after Holm's sequential Bonferroni correction; DMT = disease modifying treatment

Table 7: Multinomial logit with current disease modifying treatment as dependent variable and stated preferences for discrete choice experiment attributes as independent variables

Stated preference	Current disease modifying treatment					
	Alemtuzumab	Fingolimod	Glatiramer Acetate	Interferon beta	Natalizumab	Teriflunomide
Number of relapses	0.807	1.08	1.45	1.74	0.866	1.25
	(0.585, 1.11)	(0.739, 1.57)	(0.975, 2.16)	(1.20, 2.54)	(0.639, 1.17)	(0.672, 2.31)
Relapse severity						
Mild			Baseline			
Moderate	0.924	0.821	0.839	0.927	1.06	0.892
	(0.576, 1.48)	(0.602, 1.12)	(0.621, 1.13)	(0.697, 1.23)	(0.726, 1.56)	(0.586, 1.36)
Severe	0.877	1.02	1.16	1.15	0.915	1.13
	(0.577, 1.34)	(0.776, 1.34)	(0.834, 1.63)	(0.818, 1.62)	(0.711, 1.18)	(0.695, 1.83)
% chance worse future functioning	1.08	1.56	1.81	1.5	1.19	1.67
	(0.825, 1.41)	(1.07, 2.28)	(1.22, 2.69)	(1.09, 2.08)	(0.899, 1.58)	(0.843, 3.31)
Side effects						
Mild			Baseline			
Moderate	0.603	0.763	0.628	0.726	0.68	0.732
	(0.385, 0.944)	(0.489, 1.19)	(0.415, 0.951)	(0.476, 1.11)	(0.431, 1.07)	(0.471, 1.14)
Severe	0.99	0.857	0.747	0.962	0.942	0.682
	(0.620, 1.58)	(0.610, 1.20)	(0.540, 1.03)	(0.711, 1.30)	(0.657, 1.35)	(0.445, 1.05)
% chance additional long-term condition	0.842	0.747	0.834	0.839	0.573	0.529
	(0.492, 1.44)	(0.461, 1.21)	(0.551, 1.26)	(0.564, 1.25)	(0.391, 0.839)	(0.357, 0.783)
% chance life-threatening condition	1.01	0.925	0.822	1.02	0.758	0.804
	(0.698, 1.46)	(0.620, 1.38)	(0.634, 1.07)	(0.753, 1.39)	(0.563, 1.02)	(0.607, 1.06)
Mode of administration						
Pill			Baseline			
Injection			[a]1.63*	[a]1.63*		
			(1.30, 2.05)	(1.30, 2.05)		
Monthly infusion					1.41	
					(0.968, 2.06)	
Two infusions a year apart	2.22*					
	(1.53, 3.22)					
Constant	0.298*	0.525*	0.424*	0.607	0.479*	0.226*
	(0.188, 0.471)	(0.371, 0.743)	(0.294, 0.611)	(0.430, 0.856)	(0.330, 0.694)	(0.140, 0.366)

Note. Dependent variable baseline dimethyl fumarate; coefficients are odds ratios; *N*=414; Bayesian information criterion=1767.09; 95% confidence intervals in parentheses; a=parameters restricted to be equal; * = statistical significance at 5% level after Holm's sequential Bonferroni correction



(a)

(b)

Figure 1: (a) Example DCE task; (b) Example icon arrays representing a 40% probability

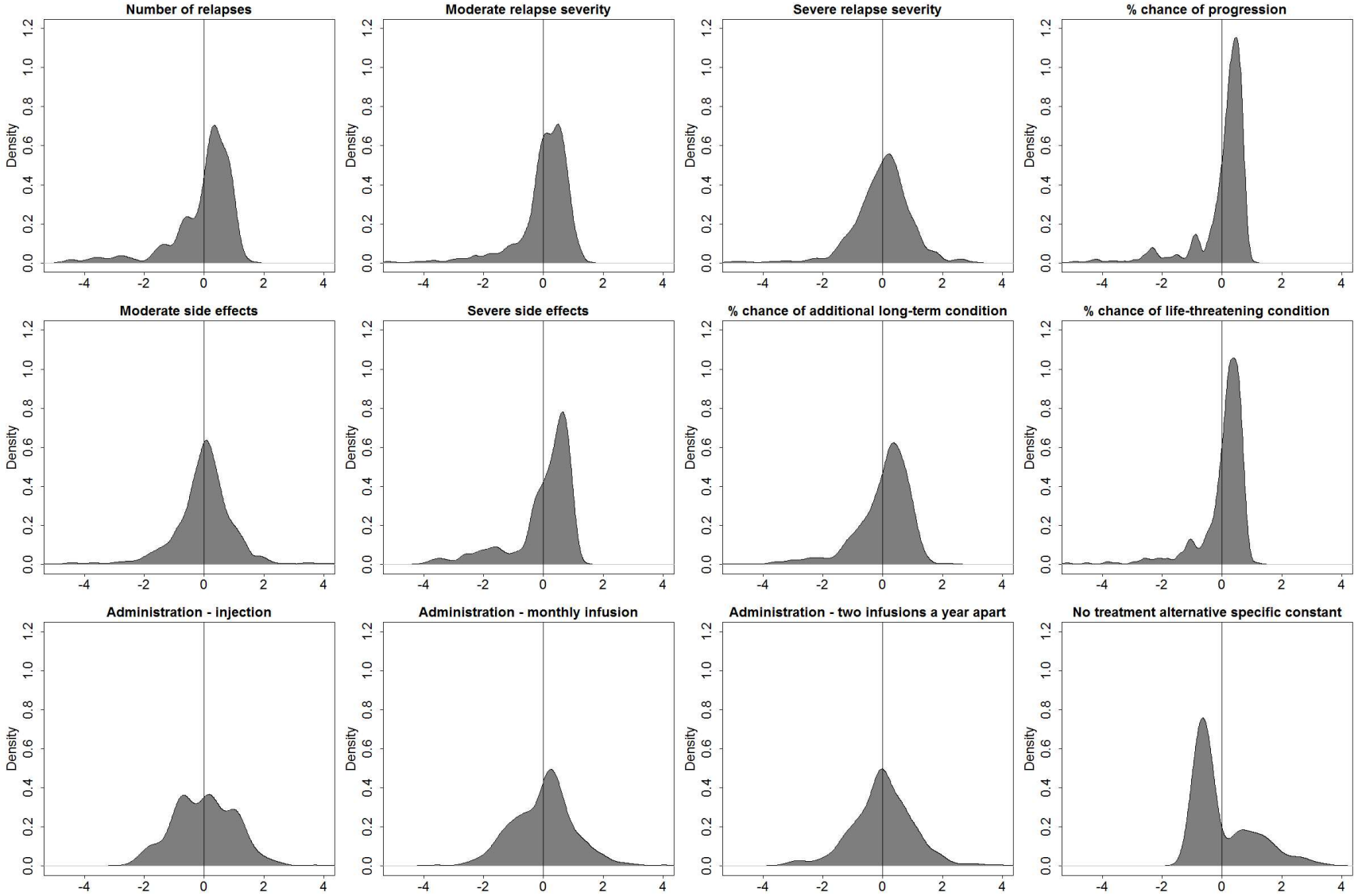


Figure 2: Distributions of stated preferences for discrete choice expreiment attributes used as independent varibles in Tables 5, 6 and 7

Supplementary online material

1. Patience measures

Participants made a series of hypothetical choices between a smaller amount of money immediately or a larger sum in one year, with the smaller sum increasing in each question. They then made a similar set of choices between a smaller sum of money in one year or a larger sum in two years [65, 66]. Long-term patience is calculated as the number of times the larger-later sum was chosen with a one/two-year horizon. Present bias was calculated as the difference between long-term patience and the number of times the larger-later sum was chosen with a now/one year horizon.

2. Utility equation definitions

a) Binary logit of DMT vs. no DMT

$$u_i^{DMT} = \delta_i + \gamma^{DMT}_{i,relapse\ number}\bar{\beta}'_{i,relapse\ number} + \gamma^{DMT}_{i,moderate\ relapse}\bar{\beta}'_{i,moderate\ relapse} + \gamma^{DMT}_{i,severe\ relapse}\bar{\beta}'_{i,severe\ relapse} + \gamma^{DMT}_{i,future\ functioning}\bar{\beta}'_{i,future\ functioning} + \gamma^{DMT}_{i,moderate\ side\ effects}\bar{\beta}'_{i,moderate\ side\ effects} + \gamma^{DMT}_{i,severe\ side\ effects}\bar{\beta}'_{i,severe\ side\ effects} + \gamma^{DMT}_{i,long-term}\bar{\beta}'_{i,long-term} + \gamma^{DMT}_{i,life-threatening}\bar{\beta}'_{i,life-threatening} + \gamma^{DMT}_{i,injection}\bar{\beta}'_{i,injection} + \gamma^{DMT}_{i,monthly\ IV}\bar{\beta}'_{i,monthly\ IV} + \gamma^{DMT}_{i,yearly\ IV}\bar{\beta}'_{i,yearly\ IV} + \varepsilon_i^{DMT}$$

$$u_i^{no\ DMT} = 0$$

b) Multinomial logit of DMT mode of administration

$$u_i^{injection} = \delta_i^{injection} + \gamma^{injection}_{i,injection}\bar{\beta}'_{i,injection} + \varepsilon_i^{injection}$$

$$u_i^{monthly\ IV} = \delta_i^{monthly\ IV} + \gamma^{monthly\ IV}_{i,monthly\ IV}\bar{\beta}'_{i,monthly\ IV} + \varepsilon_i^{monthlyIV}$$

$$u_i^{yearly\ IV} = \delta_i^{yearly\ IV} + \gamma^{yearly\ IV}_{i,yearly\ IV}\bar{\beta}'_{i,yearly\ IV} + \varepsilon_i^{yearly\ IV}$$

$$u_i^{pill} = 0$$

c) Multinomial logit of DMT choice

$$u_i^{alem} = \delta_i^{alem} + \gamma_{i,relapse\ number}^{alem}\overline{\beta'}_{i,relapse\ number} + \gamma_{i,relapse\ severity}^{alem}\overline{\beta'}_{i,relapse\ severity} + \gamma_{i,moderate\ relapse}^{alem}\overline{\beta'}_{i,moderate\ relapse} + \gamma_{i,severe\ relapse}^{alem}\overline{\beta'}_{i,severe\ relapse} + \gamma_{i,future\ funtioning}^{alem}\overline{\beta'}_{i,future\ functioning} + \gamma_{i,moderate\ side\ effects}^{alem}\overline{\beta'}_{i,moderate\ side\ effects} + \gamma_{i,severe\ side\ effects}^{alem}\overline{\beta'}_{i,severe\ side\ effects} + \gamma_{i,long-term}^{alem}\overline{\beta'}_{i,long-term} + \gamma_{i,life-threateneing}^{alem}\overline{\beta'}_{i,life-threatening} + \gamma_{i,yearly\ IV}^{alem}\overline{\beta'}_{i,yearly\ IV} + \varepsilon_i^{alem}$$

$$u_i^{fing} = \delta_i^{fing} + \gamma_{i,relapse\ number}^{fing}\overline{\beta'}_{i,relapse\ number} + \gamma_{i,relapse\ severity}^{fing}\overline{\beta'}_{i,relapse\ severity} + \gamma_{i,moderate\ relapse}^{fing}\overline{\beta'}_{i,moderate\ relapse} + \gamma_{i,severe\ relapse}^{fing}\overline{\beta'}_{i,severe\ relapse} + \gamma_{i,future\ funtioning}^{fing}\overline{\beta'}_{i,future\ functioning} + \gamma_{i,moderate\ side\ effects}^{fing}\overline{\beta'}_{i,moderate\ side\ effects} + \gamma_{i,severe\ side\ effects}^{fing}\overline{\beta'}_{i,severe\ side\ effects} + \gamma_{i,long-term}^{fing}\overline{\beta'}_{i,long-term} + \gamma_{i,life-threateneing}^{fing}\overline{\beta'}_{i,life-threatening} + \varepsilon_i^{fing}$$

$$u_i^{glat} = \delta_i^{glat} + \gamma_{i,relapse\ number}^{glat}\overline{\beta'}_{i,relapse\ number} + \gamma_{i,relapse\ severity}^{glat}\overline{\beta'}_{i,relapse\ severity} + \gamma_{i,moderate\ relapse}^{glat}\overline{\beta'}_{i,moderate\ relapse} + \gamma_{i,severe\ relapse}^{glat}\overline{\beta'}_{i,severe\ relapse} + \gamma_{i,future\ funtioning}^{glat}\overline{\beta'}_{i,future\ functioning} + \gamma_{i,moderate\ side\ effects}^{glat}\overline{\beta'}_{i,moderate\ side\ effects} + \gamma_{i,severe\ side\ effects}^{glat}\overline{\beta'}_{i,severe\ side\ effects} + \gamma_{i,long-term}^{glat}\overline{\beta'}_{i,long-term} + \gamma_{i,life-threateneing}^{glat}\overline{\beta'}_{i,life-threatening} + \gamma_{i,injection}^{glat}\overline{\beta'}_{i,injection} + \varepsilon_i^{glat}$$

$$u_i^{inter} = \delta_i^{inter} + \gamma_{i,relapse\ number}^{inter}\overline{\beta'}_{i,relapse\ number} + \gamma_{i,relapse\ severity}^{inter}\overline{\beta'}_{i,relapse\ severity} + \gamma_{i,moderate\ relapse}^{inter}\overline{\beta'}_{i,moderate\ relapse} + \gamma_{i,severe\ relapse}^{inter}\overline{\beta'}_{i,severe\ relapse} + \gamma_{i,future\ funtioning}^{inter}\overline{\beta'}_{i,future\ functioning} + \gamma_{i,moderate\ side\ effects}^{inter}\overline{\beta'}_{i,moderate\ side\ effects} + \gamma_{i,severe\ side\ effects}^{inter}\overline{\beta'}_{i,severe\ side\ effects} + \gamma_{i,long-term}^{inter}\overline{\beta'}_{i,long-term} + \gamma_{i,life-threateneing}^{inter}\overline{\beta'}_{i,life-threatening} + \gamma_{i,injection}^{inter}\overline{\beta'}_{i,injection} + \varepsilon_i^{inter}$$

$$u_i^{nat} = \delta_i^{nat} + \gamma_{i,relapse\ number}^{nat}\overline{\beta'}_{i,relapse\ number} + \gamma_{i,relapse\ severity}^{nat}\overline{\beta'}_{i,relapse\ severity} + \gamma_{i,moderate\ relapse}^{nat}\overline{\beta'}_{i,moderate\ relapse} + \gamma_{i,severe\ relapse}^{nat}\overline{\beta'}_{i,severe\ relapse} + \gamma_{i,future\ funtioning}^{nat}\overline{\beta'}_{i,future\ functioning} + \gamma_{i,moderate\ side\ effects}^{nat}\overline{\beta'}_{i,moderate\ side\ effects} + \gamma_{i,severe\ side\ effects}^{nat}\overline{\beta'}_{i,severe\ side\ effects} + \gamma_{i,long-term}^{nat}\overline{\beta'}_{i,long-term} + \gamma_{i,life-threateneing}^{nat}\overline{\beta'}_{i,life-threatening} + \gamma_{i,monthly\ IV}^{nat}\overline{\beta'}_{i,monthly\ IV} + \varepsilon_i^{nat}$$

$$u_i^{teri} = \delta_i^{teri} + \gamma_{i,relapse\ number}^{teri}\overline{\beta}'_{i,relapse\ number} + \gamma_{i,relapse\ severity}^{teri}\overline{\beta}'_{i,relapse\ severity} + \gamma_{i,moderate\ relapse}^{teri}\overline{\beta}'_{i,moderate\ relapse} + \gamma_{i,severe\ relapse}^{teri}\overline{\beta}'_{i,severe\ relapse} + \gamma_{i,future\ funtioning}^{teri}\overline{\beta}'_{i,future\ functioning} + \gamma_{i,moderate\ side\ effects}^{teri}\overline{\beta}'_{i,moderate\ side\ effects} + \gamma_{i,severe\ side\ effects}^{teri}\overline{\beta}'_{i,severe\ side\ effects} + \gamma_{i,long-term}^{teri}\overline{\beta}'_{i,long-term} + \gamma_{i,life-threateneing}^{teri}\overline{\beta}'_{i,life-threatening} + \varepsilon_i^{teri}$$

$$u_i^{dimethyl} = 0$$

Restrictions: $\gamma_{,injection}^{glat} = \gamma_{i,injection}^{inter}$

3. Summary statistics for participants' health status

Table A 1:Participants' health status

Variable		Before imputation		Missing		After imputation	
		N	(%)	N	(%)	N	(%)
MSIS-29							
physical score - *mean (standard deviation)*		51.4	(18.4)	79	(13.2)	50.9	(17.3)
psychological score - *mean (standard deviation)*		53.8	(18.3)	79	(13.2)	53.2	(17.3)
HADS							
anxiety score - *mean (standard deviation)*		7.7	(5)	81	(13.5)	7.4	(4.7)
depression score – *mean (standard deviation)*		6.8	(4.5)	79	(13.2)	6.6	(4.3)
FSS - *mean (standard deviation)*		43.4	(13.7)	108	(18)	43.3	(12.7)
EQ-5D							
Mobility	Level 1	321	(95.8)	265	(44.2)	584	(97.3)
	Level 2	14	(4.2)			16	(2.7)
	Level 3	0	(0)			0	(0)
Self-care	Level 1	174	(95.6)	418	(69.7)	591	(98.5)
	Level 2	8	(4.4)			9	(1.5)
	Level 3	0	(0)			0	(0)
Usual activities	Level 1	307	(87.7)	250	(41.7)	554	(92.3)
	Level 2	41	(11.7)			44	(7.3)
	Level 3	2	(0.6)			2	(0.3)
Anxiety or depression	Level 1	314	(86)	235	(39.2)	544	(90.7)
	Level 2	47	(12.9)			52	(8.7)
	Level 3	4	(1.1)			4	(0.7)
Pain or discomfort	Level 1	249	(85)	307	(51.2)	552	(92)
	Level 2	44	(15)			48	(8)
	Level 3	0	(0)			0	(0)
Visual analogue scale - *mean (standard deviation)*		66.2	(21.3)	74	(12.3)	66.9	(20.1)

Note. *N*=600; MSIS-29 = Multiple Sclerosis Impact Scale; HADS = Hospital Anxiety and Depression Scale; FSS = Fatigue Severity Scale.

4. Results from robustness tests interacting stated preferences with time on current disease modifying treatment

Table A 2: Multinomial logit with mode of administration for current real-world disease modifying treatment as dependent variable and stated preferences for mode of administration as independent variables interacted with time on current disease modifying treatment

Stated preference	Current DMT mode of administration		
	Injection	Monthly infusion	Two infusions a year apart
Mode of administration			
Pill		Baseline	
Injection	1.68* (1.28, 2.20)		
Injection x time on current DMT	0.998 (0.991, 1.01)		
Monthly infusion		1.2 (0.817, 1.77)	
Monthly infusion x time on current DMT		1 (0.996, 1.01)	
Two infusions a year apart			2.46* (1.65, 3.65)
Two infusions a year apart x time on current DMT			0.996 (0.990, 1.00)
Constant	0.587* (0.464, 0.744)	0.272* (0.198, 0.372)	0.179* (0.122, 0.264)

Note. Dependent variable baseline pill; coefficients are odds ratios; *N*=414*;* Bayesian information criterion=1017.25; 95% confidence intervals in parentheses; * = statistical significance at 5% level after Holm's sequential Bonferroni correction; DMT = disease modifying treatment

Table A 3: Multinomial logit with current disease modifying treatment as dependent variable and stated preferences for discrete choice experiment attributes as independent variables interacted with time on current disease modifying treatment

Stated preference	Current disease modifying treatment					
	Alemtuzumab	Fingolimod	Glatiramer Acetate	Interferon beta	Natalizumab	Teriflunomide
Number of relapses	0.749	0.942	1.42	1.28	0.8	1.09
	(0.485, 1.16)	(0.600, 1.48)	(0.864, 2.33)	(0.805, 2.03)	(0.528, 1.21)	(0.470, 2.51)
Number of relapses x time on current DMT	1	1.01	1	1.01	1	1.01
	(0.993, 1.01)	(0.995, 1.02)	(0.989, 1.02)	(0.994, 1.03)	(0.989, 1.01)	(0.992, 1.02)
Relapse severity						
Mild				Baseline		
Moderate	1.18	0.764	0.777	0.841	0.877	0.828
	(0.558, 2.50)	(0.537, 1.09)	(0.544, 1.11)	(0.603, 1.17)	(0.598, 1.29)	(0.490, 1.40)
Moderate x time on current DMT	0.991	1	1.01	1	1.01	1
	(0.976, 1.01)	(0.991, 1.02)	(0.992, 1.02)	(0.988, 1.02)	(0.989, 1.03)	(0.993, 1.02)
Severe	0.767	0.96	1.1	0.932	0.859	1.13
	(0.498, 1.18)	(0.699, 1.32)	(0.706, 1.71)	(0.639, 1.36)	(0.635, 1.16)	(0.586, 2.19)
Severe x time on current DMT	1.01	1	1	1	1	0.999
	(0.998, 1.02)	(0.995, 1.01)	(0.993, 1.01)	(0.994, 1.02)	(0.992, 1.01)	(0.987, 1.01)
% chance worse future functioning	0.874	1.28	1.39	1.12	1.46	1.57
	(0.583, 1.31)	(0.849, 1.93)	(0.819, 2.35)	(0.710, 1.75)	(0.836, 2.56)	(0.543, 4.52)
% chance worse future functioning x time on current DMT	1.01	1.01	1.01	1.01	0.994	1
	(0.999, 1.02)	(0.994, 1.03)	(0.997, 1.03)	(0.991, 1.04)	(0.984, 1.00)	(0.989, 1.02)
Side effects						
Mild				Baseline		
Moderate	0.472	0.616	0.559	0.547	0.518	0.577
	(0.272, 0.822)	(0.355, 1.07)	(0.335, 0.932)	(0.323, 0.928)	(0.289, 0.929)	(0.347, 0.961)
Moderate x time on current DMT	1.01	1.01	1.01	1.01	1.01	1.01
	(1.00, 1.02)	(0.999, 1.02)	(0.993, 1.02)	(0.994, 1.03)	(0.999, 1.03)	(0.997, 1.03)
Severe	0.757	0.721	0.547	0.906	1.08	0.543
	(0.426, 1.35)	(0.469, 1.11)	(0.361, 0.830)	(0.597, 1.37)	(0.663, 1.75)	(0.329, 0.894)
Severe x time on current DMT	1.01	1.01	1.02	1	0.997	1.01
	(1.00, 1.02)	(1.00, 1.02)	(1.00, 1.03)	(0.995, 1.01)	(0.986, 1.01)	(0.994, 1.03)
	0.639	0.66	0.683	0.536	0.481	0.418

% chance additional long-term condition	(0.328, 1.25)	(0.372, 1.17)	(0.381, 1.22)	(0.307, 0.935)	(0.286, 0.809)	(0.252, 0.692)
% chance additional long-term condition x time on current DMT	1.01 (1.00, 1.02)	1 (0.995, 1.01)	1.01 (0.996, 1.02)	1.02 (0.993, 1.04)	1 (0.995, 1.01)	1.01 (0.998, 1.02)
% chance life-threatening condition	0.863 (0.597, 1.25)	0.891 (0.573, 1.38)	0.876 (0.655, 1.17)	0.931 (0.692, 1.25)	0.801 (0.559, 1.15)	0.832 (0.581, 1.19)
% chance life-threatening condition x time on current DMT	1.01 (0.999, 1.02)	1 (0.993, 1.01)	0.999 (0.990, 1.01)	1 (0.993, 1.02)	0.995 (0.982, 1.01)	0.999 (0.990, 1.01)
Mode of administration						
Pill			Baseline			
Injection			1.72* (1.30, 2.28)	1.72* (1.30, 2.28)		
Injection x time on current DMT			1 (0.994, 1.01)	1 (0.994, 1.01)		
Monthly infusion					1.19 (0.729, 1.93)	
Monthly infusion x time on current DMT					1.01 (0.998, 1.02)	
Two infusions a year apart	2.50* (1.61, 3.87)					
Two infusions a year apart x time on current DMT	0.994 (0.987, 1.00)					
Constant	0.286* (0.181, 0.454)	0.528 (0.371, 0.754)	0.400* (0.274, 0.583)	0.56 (0.384, 0.817)	0.428* (0.288, 0.637)	0.222* (0.136, 0.362)

Note. Dependent variable baseline dimethyl fumarate; coefficients are odds ratios; *N*=414; Bayesian information criterion=1767.09; 95% confidence intervals in parentheses; a=parameters restricted to be equal; * = statistical significance at 5% level after Holm's sequential Bonferroni correction; DMT = disease modifying treatment

5. Results of robustness tests including only participant demographics/health status as dependent variables

5.1 Participant characteristics

Table A 4: Binary logit model with real-world on-disease modifying treatment status as dependent variable and participant characteristics as independent variables

Variable	Odds ratio
Age	0.963*
	(0.940, 0.986)
Female	0.709
	(0.344, 1.46)
MSIS-29	
physical score	1.08
	(1.01, 1.15)
psychological score	0.95
	(0.897, 1.00)
Employed/self-employed	0.748
	(0.897, 1.00)
Degree level qualification	1.39
	(0.941, 2.05)
One or more dependent children in household	1.48
	(0.983, 2.22)
Risk attitude	1.02
	(0.934, 1.11)
Patience	1.02
	(0.909, 1.15)
Present bias	0.956
	(0.851, 1.07)
Number of relapses in last year	0.968
	(0.804, 1.16)
Constant	5.73
	(1.10, 29.9)

Note. Dependent variable baseline no treatment; *N*=600*;* Bayesian information criterion=763.11; 95% confidence intervals in parentheses; * = statistical significance at 5% level after Holm's sequential Bonferroni correction; MSIS-29 = Multiple Sclerosis Impact Scale

Table A 5: Multinomial logit with mode of administration for current real-world disease modifying treatment as dependent variable and participant characteristics as independent variables

Variable	Current DMT mode of administration		
	Injection	Monthly infusion	Two infusions a year apart
Age	1.01	0.971	0.918*
	(0.981, 1.05)	(0.935, 1.01)	(0.881, 0.955)
Female	0.788	0.577	0.801
	(0.345, 1.80)	(0.210, 1.59)	(0.277, 2.32)
MSIS-29			
physical score	1.06	1.02	1.08
	(0.983, 1.14)	(0.948, 1.10)	(1.00, 1.16)
psychological score	0.942	1.01	0.938
	(0.878, 1.01)	(0.935, 1.09)	(0.875, 1.01)
Employed/self-employed	1.38	0.578	0.835
	(0.822, 2.33)	(0.293, 1.14)	(0.380, 1.84)
Degree level qualification	0.548	0.788	1.03
	(0.329, 0.914)	(0.393, 1.58)	(0.522, 2.05)
One or more dependent children in household	1.43	1.91	1.92
	(0.830, 2.46)	(0.999, 3.66)	(0.957, 3.85)
Risk attitude	0.791*	1.2	1.09
	(0.702, 0.890)	(1.02, 1.40)	(0.931, 1.28)
Patience	1.06	1.06	1.2
	(0.912, 1.23)	(0.854, 1.32)	(0.971, 1.48)
Present bias	1.09	1.18	1.05
	(0.934, 1.27)	(0.998, 1.39)	(0.849, 1.29)
Number of relapses in last year	0.933	0.748	1.13
	(0.716, 1.22)	(0.488, 1.15)	(0.855, 1.49)
Constant	1.5	0.135	2.9
	(0.136, 16.6)	(0.0104, 1.76)	(0.222, 37.9)

Note. Dependent variable baseline pill; coefficients are odds ratios; *N*=414*;* Bayesian information criterion=990.40; 95% confidence intervals in parentheses; * = statistical significance at 5% level after Holm's sequential Bonferroni correction; DMT= disease modifying treatment; MSIS-29 = Multiple Sclerosis Impact Scale

Table A 6: Multinomial logit with current disease modifying treatment as dependent variable and participant characteristics as independent variables

Variable	Current disease modifying treatment					
	Alemtuzumab	Fingolimod	Glatiramer Acetate	Interferon beta	Natalizumab	Terimflunomide
Age	0.931	1.05	1.03	1.03	0.986	1.03
	(0.891, 0.972)	(1.01, 1.10)	(0.984, 1.09)	(0.986, 1.08)	(0.946, 1.03)	(0.984, 1.08)
Female	0.792	1.03	2.14	0.528	0.581	1.59
	(0.231, 2.71)	(0.297, 3.58)	(0.577, 7.97)	(0.168, 1.66)	(0.181, 1.87)	(0.470, 5.41)
MSIS-29						
physical score	1.11	1.05	1.02	1.13	1.06	1.06
	(1.01, 1.23)	(0.939, 1.17)	(0.885, 1.17)	(1.02, 1.24)	(0.965, 1.16)	(0.960, 1.17)
psychological score	0.933	1.01	0.97	0.927	1	0.988
	(0.858, 1.01)	(0.905, 1.12)	(0.855, 1.10)	(0.848, 1.01)	(0.921, 1.09)	(0.895, 1.09)
Employed/self-employed	0.751	0.813	0.852	1.47	0.525	0.514
	(0.319, 1.77)	(0.386, 1.71)	(0.404, 1.80)	(0.715, 3.04)	(0.244, 1.13)	(0.186, 1.42)
Degree level qualification	0.985	1.25	0.372	0.653	0.76	0.387
	(0.476, 2.04)	(0.617, 2.52)	(0.171, 0.812)	(0.337, 1.26)	(0.362, 1.60)	(0.145, 1.03)
One or more dependent	2.09	0.992	1.2	1.81	2.1	1.7
children in household	(0.996, 4.41)	(0.441, 2.23)	(0.562, 2.57)	(0.891, 3.70)	(1.03, 4.26)	(0.683, 4.24)
Risk attitude	1.1	1.09	0.700*	0.868	1.21	0.911
	(0.928, 1.31)	(0.910, 1.30)	(0.582, 0.842)	(0.745, 1.01)	(1.01, 1.44)	(0.753, 1.10)
Patience	1.22	0.999	1.11	1.07	1.08	1.14
	(0.970, 1.53)	(0.812, 1.23)	(0.890, 1.38)	(0.874, 1.30)	(0.857, 1.37)	(0.882, 1.48)
Present bias	1.06	1.04	1.03	1.15	1.19	1.02
	(0.851, 1.33)	(0.839, 1.29)	(0.822, 1.29)	(0.948, 1.41)	(0.992, 1.44)	(0.774, 1.33)
Number of relapses in last	1.18	1.14	1.03	0.925	0.789	1.04
year	(0.867, 1.61)	(0.827, 1.57)	(0.737, 1.45)	(0.619, 1.38)	(0.504, 1.24)	(0.697, 1.56)
Constant	0.782	1.89×10^{-3}*	1.29	0.0589	0.0311	0.0149
	(0.0389, 15.7)	(7.09×10^{-5}, 0.0507)	(0.0342, 48.7)	(2.19×10^{-3}, 1.59)	(1.50×10^{-3}, 0.646)	(4.25×10^{-4}, 0.523)

Note. Dependent variable baseline dimethyl fumarate; coefficients are odds ratios; *N*=414*;* Bayesian information criterion=1825.59; 95% confidence intervals in parentheses; * = statistical significance at 5% level after Holm's sequential Bonferroni correction; MSIS-29 = Multiple Sclerosis Impact Scale

5.2 Participant characteristics and Hospitable Anxiety and Depression Scale

Table A 7: Binary logit model with real-world on-disease modifying treatment status as dependent variable and participant characteristics/ Hospital Anxiety and Depression Scale as independent variables

Variable	Odds ratio
Age	0.979
	(0.958, 1.00)
Female	0.839
	(0.505, 1.39)
HADS	
anxiety score	0.979
	(0.919, 1.04)
depression score	1.06
	(0.991, 1.13)
Employed/self-employed	0.695
	(0.474, 1.02)
Degree level qualification	1.25
	(0.861, 1.82)
One or more dependent children in household	1.33
	(0.889, 1.98)
Risk attitude	1.03
	(0.945, 1.12)
Patience	1.04
	(0.921, 1.16)
Present bias	0.937
	(0.921, 1.16)
Number of relapses in last year	0.959
	(0.796, 1.16)
Constant	5.64
	(1.28, 24.8)

Note. Dependent variable baseline no treatment; *N*=600*;* Bayesian information criterion=767.40; 95% confidence intervals in parentheses; * = statistical significance at 5% level after Holm's sequential Bonferroni correction; HADS = Hospital Anxiety and Depression Scale

Table A 8: Multinomial logit with mode of administration for current real-world disease modifying treatment as dependent variable and participant characteristics/Hospital Anxiety and Depression Scale as independent variables

Variable	Current DMT mode of administration		
	Injection	Monthly infusion	Two infusions a year apart
Age	1.03	0.985	0.926*
	(1.00, 1.06)	(0.948, 1.02)	(0.889, 0.965)
Female	0.941	1.76	0.887
	(0.497, 1.78)	(0.644, 4.84)	(0.319, 2.47)
HADS			
anxiety score	1.08	1.05	0.927
	(0.990, 1.17)	(0.952, 1.16)	(0.824, 1.04)
depression score	0.936	1.04	1.07
	(0.856, 1.02)	(0.945, 1.15)	(0.937, 1.22)
Employed/self-employed	1.4	0.53	0.743
	(0.844, 2.31)	(0.271, 1.03)	(0.357, 1.54)
Degree level qualification	0.533	0.752	0.899
	(0.326, 0.869)	(0.380, 1.49)	(0.442, 1.83)
One or more dependent children in household	1.37	1.72	1.79
	(0.818, 2.30)	(0.906, 3.27)	(0.877, 3.67)
Risk attitude	0.799*	1.22	1.11
	(0.711, 0.899)	(1.04, 1.43)	(0.950, 1.31)
Patience	1.06	1.09	1.2
	(0.909, 1.23)	(0.883, 1.35)	(0.968, 1.50)
Present bias	1.09	1.15	1.04
	(0.937, 1.27)	(0.971, 1.37)	(0.840, 1.28)
Number of relapses in last year	0.908	0.706	1.14
	(0.689, 1.20)	(0.474, 1.05)	(0.855, 1.51)
Constant	0.433	0.0794	2.89
	(0.0664, 2.83)	(5.27×10^{-3}, 1.20)	(0.209, 40.1)

Note. Dependent variable baseline pill; coefficients are odds ratios; *N*=414*;* Bayesian information criterion=984.71; 95% confidence intervals in parentheses; * = statistical significance at 5% level after Holm's sequential Bonferroni correction; DMT = disease modifying treatment; HADS = Hospital Anxiety and Depression Scale

Table A 9: Multinomial logit with current disease modifying treatment as dependent variable and participant characteristics/Hospital Anxiety and Depression Scale as independent variables

Variable	Current disease modifying treatment					
	Alemtuzumab	Fingolimod	Glatiramer Acetate	Interferon beta	Natalizumab	Terimflunomide
Age	0.949	1.08	1.04	1.07*	1.01	1.05
	(0.909, 0.990)	(1.03, 1.12)	(0.998, 1.08)	(1.03, 1.12)	(0.971, 1.05)	(0.999, 1.10)
Female	0.628	0.541	0.485	0.788	1.2	0.362
	(0.208, 1.90)	(0.210, 1.39)	(0.183, 1.29)	(0.318, 1.95)	(0.393, 3.64)	(0.124, 1.06)
HADS						
anxiety score	0.943	1.07	1.03	1.15	1.07	0.99
	(0.834, 1.07)	(0.942, 1.21)	(0.899, 1.18)	(1.04, 1.28)	(0.960, 1.20)	(0.857, 1.14)
depression score	1.08	1.03	0.99	0.92	1.06	1.05
	(0.951, 1.24)	(0.906, 1.18)	(0.859, 1.14)	(0.825, 1.03)	(0.950, 1.18)	(0.917, 1.21)
Employed/self-employed	0.588	0.653	0.832	1.25	0.413	0.422
	(0.273, 1.26)	(0.320, 1.33)	(0.405, 1.71)	(0.643, 2.45)	(0.201, 0.848)	(0.158, 1.13)
Degree level qualification	0.809	1.12	0.384	0.562	0.684	0.34
	(0.382, 1.72)	(0.560, 2.23)	(0.184, 0.801)	(0.297, 1.07)	(0.328, 1.43)	(0.129, 0.894)
One or more dependent	1.75	0.804	1.22	1.43	1.66	1.44
children in household	(0.827, 3.70)	(0.366, 1.76)	(0.583, 2.54)	(0.727, 2.81)	(0.833, 3.32)	(0.585, 3.55)
Risk attitude	1.12	1.1	0.716*	0.883	1.24	0.912
	(0.944, 1.34)	(0.919, 1.30)	(0.600, 0.853)	(0.757, 1.03)	(1.04, 1.48)	(0.755, 1.10)
Patience	1.24	1.01	1.12	1.07	1.12	1.17
	(0.977, 1.56)	(0.815, 1.26)	(0.900, 1.39)	(0.876, 1.31)	(0.893, 1.42)	(0.906, 1.50)
Present bias	1.03	1.01	1.03	1.13	1.15	0.982
	(0.831, 1.29)	(0.819, 1.25)	(0.827, 1.29)	(0.933, 1.37)	(0.954, 1.39)	(0.759, 1.27)
Number of relapses in last	1.16	1.07	0.999	0.871	0.724	1.03
year	(0.848, 1.59)	(0.779, 1.46)	(0.696, 1.43)	(0.581, 1.31)	(0.474, 1.11)	(0.686, 1.53)
Constant	1.96	8.12×10^{-3}	0.858	0.0315	0.0469	0.114
	(0.120, 32.2)	(4.55×10^{-4}, 0.145)	(0.0520, 14.1)	(2.69×10^{-3}, 0.368)	(2.46×10^{-3}, 0.894)	(5.89×10^{-3}, 2.23)

Note. Dependent variable baseline dimethyl fumarate; coefficients are odds ratios; *N*=414*;* Bayesian information criterion=1821.63; 95% confidence intervals in parentheses; * = statistical significance at 5% level after Holm's sequential Bonferroni correction; HADS = Hospital Anxiety and Depression Scale

5.3 Participant characteristics and EQ-5D

Table A 10: Binary logit model with real-world on-disease modifying treatment status as dependent variable and participant characteristics/EQ-5D as independent variables

Variable	Odds ratio
Age	0.979
	(0.960, 0.999)
Female	0.834
	(0.503, 1.38)
EQ-5D	
level sum	1.04
	(0.816, 1.32)
VAS	0.993
	(0.983, 1.00)
Employed/self-employed	0.713
	(0.485, 1.05)
Degree level qualification	1.26
	(0.865, 1.82)
One or more dependent children in household	1.32
	(0.887, 1.98)
Risk attitude	1.03
	(0.943, 1.12)
Patience	1.03
	(0.915, 1.15)
Present bias	0.944
	(0.843, 1.06)
Number of relapses in last year	0.946
	(0.783, 1.14)
Constant	9.5
	(1.20, 74.9)

Note. Dependent variable baseline no treatment; *N*=600*;* Bayesian information criterion=768.07; 95% confidence intervals in parentheses; * = statistical significance at 5% level after Holm's sequential Bonferroni correction; VAS = visual analogue scale

Table A 11: Multinomial logit with mode of administration for current real-world disease modifying treatment as dependent variable and participant characteristics/EQ-5D as independent variables

Variable	Current DMT mode of administration		
	Injection	Monthly infusion	Two infusions a year apart
Age	1.03	0.971	0.936*
	(0.999, 1.06)	(0.937, 1.01)	(0.902, 0.972)
Female	0.926	1.97	0.857
	(0.485, 1.77)	(0.723, 5.35)	(0.313, 2.35)
EQ-5D			
level sum	1.37	1.08	1.07
	(0.990, 1.90)	(0.769, 1.52)	(0.684, 1.68)
VAS	1.01	0.970*	1
	(0.999, 1.03)	(0.954, 0.986)	(0.980, 1.03)
Employed/self-employed	1.33	0.624	0.754
	(0.807, 2.20)	(0.319, 1.22)	(0.358, 1.59)
Degree level qualification	0.522	0.79	0.938
	(0.320, 0.853)	(0.404, 1.54)	(0.461, 1.91)
One or more dependent children in household	1.4	1.63	1.77
	(0.826, 2.37)	(0.852, 3.11)	(0.869, 3.60)
Risk attitude	0.798*	1.23	1.1
	(0.710, 0.896)	(1.05, 1.45)	(0.939, 1.30)
Patience	1.07	1.09	1.21
	(0.920, 1.24)	(0.884, 1.35)	(0.972, 1.50)
Present bias	1.09	1.16	1.04
	(0.940, 1.27)	(0.974, 1.38)	(0.847, 1.29)
Number of relapses in last year	0.937	0.632	1.13
	(0.707, 1.24)	(0.412, 0.969)	(0.850, 1.51)
Constant	0.0476	1.14	0.988
	(2.69×10^{-3}, 0.841)	(0.0356, 36.5)	(0.0201, 48.6)

Note. Dependent variable baseline pill; coefficients are odds ratios; *N*=414*;* Bayesian information criterion=1117.29; 95% confidence intervals in parentheses; * = statistical significance at 5% level after Holm's sequential Bonferroni correction; DMT = disease modifying treatment; VAS = visual analogue scale

Table A 12: Multinomial logit with current disease modifying treatment as dependent variable and participant characteristics/EQ-5D as independent variables

Variable	Current disease modifying treatment					
	Alemtuzumab	Fingolimod	Glatiramer Acetate	Interferon beta	Natalizumab	Terimflunomide
Age	0.949	1.08	1.04	1.07*	1.01	1.05
	(0.909, 0.990)	(1.03, 1.12)	(0.998, 1.08)	(1.03, 1.12)	(0.971, 1.05)	(0.999, 1.10)
Female	0.628	0.541	0.485	0.788	1.2	0.362
	(0.208, 1.90)	(0.210, 1.39)	(0.183, 1.29)	(0.318, 1.95)	(0.393, 3.64)	(0.124, 1.06)
EQ-5D						
level sum	0.943	1.07	1.03	1.15	1.07	0.99
	(0.834, 1.07)	(0.942, 1.21)	(0.899, 1.18)	(1.04, 1.28)	(0.960, 1.20)	(0.857, 1.14)
VAS	1.08	1.03	0.99	0.92	1.06	1.05
	(0.951, 1.24)	(0.906, 1.18)	(0.859, 1.14)	(0.825, 1.03)	(0.950, 1.18)	(0.917, 1.21)
Employed/self-employed	0.588	0.653	0.832	1.25	0.413	0.422
	(0.273, 1.26)	(0.320, 1.33)	(0.405, 1.71)	(0.643, 2.45)	(0.201, 0.848)	(0.158, 1.13)
Degree level qualification	0.809	1.12	0.384	0.562	0.684	0.34
	(0.382, 1.72)	(0.560, 2.23)	(0.184, 0.801)	(0.297, 1.07)	(0.328, 1.43)	(0.129, 0.894)
One or more dependent	1.75	0.804	1.22	1.43	1.66	1.44
children in household	(0.827, 3.70)	(0.366, 1.76)	(0.583, 2.54)	(0.727, 2.81)	(0.833, 3.32)	(0.585, 3.55)
Risk attitude	1.12	1.1	0.716*	0.883	1.24	0.912
	(0.944, 1.34)	(0.919, 1.30)	(0.600, 0.853)	(0.757, 1.03)	(1.04, 1.48)	(0.755, 1.10)
Patience	1.24	1.01	1.12	1.07	1.12	1.17
	(0.977, 1.56)	(0.815, 1.26)	(0.900, 1.39)	(0.876, 1.31)	(0.893, 1.42)	(0.906, 1.50)
Present bias	1.03	1.01	1.03	1.13	1.15	0.982
	(0.831, 1.29)	(0.819, 1.25)	(0.827, 1.29)	(0.933, 1.37)	(0.954, 1.39)	(0.759, 1.27)
Number of relapses in last	1.16	1.07	0.999	0.871	0.724	1.03
year	(0.848, 1.59)	(0.779, 1.46)	(0.696, 1.43)	(0.581, 1.31)	(0.474, 1.11)	(0.686, 1.53)
Constant	1.96	0.00812	0.858	0.0315	0.0469	0.114
	(0.120, 32.2)	(4.55×10^{-4}, 0.145)	(0.0520, 14.1)	(2.69×10^{-3}, 0.368)	(2.46×10^{-3}, 0.894)	(5.89×10^{-3}, 2.23)

Note. Dependent variable baseline dimethyl fumarate; coefficients are odds ratios; *N*=414*;* Bayesian information criterion=1813.17; 95% confidence intervals in parentheses; * = statistical significance at 5% level after Holm's sequential Bonferroni correction; VAS = visual analogue scale

5.4 Participant characteristics and Fatigue Severity Scale

Table A 13: Binary logit model with real-world on-disease modifying treatment status as dependent variable and participant characteristics/ Fatigue Severity Scale as independent variables

Variable	Odds ratio
Age	0.981
	(0.961, 1.00)
Female	0.795
	(0.481, 1.32)
FSS score	1.01
	(0.999, 1.03)
Employed/self-employed	0.721
	(0.490, 1.06)
Degree level qualification	1.24
	(0.857, 1.81)
One or more dependent children in household	1.3
	(0.867, 1.94)
Risk attitude	1.02
	(0.935, 1.11)
Patience	1.03
	(0.917, 1.16)
Present bias	0.94
	(0.839, 1.05)
Number of relapses in last year	0.953
	(0.793, 1.15)
Constant	3.99
	(0.947, 16.8)

Note. Dependent variable baseline no treatment; *N*=414*;* Bayesian information criterion=761.31; 95% confidence intervals in parentheses; * = statistical significance at 5% level after Holm's sequential Bonferroni correction; FSS = Fatigue Severity Scale

Table A 14: Multinomial logit with mode of administration for current real-world disease modifying treatment as dependent variable and participant characteristics/Fatigue Severity Scale as independent variables

Variable	Current DMT mode of administration		
	Injection	Monthly infusion	Two infusions a year apart
Age	1.02	0.979	0.936*
	(0.997, 1.05)	(0.944, 1.01)	(0.902, 0.971)
Female	0.956	1.52	0.862
	(0.513, 1.78)	(0.578, 3.98)	(0.340, 2.19)
FSS	0.999	1.03	1
	(0.980, 1.02)	(1.01, 1.06)	(0.967, 1.03)
Employed/self-employed	1.35	0.591	0.751
	(0.812, 2.25)	(0.308, 1.13)	(0.361, 1.56)
Degree level qualification	0.523	0.75	0.939
	(0.321, 0.852)	(0.381, 1.47)	(0.467, 1.89)
One or more dependent children in household	1.38	1.67	1.76
	(0.821, 2.32)	(0.888, 3.15)	(0.868, 3.56)
Risk attitude	0.802*	1.18	1.1
	(0.715, 0.900)	(1.01, 1.38)	(0.940, 1.30)
Patience	1.07	1.09	1.21
	(0.920, 1.24)	(0.881, 1.34)	(0.969, 1.51)
Present bias	1.08	1.15	1.04
	(0.930, 1.26)	(0.968, 1.36)	(0.839, 1.29)
Number of relapses in last year	0.927	0.724	1.13
	(0.706, 1.22)	(0.485, 1.08)	(0.865, 1.49)
Constant	0.673	0.0577	1.72
	(0.0916, 4.95)	(4.61×10^{-3}, 0.722)	(0.110, 26.6)

Note. Dependent variable baseline pill; coefficients are odds ratios; *N*=414*;* Bayesian information criterion=1118.38; 95% confidence intervals in parentheses; * = statistical significance at 5% level after Holm's sequential Bonferroni correction; DMT = disease modifying treatment; FSS = Fatigue Severity Scale

Table A 15: Multinomial logit with current disease modifying treatment as dependent variable and participant characteristics/Fatigue Severity Scale as independent variables

Variable	Current disease modifying treatment					
	Alemtuzumab	Fingolimod	Glatiramer Acetate	Interferon beta	Natalizumab	Terimflunomide
Age	0.957 (0.920, 0.994)	1.07 (1.03, 1.11)	1.04 (0.997, 1.08)	1.06 (1.02, 1.10)	1 (0.965, 1.04)	1.05 (1.00, 1.10)
Female	0.588 (0.209, 1.65)	0.484 (0.186, 1.25)	0.468 (0.179, 1.22)	0.745 (0.304, 1.83)	0.996 (0.338, 2.93)	0.332 (0.112, 0.989)
FSS	1.01 (0.973, 1.04)	1.03 (0.999, 1.06)	1 (0.977, 1.03)	1.01 (0.988, 1.04)	1.04 (1.01, 1.07)	1.01 (0.968, 1.05)
Employed/self-employed	0.605 (0.279, 1.31)	0.7 (0.340, 1.44)	0.838 (0.405, 1.73)	1.23 (0.631, 2.38)	0.473 (0.234, 0.955)	0.428 (0.149, 1.23)
Degree level qualification	0.836 (0.399, 1.75)	1.06 (0.532, 2.11)	0.388 (0.189, 0.796)	0.518 (0.272, 0.987)	0.668 (0.323, 1.38)	0.341 (0.128, 0.909)
One or more dependent children in household	1.7 (0.807, 3.57)	0.777 (0.351, 1.72)	1.2 (0.569, 2.53)	1.44 (0.740, 2.81)	1.61 (0.815, 3.19)	1.43 (0.577, 3.55)
Risk attitude	1.1 (0.929, 1.31)	1.07 (0.899, 1.28)	0.715* (0.602, 0.850)	0.873 (0.749, 1.02)	1.19 (0.997, 1.41)	0.905 (0.742, 1.10)
Patience	1.24 (0.974, 1.57)	1.01 (0.817, 1.25)	1.12 (0.899, 1.40)	1.09 (0.891, 1.33)	1.12 (0.887, 1.40)	1.15 (0.880, 1.49)
Present bias	1.04 (0.833, 1.30)	1.01 (0.814, 1.25)	1.03 (0.826, 1.29)	1.12 (0.920, 1.36)	1.15 (0.952, 1.39)	0.996 (0.762, 1.30)
Number of relapses in last year	1.17 (0.863, 1.58)	1.1 (0.803, 1.50)	1.02 (0.719, 1.46)	0.9 (0.601, 1.35)	0.749 (0.490, 1.14)	1.04 (0.704, 1.54)
Constant	1.25 (0.0707, 22.0)	0.00736 (3.11×10^{-4}, 0.174)	1.06 (0.0685, 16.6)	0.0704 (4.92×10^{-3}, 1.01)	0.0374 (2.58×10^{-3}, 0.544)	0.136 (6.93×10^{-3}, 2.67)

Note. Dependent variable baseline dimethyl fumarate; coefficients are odds ratios; *N*=414*;* Bayesian information criterion=1797.01; 95% confidence intervals in parentheses; * = statistical significance at 5% level after Holm's sequential Bonferroni correction; FSS = Fatigue Severity Scale