

Informed shared decision making about immunotherapy for patients with multiple sclerosis (ISDIMS): a randomized controlled trial

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Background and purpose: To evaluate the effects of an evidence-based patient decision aid (DA) on multiple sclerosis (MS) immunotherapy. **Methods:** Two hundred and ninety-seven MS patients who were considering or reconsidering immunotherapy participated in a randomized community-based controlled trial in Germany. An intervention group (IG) received the DA and a control group (CG) received standard information. Primary outcome measure was the match between the patient's preferred and actual roles during consultation with the physician. Secondary end-point was treatment choice. The course of the decision-making process and patients' evaluation of the decision were also evaluated. Data were collected at baseline, after receiving the information, after consultation with the physician and 6 months after baseline. **Results:** The percentage of preference matches did not differ between groups (IG 49%, CG 51%, $P = 0.71$). There were no differences in immunotherapy choices between groups. IG patients temporarily became more critical of immunotherapy and rated the information as significantly more helpful. **Conclusions:** Although the intervention led to intensified processing of the information it affected neither the roles adopted in physician–patient encounters nor the immunotherapy choices made. Providing patients with balanced information may not be sufficient to alter the decision-making process.

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Introduction

Shared decision making (SDM) is a method for physician–patient communication of risks aiming at enhanced patient involvement via a two way exchange of information [1]. It is assumed that this process leads to decisions that accord with patients' individual values [2]. Decisions with high and sustainable impact on a person's quality of life, such as treatment decisions in chronic diseases, are predestined for SDM, particularly when several different options exist and the evidence is complex, ambiguous or insufficient [1].

The decision about immunotherapy treatment of multiple sclerosis (MS) meets all these criteria [3,4]. Since 1995, a number of new 'immunomodulatory' therapies have been available which are intended to affect disease progress. The chance of benefitting from immunotherapy depends on the substance, the stage of disease and unknown factors related to disease heterogeneity [5]. Of 100 MS patients treated with

immunotherapy for 2 years, seven to 12 benefit in terms of delaying disease progression during this period [6]. However, evidence is largely restricted to patients with a highly active relapsing–remitting course of MS. Long-term efficacy still remains an open question. Patients have to weigh up this uncertain benefit against considerable side-effects which cause up to one-third of patients to interrupt or stop treatment early [7].

To support MS patients' weighing of treatment options in the light of their personal values, we have developed an evidence-based patient decision aid (DA). DAs are interventions designed to help people make specific and deliberative choices amongst options by providing information about the options and outcomes that are relevant to their own health status [2]. In this paper, we report the results of a randomized controlled trial (RCT) evaluating effects of this DA. We hypothesized that the intervention would encourage and enable patients to establish their preferred social role in the decision-making process during encounters with their physicians. Considering the ambiguous evidence on immunotherapy, we expected recipients of the DA to appraise immunotherapy more critically and to delay or refrain from treatment more often.

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Statistical analyses were conducted by Jürgen Kasper and Matthias Nübling.

Participants and methods

We recruited participants between October 2004 and February 2006. MS patients were alerted by advertisements in local newspapers all over Germany, on websites and in the national self-help group journal. Patients at Hamburg university hospital were also approached personally. Patients were eligible, if they had a confirmed diagnosis of MS and were considering or reconsidering immunotherapy. We excluded patients with cognitive impairment who found it hard to adequately follow a telephone conversation, patients under 18 years of age, and patients who had already participated in other studies related to informed decision making. Of 562 people seeking information about the study 304 were eligible (Fig. 1). Patients were included after a telephone screening interview. Thereafter, study information, consent form and baseline questionnaires were

sent to be completed before randomization. Patients were randomized when they confirmed an appointment with their physician within 8 weeks intended to discuss immunotherapy. Screening took place consecutively until the planned sample size was achieved.

Study design

Protocol

The protocol of this study has been published with the trial registration at <http://controlled-trials.com/ISRCTN25267500> [8]. This study was approved by the ethics committee of the Hamburg Chamber of Physicians.

Assignment

Randomization was carried out by concealed allocation using computer generated random numbers.

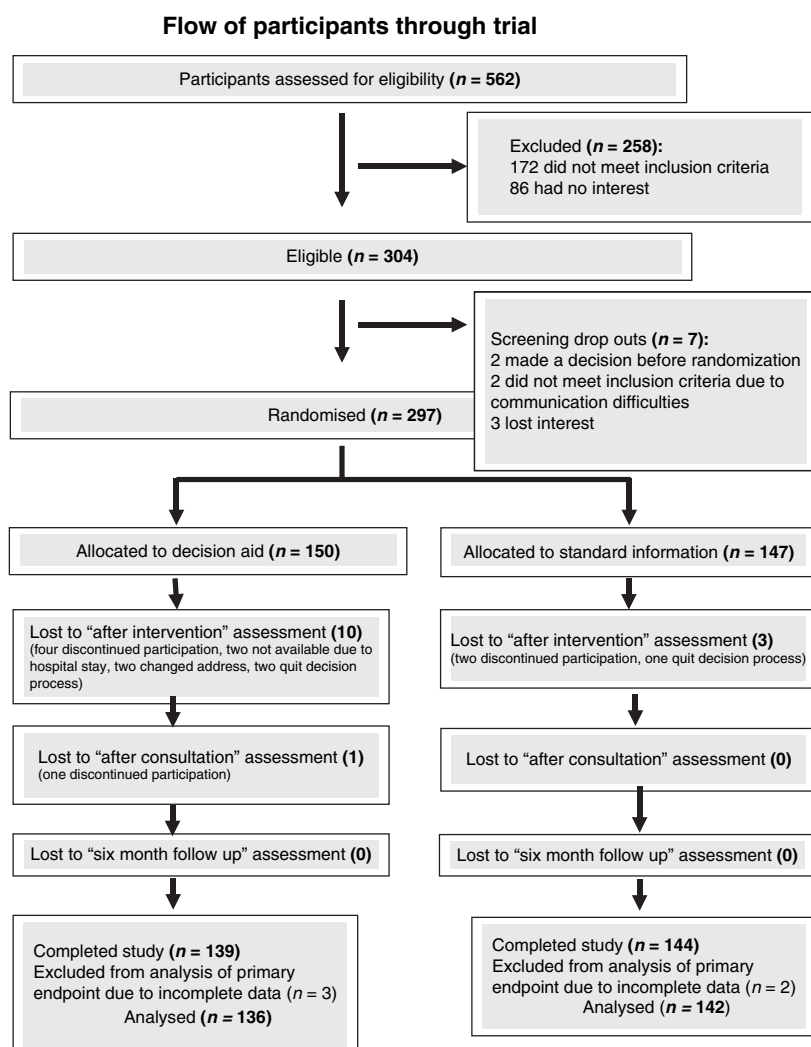


Figure 1 Flow of participants through trial.

Masking

Participants and assessors were not told whether the information they received was standard information or the newly developed DA. To preserve blinding assessors explicitly asked patients not to refer to details of the information material. The treating physicians indirectly involved were informed about the study. However, they were not informed about their patients' allocation and did not receive the patient information.

Sample size

We calculated sample size on the basis of the primary outcome measure (proportion of patients achieving their preferred roles). If 50% of the control group (CG) were to achieve their preferred roles, and if a clinically relevant increase to 70% were to occur in the DA group, 143 participants would be needed in each arm of the study to detect this effect. The calculation was based on a two sided 5% test significance level and a power of 80%, a 10% dropout rate and 25% invalid ranking orders on the Degner-Control Preference Scale (CPS) used to assess the primary end-point [9]. Therefore, 286 patients had to be enrolled in the study. No interim analysis was carried out and no stopping rules applied.

Interventions

The DA (see Table 1) consisted of a comprehensive evidence-based MS patient information booklet about immunotherapy options and an interactive worksheet. The development process considered international standards for the development of evidence-based decision support tools [10,11]. The development of the DA included a series of preliminary studies investigating patients' needs and the feasibility of the methods intended for use in the efficacy trial [12,13]. Since DAs are complex interventions, they require a phased evaluation approach as recommended by the UK Medical Research Council [14]. This approach aims to increase the amount of evidence available on the intervention by qualitative and quantitative studies modelling the intervention and supporting the underlying theory. A pilot study on MS patients' attitudes towards decision-making showed pronounced autonomy preferences and unmet information needs [12]. Risk knowledge of MS-patients was shown to be associated with autonomy preferences [12]. Another study evaluating the basic module of the DA showed patients' ability to understand the given information and to apply the handling of absolute and relative risk information to varying tasks [13]. This study found no negative effects such as emotional discomfort associated with the disclosure of fragile and conflicting evidence [13]. The CG received

Table 1 The ISDIMS-decision aid

The decision aid (DA) is structured with reference to course of disease and complexity. After introducing essential basics to the reader, such as the way probabilities of effects are presented and types of disease course, the DA targets varying needs and conditions. Patients are encouraged to assign themselves to 'their' chapter according to disease course: clinically isolated syndrome (CIS), relapsing remitting, secondary progressive and primary progressive. Furthermore, the DA is organized on three difficulty levels. Each chapter discusses all available immunotherapy options giving numerical data if possible. Effects of treatments found by clinical studies are illustrated using pictograms of 100 human stick figures. Proportions of patients remaining relapse-free and progression-free are indicated by the colour of the stick figures. Effect sizes are given in absolute numbers. Each statement on the amount of people benefiting is complemented by the reverse proportion, stating how many patients experienced no benefit (Kasper 2006). To present side-effects as an equally important aspect for consideration, these are presented with the data for each treatment using similar pictograms. Relevant criteria for the treatment decision as outlined in the booklet are presented on an additional worksheet. The sheet proposes a structure for the decision subdivided into the decision 'whether immunotherapy' and the decision 'which immunotherapy'. Decision criteria are provided for each aspect of the decision and users are advised to allocate weights to the different criteria out of a given limited amount. The worksheet is supposed to emphasize the individual appraisal of the information.

information material on available forms of immunotherapy recommended by the main German self help organization (DMSG). The amount of information was comparable (80 pages). This information was not considered as a 'sham intervention' but to represent standard care, as the material is available on the internet.

Outcome measures

Data were collected via telephone and post at baseline, after the intervention, after consultation with the MS physician and 6 months after randomization. Telephone calls were performed by trained assessors and followed standardized questionnaires.

Achievement of role preferences

As we had already found evidence-based patient information to be associated with autonomy preferences and autonomous behaviour [12], we assumed that the DA would support patients in making the communication with the physician match their preference. We used the CPS which is a one item, five stimuli ranking instrument [9]. The instrument provides five descriptions of social role distributions in the physician-patient interaction printed on cards: 1 – 'I want to make my decision alone'; 2 – 'I want to make my decision alone considering what my doctor says'; 3 – 'I want to share the decision with my

doctor'; 4 – 'I want my doctor to decide considering my preferences'; 5 – 'I want my doctor to decide'. We presented the cards twice, at baseline and after the consultation. The primary end-point was defined as the consistency of the previous reported role preference and the locus of the decision as experienced in the physician encounter.

Treatment choice

As the decision process can extend for a while before a choice is made, we evaluated treatment choice 6 months after randomization. We distinguished between participants already receiving immunotherapy, who were deciding about whether to change, interrupt or continue immunotherapy, and participants not yet receiving medication, who were deciding about initiating, delaying or refraining from immunotherapy.

Measures of the decision process

The study design included a 4-week delay between receipt of the study information and the physician encounter to allow for thorough processing of the treatment decision. As indicators for the process we monitored patients' attitude towards immunotherapy and their stage of progress in the decision. At baseline, after the intervention and after the encounter patients' attitude towards immunotherapy was assessed using a Likert scale ranging from -5 ('in no case immunotherapy') to +5 ('in any case immunotherapy'). At the same time the degree of progress ranging from 'I am still completely undecided' to 'I have made my decision' was assessed on a 100-point scale (Fig. S1). We hypothesized that intervention group (IG)-patients would show more change in attitude within the decision process and would make fewer premature decisions.

Patients' evaluation of interventions and decision making

To facilitate attribution of potential effects to the intervention we assessed subjective reports of reading intensity and helpfulness of the DA. Additionally, patients were asked to rate the received information on a 5-point scale ranging from 'not helpful at all' to 'very helpful'. Patients were asked to specify the kind of support provided by the DA using the categories 'getting information', 'getting my questions answered', 'raising questions', 'becoming clear on my role in the decision'. Patients provided with evidence-based information were assumed to achieve the competence to estimate chances of benefit and side-effects more precisely and realistically than control patients. Therefore, 6 months after randomization, patients on immunotherapy were asked to rate the extent to which their expectations about any side-effects had been in

agreement with what they had experienced in the meantime.

Statistical analysis

All statistical analyses were carried out using SPSS for Windows Release 14. We used descriptive statistics to outline the characteristics of the trial participants. The ordinal structure of the CPS data provides the opportunity to verify the subjects' use of the instrument in accordance with the theoretic model. For a given 5-point hypothetical scale, there are a possible 120 ordered permutations. The grading structure of the given autonomy model including the rigorous requirement of equidistance of the five stimuli implies, however, that only a small subset of 11 out of the 120 possible sequences is valid. In this context, 'valid' means the subjects' response indicates they share the underpinning construct building a continuum from A to E (Degner 1997). A proportion of more than 50% valid sequences in the data was seen by Degner (1997) to indicate sufficient model fit.

To facilitate data analysis and presentation, the 5-point CPS-scale was transformed into a 3-point scale, consisting of 'autonomous', 'shared' and 'paternalistic' decision-making. The first preference in the order assessed at baseline was taken for analysis of the research questions. The -5 to +5 attitude scale was transformed into a 100-point scale on which 0 represented 'in no case immunotherapy' and 100 represented 'in any case immunotherapy'. For comparative analyses of the proportions of participants reaching the primary or the secondary end-point Pearson's Chi-squared tests were performed. Treatment decisions were analysed separately for patients already on immunotherapy and patients not yet on immunotherapy at baseline. For comparison of means analyses of variance (ANOVAS) or unpaired *t*-tests were used. Change in attitude towards immunotherapy or progress in making the treatment decision over three measurement points were analysed using ANOVAS for repeated measures.

Results

Participant flow and follow up

In total, 562 people requested information about the study. Two hundred and ninety-seven patients were randomly assigned to the two study groups (Fig. 1). Thirty-six per cent of them were reconsidering their current immunotherapy and 64% of them were deciding whether to start immunotherapy. At baseline, the two patient groups were comparable with respect to characteristics such as age, sex, course of

Table 2 Baseline characteristics of study groups

	IG (n = 150)	CG (n = 147)	P-value
Mean (SD) age (years)	43.1 (12.1)	43.1 (9.9)	0.98
Female	104 (69)	114 (78)	0.12
Patients already on immunotherapy	54 (36)	53 (36)	0.99
Patients without immunotherapy	96 (64)	94 (64)	
12 or more years of education	80 (53)	76 (52)	0.82
Course of disease			
CIS	21 (14)	24 (16.3)	0.94
RR	79 (52.7)	74 (50.3)	
SP	29 (19.3)	30 (20.4)	
PP	16 (10.7)	15 (10.2)	
Not clear	5 (3.3)	4 (2.7)	
Mean (SD) years since diagnosis	8.5 (8.9)	8.8 (8.3)	0.80
Mean (SD) UNDS	10 (7.0)	9.2 (5.8)	0.26

IG, intervention group; CG, control group; CIS, clinically isolated syndrome; RR, relapsing-remitting; PP, primary progressive; SP, secondary progressive; UNDS, United Kingdom Neurological Disability Scale.

Values are numbers and (%) unless stated otherwise.

Table 3 Preferred interaction style in the decision process

Preferred interaction style	IG	CG	P-value
Baseline			
Autonomous	109 (78)	93 (65)	0.04
Shared	18 (13)	34 (24)	
Physician	13 (9)	16 (11)	
Post-intervention			
Autonomous	109 (81)	103 (74)	0.34
Shared	19 (14)	26 (19)	
Physician	6 (5)	10 (7)	

IG, intervention group; CG, control group.

Analysis at baseline was based on 140 (IG) group and 143 (CG). Analysis after intervention was based on 134 (IG) and 139 (CG) respectively. Values are numbers and (percentages).

disease, disability status and history of immunotherapy (Table 2). However, there was a difference in preferred interaction style between the groups at baseline (Table 3).

Realization of role preferences

A high rate of 82% of the CPS sequences (CG 83%; IG 81%) assessed in this study meet the most restrictive validation criterion indicating high fit of our data to the underpinning model (Degner 1997). Preferences for an autonomous interaction style were remarkably high in both groups at baseline (78% IG and 65% CG) and even higher after the intervention (81% and 74%,

Table 3). Only a minority wished the physician to decide. About 50% of participants reported autonomous decision making within the consultation (49% IG, 53% CG). Table 4 shows the frequencies with which preferred interaction styles were matched within the physician encounter. Preferences to decide autonomously were matched by about 40% in the consultation (IG 42% and CG 38% of patients). Regarded over the three interaction styles, which was the primary end-point, 50% of all patients achieved a level of involvement matching their preferred level. The two study groups did not differ in the rates with which patients achieved their preferred roles in the decision ($P = 0.709$).

Treatment choices

Fifty per cent of the patients reconsidering current immunotherapy continued their therapy, 18% interrupted treatment and 32% changed type of immunotherapy. No differences were found between groups (Table 5). In the group of patients deciding about immunotherapy for the first time 3% were still undecided 6 months after randomization, whereas 56% had made a decision against immunotherapy. Forty-one per cent began immunotherapy. Again, no differences were found between groups.

Decision-making process

Patients from both groups reported a moderately positive attitude towards immunotherapy at baseline (CG 62%, IG 65% on average) and reflected their degree of progress in making their decision equally (CG 45%, IG 49%). Attitudes to immunotherapy in the two groups changed in opposite directions following the intervention (Fig. S2). Whilst CG-patients stabilized their attitude, or were increasingly in favour of treatment, IG-patients appraised immunotherapy more critically. This trend evened out after the physician-patient consultation. However, the IG remained more critical towards immunotherapy (MANOVA factor time: $P = 0.868$, factor time \times group: $P = 0.008$, factor group 0.404). Both groups progressed significantly in making their decision. However, they did not show differences in their course of progress over the three measurement points (MANOVA factor time: $P < 0.00$, factor time \times group: $P = 0.42$, factor group 0.754).

Patients' evaluation of the decision aid

Patients in the IG rated the value of the received information for the decision-making process significantly higher than did those in the CG ($P < 0.001$).

Table 4 Matching of interaction style preferences

	Actual interaction styles in the physician encounter					
	IG			CG		
	Autonomous	Shared	Paternalistic	Autonomous	Shared	Paternalistic
Preferred inter-action style at baseline						
Autonomous	57 (42)	37 (27)	5 (4)	54 (38)	28 (20)	2 (1)
Shared	9 (7)	8 (6)	1 (1)	15 (11)	16 (11)	–
Paternalistic	–	10 (7)	2 (2)	5 (4)	9 (6)	2
Patients reaching primary end-point (<i>n</i> = 260)	67 (49.3)			72 (50.7)		

IG, intervention group; CG, control group.

No decision had been made at the time of assessment by 7 (IG) and 11 (CG) respectively. Baseline control preferences and interaction style after the physician encounter were completed by 129 (IG) and by 131 (CG). Values are numbers and (%).

Table 5 Treatment decisions

	IG	CG
A. Patients already on immunotherapy at baseline		
Continue immunotherapy	28 (56)	22 (44)
Interrupt immunotherapy	9 (18)	9 (18)
Change immunotherapy	13 (26)	19 (38)
B. Patients not yet on immunotherapy at baseline		
Delay treatment decision	3 (4)	2 (2)
Take up immunotherapy	34 (41)	37 (42)
No immunotherapy	47 (56)	49 (56)

IG, intervention group; CG, control group.

Analyses were based on 50 (IG) and 50 (CG) patients on therapy and on 84 (IG) and 88 (CG) patients not yet on therapy at baseline.

Pearson's chi square *P*-value for this table is not significant in A (*P* = 0.87) and B (*P* = 0.4). Values are numbers and (%).

This result refers to the IG patients' feeling of being better informed (*P* < 0.001), getting important questions more adequately answered (*P* < 0.01), and being better supported in finding their preferred role (*P* < 0.05), compared to patients in the CG.

Patients' evaluation of the decision

Six months after randomization, the two groups did not show any significant differences in their evaluation of their decisions. The expectations of side-effects were not more realistic in one of the groups. Satisfaction with the current treatment did not differ between groups at that time.

Discussion

Patients differ in their individual preferences for information and control whilst processing a medical decision [15]. Matching communication to patients' desired levels of information and control may therefore be a more rational response to medical ethics and

consumerism than advocating increasing control for everyone irrespective of preference [15]. Aiming to support patients in achieving their preferred interaction styles within the medical encounter, we developed a patient treatment DA for people with MS. This was to be accomplished by patients processing evidence-based information on one hand and by recognizing the importance of individual appraisal and preferences for making a decision on the other hand. Other pre-consultation interventions have been shown to increase the frequency with which patients ask questions, give opinions, express concerns, disclose information and participate in treatment decisions [16–19]. In the present trial, the DA neither affected the match of role preferences nor did it change treatment decisions. However, the decisional process indicated a higher degree of critical appraisal in the DA group and higher supportive value of the DA compared to standard information (CG).

Why was no difference seen between patients receiving standard information and patients receiving evidence-based information included in a DA? First, since the study did not test a condition without any information, it is not clear to what extent participants made use of information recommended by the main German self help organization (DMSG). Secondly, due to our enrolment strategy the study sample has to be seen as selective in terms of the courage and self-reliance that are necessary to participate in a project carried out at another place in Germany. This assumption is supported by the degree of autonomy preference in the present study, which even exceeds the high degrees of autonomy preference shown by MS patients in our previous studies [12,20]. Although the Hamburg subsample (*n* = 123), which was most likely to be affected by contamination with the evidence-based patient information, did not show any difference in the results, occurrence of some contamination over the whole study

group cannot be completely excluded. A ceiling effect in these respects might partially explain the lack of a difference between the two groups.

The 50% of patients in this study who experienced a level of decision making that matched their desired role is not unusual compared to findings from the literature [15].

This is the first evaluation study of a decision support tool that monitors the subjective patient view on making a medical decision over several measurement points. Although this procedure was intended to evaluate mediating principles, it could also have interfered with the effects of the DA. Intensive process monitoring over a period of about 4 weeks might have enhanced participants' consciousness of the decision as a process in the time, in both groups. This phenomenon known as 'Hawthorne effect' [21], might have caused an enhanced motivation for thorough evaluation of the decision by the method of measurement. This could have clouded a potential effect of the DA on patients' interpersonal competences in the consultation.

In the present study, we were not able to assess physician-related indicators such as the physicians' attitudes towards patient participation in medical decision making or towards evidence-based patient information. However, we found no differences in results between patients treated at the study centre at the University Clinic in Hamburg ($n = 123$) and the patients from other settings ($n = 74$).

From a methodological point of view, the CPS [9] is an optimal instrument to operationalize components of the primary end-point, control preferences and locus of decision. Nevertheless, the interpretation of preferences and role reports in terms of match and mismatch can be challenged. As control preferences can change over time, it is not safe to say whether the interaction during the consultation finally matched the patients' actual preference. Also, we found no differences in satisfaction with the decision making process between patients whose role preferences did and did not match those at baseline.

In contrast to the immunotherapy DA our DA on management of acute relapses was highly effective in changing treatment decisions [22]. This may be due to the type and context of the decision as well as to the didactic strategy. The relapse management DA included an interactive group education programme, which might have been the more effective way to influence acceptance of responsibility and strengthen autonomy.

The question of how to adequately measure DA quality is an ongoing matter of discussion [23,24]. Very few patient decision support techniques have been evaluated using outcome parameters suited to the basic

goals of patient autonomy, evidence-based informed choice or SDM [2,23,24]. More research is also needed addressing the effects of varying matches of communication preferences on outcomes such as symptom reduction or quality of life [15].

Previous findings indicate that MS patients are capable of coping with the uncertainty of scientific evidence without becoming emotionally distressed or experiencing therapeutic nihilism [13]. The present study shows that the DA has the potential to change patients' attitudes to a more critical appraisal of the evidence. These are important, but not sufficient, preconditions for its implementation.

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Contributors

IM and CH initiated the study. CH, JK, IM and SK wrote the study protocol. CH, SK and JK developed the decision aid and coordinated the study, data collection, analysis and interpretation. JK wrote the paper, SK, IM and CH commented on drafts and approved the final draft. JK calculated the sample size. JK and MN designed and performed statistical analyses. JK, SK and CH are guarantors.

Competing interest

CH has received financial support from Biogen Elan, Bayer-Health Care, Serono and Teva, SK, JK, IM and MN have nothing to declare.

Ethical approval

This study was approved by the Ethics committee of the Hamburg Chamber of Physicians.

Supporting information

Additional Supporting information may be found in the online version of this article:

Figure S1. Scale used to assess progress in decision making.

Figure S2. Decision process.

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