Improving MS patients' understanding of treatment risks and benefits in clinical consultations: A randomised crossover trial

Gurpreet K Reen, PhD[a]*, Eli Silber, MD[b] & Dawn W Langdon, PhD[a]

[a] Department of Psychology, Royal Holloway, University of London, Egham, UK & Department of Experimental Psychology, University of Oxford, Oxford, UK

[b] Department of Neurology, King's College Hospital NHS Foundation Trust, Denmark Hill, London, UK

[c] Department of Psychology, Royal Holloway, University of London, Egham, UK

* Corresponding author: Gurpreet K Reen, Department of Experimental Psychology, Radcliffe Observatory Quarter, University of Oxford, OX2 6GG, UK. Email: Gurpreet.reen@psy.ox.ac.uk

Acknowledgments

This study was supported by an investigator initiated research grant from Biogen and matched funding from Royal Holloway, University of London. The funders had no role in study design, data collection and analysis, decision to publish or preparation of the manuscript, beyond courtesy review.

Abstract

Background. Multiple Sclerosis (MS) patients find it difficult to understand the complex risk-benefit profiles of disease-modifying drugs. An evidence-based protocol was designed to improve patient's understanding of treatment information: Benefit and Risk Information for Medication in Multiple Sclerosis (BRIMMS).

Objective. A feasibility study to evaluate whether the BRIMMS protocol can improve MS patients' treatment understanding and reduce conflict in treatment decisions compared to consultation as usual.

Design. Single-blind 4-condition 4-period randomised crossover trial. Hypothetical treatment information was presented to MS patients in a faux 20 minute consultation session using the BRIMMS protocol (aural and visual) or as a usual consultation (aural and visual). Patients were randomised to the order in which they received the four consultation styles.

Participants. 24 patients diagnosed with relapsing-remitting MS.

Measures. Patients were assessed on their comprehension of treatment information, decisional conflict and feedback on consultation styles. Disease and demographic information was also collected.

Results. Treatment understanding was greater for both BRIMMS visual and BRIMMS aural, compared to usual consultations in visual or aural format. Similarly, BRIMMS visual and BRIMMS aural reduced decisional conflict compared to usual consultations in visual or aural formats. All comparisons were $p<0.001$.

Cognitive status was not related to understanding in the BRIMMS protocol, but was negatively related with usual consultation. Conversely, mood influenced understanding on the BRIMMS protocol but not for usual consultation.

Conclusions. BRIMMS protocol offers an effective, evidence-based tool for presenting treatment information in consultations with MS patients and is not influenced by cognition.

Trial Registration. ISRCTN17318966

Key words: Multiple sclerosis, medical decision making, disease-modifying drugs, randomised crossover trial, treatment understanding

1. Introduction

Multiple Sclerosis (MS) is a neurodegenerative disease of the central nervous system affecting an estimated 2.5 million people worldwide [1]. Symptoms include physical, cognitive and affective impairments which can eventually culminate in neurological disability [2]. Disease-modifying drugs (DMDs) can delay the progression of MS if taken as ongoing therapy but have complex risk-benefit profiles [3,4], making understanding of treatment risks and benefits challenging for MS patients[5]. This can be further exacerbated by the cognitive impairments associated with the disease [6–8]. A good understanding of treatment risks and benefits is necessary for patients to make shared treatment decisions with clinicians and adhere to medications [9–13]. This is a pressing concern for MS patients and the wider healthcare systems, as there are both negative health outcomes and cost implications associated with patients taking unsuitable treatments or discontinuing treatments altogether [13–15]. It should therefore be a priority to improve MS patient's understanding of treatment risks and benefits in order to support shared treatment decision-making.

Methods used to present treatment information can impact patient's understanding of treatment risks and benefits. For instance, verbal terms (e.g. "common", "rare") are more likely to be misunderstood compared to numerical formats (e.g. frequencies, percentages) [16]. Moreover, visual graphs (e.g. bar charts, line graphs) can facilitate understanding of treatment information compared to numbers alone [17–19]. There are some recommendations about how best to present treatment risks and benefits to patients to improve understanding of treatment information [20–23]. However, a limitation of these recommendations, and this research area in general, is that optimal presentation methods are either based on studies with non-clinical populations or unrelated patient groups.

Treatment information provided in regular consultations should use optimal presentation methods to facilitate patient's understanding [3]. Yet, many MS patients report receiving low quality treatment information during brief consultations with physicians [24,25] and there is a call for tools to improve how treatment risks and benefits are provided by healthcare professionals to MS patients [26,27]. Several interventions have been designed to improve treatment risk and benefit understanding for MS patients, some of which are incorporated within larger decision aids. However, these interventions only show moderate improvements in treatment understanding [28], do not rely on evidence-based methods to present treatment information [28–30], focus on improving treatment decisions outside of clinical consultations [31], or are contingent on lengthy and intensive programmes that cannot be easily implemented in brief clinical consultations [30,32–35]. The objective of the current feasibility study was to evaluate a protocol for providing treatment information to MS patients during a clinical consultation using evidence-based presentation methods. The protocol aimed to i) improve patient's understanding of treatment risks and benefits, ii) reduce conflict when making a treatment decision and iii) improve patient's experience of receiving treatment information.

2. Methods

2.1. Study Design

The present trial was a single-blind 4-period 4-condition crossover RCT, and has been reported here based on the CONSORT guidelines for randomised crossover trials [36]. The trial received ethical approval by Royal Holloway, University of London and the NHS Research Ethics Committee. The trial was registered on the ISRTCN registry before commencing recruitment.

2.2 Setting and participants

Patients were recruited from two UK NHS hospitals. The study was conducted in person by the chief investigator (GR) at patients' homes. Patients diagnosed with relapsing-remitting Multiple Sclerosis (RRMS) [2], currently taking a DMD, able to provide informed consent, and meet study sensorimotor task demands were included. Patients were excluded if their condition or medication had significantly changed in the last four weeks, or if they had a significant medical and/or psychiatric condition besides MS. All participants had visual acuity of at least 20/70 [37].

2.3 Materials

Treatment information was provided to patients either using the 'Benefit and Risk Information for Medication in Multiple Sclerosis' (BRIMMS) protocol (intervention) or as usual consultation (control). Each consultation style was presented either aurally or visually (treatment information presented visually was also read aloud). That is, there were four possible consultation styles in this study: BRIMMS aural, BRIMMS visual, usual consultation aural, usual consultation visual. Each style of consultation took approximately 20 minutes to administer. All four consultation styles were presented to patients in one session, with 15 minute breaks provided between each new consultation style.

Prior to presenting treatment information in each consultation style, all patients received information about one hypothetical disease with progressive characteristics similar to MS. Patients were then presented with two different hypothetical drugs for the hypothetical disease. This pairing of hypothetical drugs was termed a "treatment set". A hypothetical scenario was chosen to avoid giving patients actual information about MS and DMDs that

may interfere with clinician advice, but rather focusing on how different treatment risks and benefits should be communicated to this patient population.

The risk-benefit profiles of drugs within a treatment set were based on risk-benefit profiles of MS treatments to mimic real decision-making. That is, one drug in each treatment set was similar to a DMD with high risks and high benefits, and the second drug in the set was similar to a DMD with low risks and low benefits. A total of four different treatment sets were used for each of the four consultation styles (i.e. eight total drugs). An example of how the materials were presented to patients in this trial are shown in the appendix (Figure A.1). Each drug had two minor risks (e.g. flu like symptoms, eczema), one adverse risk (e.g. heart attack) and a benefit. Treatment benefit was the delay in disease progression. All treatment risks and benefits were provided for 1, 2 and 5 years of taking the drug.

2.3.1 Intervention

The BRIMMS protocol was designed by GR and DL, and was based on previous work on optimal methods to present treatment risks and benefits to MS patients [38], as well as a comprehensive review of the literature [28,39]. Specifically, all quantitative probabilities of risks and benefits were presented using N-in-N*X frequencies (e.g. 25 in 1000, 450 in 1000). Horizontal bar charts with values presented quantitative information. Only the bar charts were shown visually to patients in the BRIMMS aural consultation style. Treatment benefits of the treatment group versus a placebo group from a hypothetical clinical trial was presented using absolute numbers and with baseline information included (i.e. the total number of people with a treatment benefit in both the treatment and placebo group). See figure 1 for an example of treatment risks and benefits presented in the BRIMMS visual consultation style.

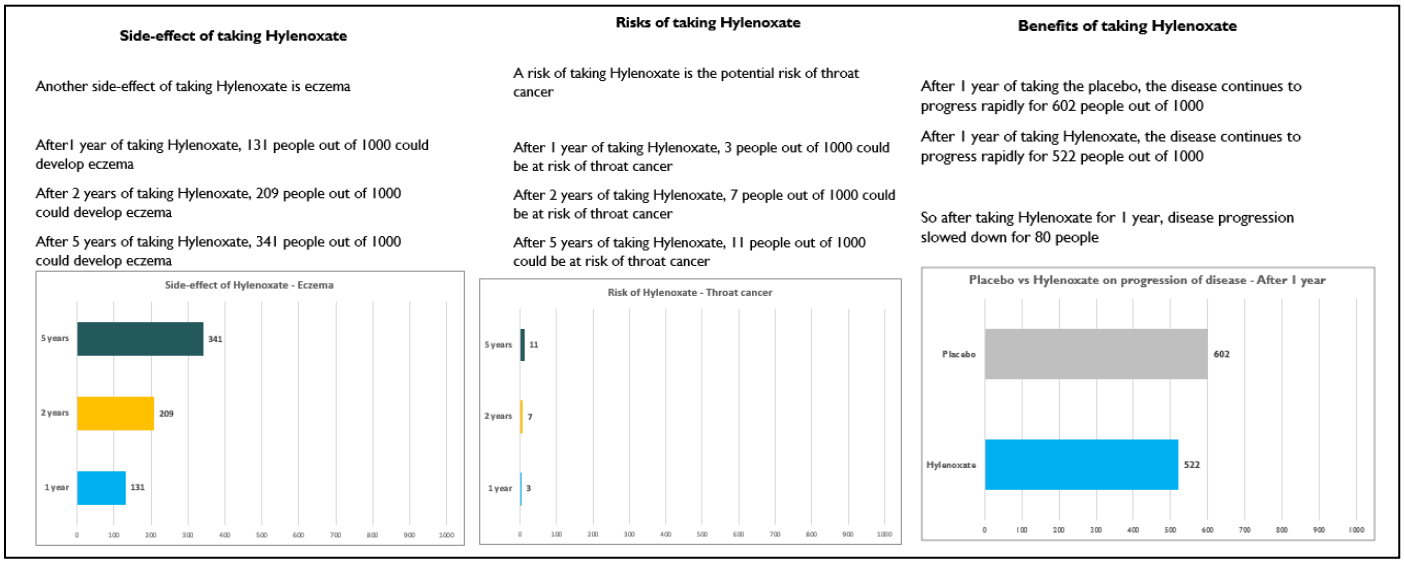

Fig. 1 An example of the BRIMMS visual consultation style to present treatment risks and benefits to patients. All text was shown visually and also read aloud.

2.3.2 Control

The control condition was treatment information provided as usual in a clinical consultation, developed in collaboration with MS nursing staff on two NHS sites and based on treatment information in existing educational booklets provided to MS patients in the UK. Treatment risks and benefits were presented using verbal terms and 1-in-X frequencies. Treatment benefits between the treatment and placebo group from a hypothetical clinical trial was presented using a relative format. No visual graphs were provided with the quantitative information.

2.4 Randomisation

The order of consultation styles was randomised and counterbalanced, such that every consultation style equally followed and preceded another consultation style based on a William's square of sequences [40]. The treatment sets, and the order of treatments

presented within each set, were also randomised. A randomised schedule was prepared and placed in sealed envelopes, one per patient, by an investigator not involved in data collection (DL). The chief investigator (GR) opened the concealed envelopes at the beginning of a study session and allocated patients to consultation styles and to treatment sets based on the concealed randomised schedule. The chief investigator was not blinded to the consultation styles during the session, but was not aware of the randomisation schedule at the time of recruitment. All patients were blinded to the consultation styles and the order in which these were presented.

2.5 Outcomes

2.5.1. Understanding

Patients' understanding of treatment information was assessed using comprehension questions immediately after presenting a treatment risk or benefit. Questions were adapted from previous experiments [41,42]. Patients had to state the total number of people who would experience the minor risk, adverse risk or benefits of the hypothetical treatment across the three time periods (i.e. 1 year/2 years/5 years). For treatment benefits, patients were also asked to report the differences in the treatment group and placebo group from a hypothetical clinical trial, using a multiple-choice format. Therefore, for each drug, patients were assessed on six questions for benefits, three questions each for the two minor risks, and three questions for an adverse risk of taking the treatment (i.e. a total of 15 questions per drug or a total of 30 questions per treatment set). Answers were marked as correct if patients stated the precise value or a value within 10%. Similar cut-offs for correct answers have been applied in previous studies [17,41,42]. Incorrect or missing answers were scored as 0.

2.5.2 Decisional conflict

Patients were required to make a treatment decision after each consultation style was presented, either one of the two drugs from a treatment set or no drug. Patients' conflict in their decision was recorded using the validated Decisional Conflict Scale (DCS) [43,44].

2.5.3 Patient feedback

Patients' feedback following each consultation style was recorded using three 10-point Likert scales, which assessed: perceived understanding, satisfaction and preference of the consultation style. A score of 0 indicated a negative rating and a score of 10 indicated a positive rating.

2.6. Confounding variables

The relationship between patients' treatment understanding for each consultation style with the following patients' characteristics and MS symptoms was also assessed.

2.6.1. Health literacy

Health literacy was assessed using a short 8-item word recognition task was employed: the Rapid Estimate of Adult Literacy in Medicine - Revised (REALM-R) [45].

2.6.2. Numerical reasoning

The series completion subtask of 25 items from the Verbal and Spatial reasoning task (VESPAR) [46] assessed patients' numerical reasoning.

2.6.3 Pre-morbid IQ

Pre-morbid intellectual function (IQ) was measured using the Wechsler Test of Adult Reading scale (WTAR), which is an untimed pronunciation task consisting of 50 irregular English words [47].

2.6.4 Anxiety and depression

Mood was assessed using the Hospital Anxiety and Depression Scale (HADS) [48]. The scale consists of 14 items equally divided between anxiety and depression each scored on a 0-3 Likert scale, and has been validated and recommended for use with MS patients [49].

2.6.4 Fatigue

Patients' fatigue was assessed via the Fatigue Severity Scale (FSS) [50]. The scale consists of nine items, each scored on a 1-7 Likert scale. The final FSS score is calculated by averaging the score of all nine items.

2.6.5 Cognitive impairment

The Brief International Cognitive Assessment for Multiple Sclerosis battery (BICAMS; [51]) assessed the following cognitive deficits, using the subtests stated in brackets: information processing speed (Symbol Digit Modalities Test (SDMT)), verbal memory (California Verbal Learning Test-II recall trials (CVLT-II)) and visual memory (Brief Visuospatial Memory Test Revised, recall trials (BVMTR).

2.7 Statistical analysis

Sample size estimates were based on power calculations to detect a 0.7 effect on the validated DCS outcome measure following intervention. This was calculated from previous randomised trials of interventions designed to improve patients' informed treatment decisions (e.g. [52]). For an alpha of 0.05 and power of 0.80 (roughly equivalent to the 'fair' precision level as stated by Senn [40]), at least 22 MS patients were required for a randomised crossover study.

All statistical analyses were conducted using SPSS 21. Means and standard deviations were provided for all continuous data. For patient's treatment understanding scores, a test of normality was conducted using the Schapiro-Wilks test and was significantly violated ($p<.001$). Therefore, a nonparametric Friedman two-analysis of variance was conducted. Pairwise comparisons, using the Wilcoxon Signed Ranks test, were conducted where necessary and Bonferroni corrections were applied.

Decisional conflict was analysed using standardised DCS scores as recommended by the authors of the scale [43]. Both the test of normality and test of sphericity were not violated ($p>.05$). Therefore, a one-way repeated measures ANOVA was used. Pairwise comparisons were conducted when necessary and Bonferroni corrections were applied.

Patient feedback scores were obtained by averaging patient ratings on perceived understanding, satisfaction and preference. Feedback scores did not violate the test of normality ($p<.05$) but the assumption of sphericity were violated ($p<.05$). Therefore, a one-way repeated measures ANOVA was used and a Greenhouse-Geisser correction was applied. Pairwise comparisons were conducted as necessary using Bonferroni corrections.

Bivariate Pearson's product-moment correlations assessed the relationship between treatment understanding scores following consultation style with raw scores on measures of numerical reasoning, health literacy, premorbid IQ and symptoms of MS. Treatment understanding scores were collapsed across aural and visual forms of each consultation style. That is, understanding scores for BRIMMS and usual consultation were computed in the correlation. Due to multiple correlations, a stringent alpha of $p<.01$ was applied and accepted as significant.

3. Results

3.1. Patient demographics

A total of 24 patients consented to take part in the study between October and December 2017. There were no dropouts or missing data, and all 24 patients received all four consultation styles. Patient demographics, disease status and other characteristics were collected (see Table 1 and 2).

Table 1: Patient demographic and disease variables for all consultation styles (n=24)

	Mean (SD)	n (%)
Age, years	42.58 (8.63)	
Gender		
Female		21 (88)
Male		3 (12)
Level of education		
High school		7 (29)
College		5 (21)
Bachelor's degree		7 (29)
Postgraduate		5 (21)
Employment status		
Full-time (>16 hours)		11 (46)
Part-time (<16 hours)		7 (29)
Unemployed		2 (8)
Medical leave		4 (17)
Time since MS diagnosis, years	7.88 (4.63)	
HAI disability scale*	1.17 (1.34)	
Current DMD		
Interferon betas		8 (33)
Glatiramer Acetate		1 (4)
Teriflunomide		0 (0)
Fingolimod		7 (29)
Alemtuzumab		1 (4)
Dimethyl Fumarate		3 (13)
Natalizumab		4 (17)

DMD= disease-modifying drugs; HAI = Hauser Ambulation Index; MS = Multiple Sclerosis
* Score of 1 on HAI scale = Able to walk normally but report fatigue interfering with athletic activities; Only one set of demographics shown as all participants received all four consultation styles

Table 2: Means, range and patients impaired on assessments of patient characteristics and MS symptoms (n=24)

	Mean (SD)	Range	Impaired, n (%)
Patient characteristics*			
Health literacy	7.79 (0.59)	6 – 8	2 (8)
Numerical reasoning	16.63 (3.00)	10 – 21	1 (4)
Premorbid IQ	35.83 (8.02)	22 – 48	1 (4)
MS symptoms*			
Anxiety	6.88 (4.20)	0 – 13	5 (33)
Depression	5.38 (4.45)	0 – 15	4 (17)
Fatigue	44.71 (12.84)	20 – 61	13 (54)
Information processing speed	63.79 (6.72)	50 – 81	0 (0)
Verbal memory	49.58 (9.82)	33 – 73	7 (29)
Visual memory	22.04 (6.08)	10 – 36	10 (42)

MS = Multiple Sclerosis; * = impairments were calculated based on cut-offs provided by the authors of the assessment measures

3.2. Treatment understanding

There was a significant effect of consultation styles on patients' understanding of treatments, $X^2(3) = 63.46$, $p<.001$ (Table 3). Pairwise comparisons revealed that understanding was greatest for BRIMMS presented visually (95% CI, 26.77-28.81), compared to BRIMMS aural (CI, 23.63-26.12, $p<.001$, $r=0.56$), usual consultation visual (CI, 2.74-4.68 $p<.001$, $r=0.62$) and usual consultation aural (CI, 2.46-4.96, $p<.001$, $r=0.62$). Understanding was also greater for BRIMMS aural compared to usual consultation visual ($p<.001$, $r=0.62$) and usual consultation aural ($p<.001$, $r=0.62$). There was no difference between understanding scores for usual consultation visual and usual consultation aural ($p=0.985$). Thus, the BRIMMS visual protocol significantly improved treatment risk and benefit understanding for MS patients.

3.3. Decision conflict

There was a significant effect of consultation styles on patients' conflict about treatment decisions, F(3,69)=75.109, p<0.001, partial η^2=.87 (see table 3). Patients were less conflicted when they received information via the BRIMMS visual consultation style (95% CI, 22.77-29.58), compared to usual consultation visual (CI, 42.60-52.71, *P*<.001) and usual consultation aural (CI, 48.40-57.20, *P*<.001). Patients were also less conflicted after receiving treatment information using the BRIMMS aural consultation style compared to usual consultation visual (*P*<.001) and usual consultation aural (*P*<.001). There was no difference in patients' conflict in treatment decisions between usual consultation visual and aural (*P*=.216). There was also no difference between BRIMMS visual and BRIMMS aural (*P*=1.00). Thus, both BRIMMS visual and BRIMMS aural consultation styles reduced decisional conflict in MS patients.

3.4. Patient feedback

There was a significant effect of consultation styles on patients' feedback scores, F(1.27, 29.24)=111.835, *P*<.001 (Table 3). BRIMMS visual (95% CI, 8.25-9.00) was rated more positively compared to BRIMMS aural (CI, 7.51-8.33), usual consultation visual (CI, 2.91-4.65, *P*<.001) and usual consultation aural (CI, 2.46-4.07, *P*<.001). More positive ratings were also given for BRIMMS aural compared to usual consultation visual (*P*<.001) and usual consultation aural (*P*<.001). There was no difference between patients' feedback scores for usual consultation visual compared to usual consultation aural (P=1.00). These results indicate that MS patients strongly preferred receiving treatment information using the BRIMMS protocol, in particular using the visual format.

Table 3: Effect of consultation formats on patients' understanding, decisional conflict and feedback (n=24)

Primary outcomes	BRIMMS consultation written	BRIMMS consultation aural	Usual consultation written	Usual consultation aural	*P* value
Understanding[a]	27.79 (2.41)	24.88 (2.94)	3.71 (2.29)	3.71 (2.96)	<.001
Decisional conflict[b] *	26.17 (8.06)	25.78 (7.99)	47.66 (11.97)	52.80 (10.43)	<.001
Patient feedback[c] **	8.63 (0.89)	7.92 (0.97)	3.78 (2.06)	3.26 (1.91)	<.001

All scores state mean and (SD); BRIMMS = Benefit and Risk Information for Medication in Multiple Sclerosis protocol; [a] Maximum understanding score=30; [b] Maximum decisional conflict score=100; [c] Maximum patient feedback score=10
* High mean score = high decisional conflict
** High patient feedback score = positive

3.5. Relationship between treatment understanding with patients' characteristics and MS symptoms

Only anxiety (r=-.523, *P*<.01) and depression (r=-.675, *P*<.001) were significantly correlated with patients' understanding of treatments following the BRIMMS protocol. For consultation as usual, the following patient characteristics and MS symptoms were correlated with patients' understanding of treatments: numerical reasoning (r=.680, *P*<.001), health literacy (r=.535, *P*<.01), pre-morbid IQ (r=.637, *P*<.01), information processing speed (r=.704, *P*<.001) and verbal memory (r=.758, *P*<.001). This indicates that comprehension of treatment risks and benefits following the BRIMMS protocol was not influenced by numerical reasoning, health literacy and cognition in MS patients. However, anxiety and depression in MS patients was positively correlated with treatment understanding scores.

4. Discussion

Improving patients' understanding of treatments is essential for shared decision-making and can also help to promote treatment adherence [9–11,13]. To ensure a good understanding of treatment risks and benefits, patients should be provided with clear and comprehensible treatment information within regular clinical consultations [3,24,25,27]. The current feasibility trial found that implementing the BRIMMS protocol with MS patients significantly improved patients' understanding of treatment risks and benefits, and reduced conflict in treatment decisions compared to consultations as usual. Patients also rated treatment information received during the BRIMMS protocol as significantly better than usual consultations.

Previous interventions that aim to improve MS patients' understanding of treatments usually do so as a secondary outcome, with the primary focus being on improving treatment decision-making. These interventions are only moderately successful in improving patient's understanding of treatment risks and benefits [28] or rely on lengthy and intensive programmes that cannot be incorporated within a regular consultation [30,32–35]. Many of these interventions also do not provide evidence-based methods to present treatment risks and benefits to MS patients, mainly due to limited studies about optimal presentation methods for this patient group. The strength of the BRIMMS protocol is that it employs optimal methods of presenting treatment information to patients based on empirical studies with a MS population [38], and can be feasibly conducted in short clinical consultation. Nevertheless, there are other components that should be considered in consultations for effective treatment decision-making. For example, treatment consultations with MS patients should ideally involve a conversation about symptomatic

medications to alleviate disease symptoms and side-effects of DMDs, as well as the importance of adhering to DMDs over time [3]. Consultations should also involve discussing patient preferences and values before treatment decisions are made by using tools such as a value clarification exercise [30,32–35]. Treatment information using suitable presentation methods should also be provided for MS patients to take away to deliberate with families and carers prior to making a treatment decision. Following further evaluation, these components could be combined with the BRIMMS protocol to improve shared treatment decision-making.

The BRIMMS protocol was presented to patients both aurally and in a visual format in the present study. The visual BRIMMS protocol was slightly better at improving MS patients' understanding of treatments than the aural BRIMMS protocol. This may be because the methods integrated into the BRIMMS protocol were primarily based on experiments which presented treatment information in a visual format [38], and because numerical information displayed visually is perhaps easier to recall. It is possible that the most optimal methods to communicate treatment information aurally to MS patients may differ and should be explored further.

The BRIMMS protocol also significantly improved treatment understanding irrespective of patients' individual characteristics and cognitive symptoms in this cohort. Only anxiety and depression had a negative impact on understanding following the BRIMMS protocol. In contrast, poor numerical reasoning, health literacy, pre-morbid IQ and cognitive impairments were associated with poor understanding in the usual consultation format. This indicates that employing BRIMMS can improve understanding for MS patients with

many different characteristics. For patients experiencing anxiety and depression, however, the BRIMMS intervention could be further adapted and improved.

There are a number of limitations to this feasibility trial. First, the experimenter was not blinded during the study. Second, treatment information was provided by a non-clinical experimenter in a hypothetical consultation. It is possible that patients interact differently when real treatment options are presented by healthcare professionals. Third, although best efforts were made to ensure that the control consultation reflected usual consultations provided to MS patients within the UK, consultations can vary greatly depending on patients and health professionals and are tailored to individual circumstances. In addition, patients had no prior knowledge about the hypothetical treatments presented in the current RCT. Yet, many MS patients report searching for treatment information prior to consultations [53], which could affect understanding of real DMD information. Furthermore, participants in the current study may have a higher education level than a population based sample and therefore may be more likely to understand the treatment risk and benefit information, irrespective of the protocol type. A further study with a more representative sample is needed to fully evaluate the BRIMMS protocol. Finally, the use of faux drug and disease information may also have led to less participant interest and emotional involvement in the study, which could have a larger impact on outcomes such as decisional conflict. To combat some of these limitations, future research should aim to evaluate the BRIMMS intervention during consultations in which clinicians provide real DMD risks and benefits across local and international healthcare services in a larger study. A multi-centre trial is planned to confirm these results.

5. Conclusion

This initial crossover RCT suggests that the BRIMMS protocol can be used by healthcare professionals in a brief consultation session to improve patients' understanding of DMD risk and benefit information and reduce conflict in treatment decisions. The BRIMMS protocol was rated more positively by patients in terms of perceived understanding, satisfaction and preference, making it likely that consultations based on the BRIMMS protocol will be better liked. Future multicentre studies, incorporating real MS DMD information and decisions, and the development of software formats for BRIMMS, will increase the validity and feasibility of this protocol for clinical and research work.

Acknowledgments

Funding

This study was supported by an investigator initiated research grant from Biogen and matched funding from Royal Holloway, University of London. The funders had no role in study design, data collection and analysis, decision to publish or preparation of the manuscript, beyond courtesy review.

Conflict of Interest

GR has no disclosures.

ES had acted as an advisor or received financial support for research and for educational purposes, and hospitality, from Merck-Serono, Biogen, TEVA, Bayer-Schering and Novartis; and through his NHS trust has also received financial support for projects/service developments from some of these companies. He has been an investigator in commercial trials sponsored by Biogen Idec, Novartis, TEVA, Receptos, Roche, GW Pharma and GSK.

DL's disclosures are: Consultancy from Celgene, Novartis, Bayer, TEVA; Speaker bureau for Almirall, TEVA, Biogen, Novartis, Bayer; Research grants from Novartis, Biogen, Bayer.

Availability of data and material

Available on request from authors GR and DL

Code availability

Not applicable

References

1. Browne P, Chandraratna D, Angood C, Tremlett H, Baker C, Taylor B V, et al. Atlas of MS 2013: A Growing Global Problem With Widespread Inequity. Neurology. 2014;83:1022–4.

2. Thompson AJ, Banwell BL, Barkhof F, Carroll WM, Coetzee T, Comi G, et al. Diagnosis of multiple sclerosis: 2017 revisions of the McDonald criteria. Lancet Neurol. 2018;17:162–73.

3. Rae-Grant A, Day GS, Marrie RA, Rabinstein A, Cree BAC, Gronseth GS, et al. Practice guideline recommendations summary: Disease-modifying therapies for adults with multiple sclerosis. Neurology. 2018;90:777–88.

4. Rommer P, Zetti U. Managing the side effects of multiple sclerosis therapy: pharmacotherapy options for patients. Expert Opin. Pharmacother. 2018;19:483–98.

5. Reen GK, Silber E, Langdon DW. Multiple sclerosis patients' understanding and preferences for risks and benefits of disease-modifying drugs: A systematic review. J. Neurol. Sci. [Internet]. Elsevier B.V.; 2017;375:107–22. Available from: http://dx.doi.org/10.1016/j.jns.2016.12.038

6. Basso MR, Candilis PJ, Johnson J, Ghormley C, Combs DR, Ward T. Capacity to make medical treatment decisions in multiple sclerosis: a potentially remediable deficit. J. Clin. Exp. Neuropsychol. Basso, Michael R., Department of Psychology, University of Tulsa, 800 South Tucker Drive, Tulsa, OK, US, 74104: Taylor & Francis; 2010;32:1050–61.

7. Langdon DW. Cognition in Multiple Sclerosis. Curr. Opin. Neurol. 2011;24:244–9.

8. Sumowski JF, Benedict R, Enzinger C, Filippi M, Geurts JJ, Hamalainen P, et al. Cognition in multiple sclerosis: State of the field and priorities for the future. Neurology. 2018;90:278–88.

9. Rieckmann P, Centonze D, Elovaara I, Giovannoni G, Havrdová E, Kesselring J, et al. Unmet needs, burden of treatment, and patient engagement in multiple sclerosis: A combined perspective from the MS in the 21st Century Steering Group. Mult. Scler. Relat. Disord. 2018;19:153–60.

10. Yeandle D, Rieckmann P, Giovannoni G, Alexandri N, Langdon D. Patient Power Revolution in Multiple Sclerosis: Navigating the New Frontier. Neurol. Ther. Springer Healthcare; 2018;7:179–87.

11. Legare F, Turcotte S, Stacey D, Ratt S, Kryworuchko J, Graham ID. Patients perceptions of sharing in decisions: A systematic review of interventions to enhance shared decision making in routine clinical practice. Patient. 2012;5:1–19.

12. Turner a P, Kivlahan DR, Sloan a P, Haselkorn JK. Predicting ongoing adherence to disease modifying therapies in multiple sclerosis: utility of the health beliefs model. Mult. Scler. 2007;13:1146–52.

13. Thomas NP, Curkendall S, Farr AM, Yu E, Hurley D. The impact of persistence with therapy on inpatient admissions and emergency room visits in the US among patients with multiple sclerosis. J. Med. Econ. 2016;19:497–505.

14. The Academy of Medical Sciences. Enhancing the use of scientific evidence to judge the potential benefits and harms of medicines. 2017;

15. Johnson FR, Beusterien K, Özdemir S, Wilson L. Giving Patients a Meaningful Voice in United States Regulatory Decision Making: The Role for Health Preference Research. Patient. 2017;10:523–6.

16. Berry DC, Knapp P, Raynor T. Expressing medicine side effects: assessing the

effectiveness of absolute risk, relative risk, and number needed to harm, and the provision of baseline risk information. Patient Educ. Couns. 2006;63:89–96.

17. McCaffery KJ, Dixon a., Hayen a., Jansen J, Smith S, Simpson JM. The Influence of Graphic Display Format on the Interpretations of Quantitative Risk Information among Adults with Lower Education and Literacy: A Randomized Experimental Study. Med. Decis. Mak. 2012;32:532–44.

18. Oudhoff JP, Timmermans DRM. The Effect of Different Graphical and Numerical Likelihood Formats on Perception of Likelihood and Choice. Med. Decis. Mak. 2015;487–500.

19. Poirier MW, Decker C, Spertus JA, McDowd JM. What eye-tracking methods can reveal about the role of information format in decision-aid processing: an exploratory study. Patient Educ. Couns. Elsevier Ireland Ltd; 2019;

20. Gigerenzer G, Edwards A. Simple tools for understanding risks: from innumeracy to insight. BMJ Br. Med. J. 2003;327:741–4.

21. Zipkin D, Umscheid C, Keating N, Allen E, Aung K, Beyth R, et al. Evidence-based risk communication: a systematic review. Ann Intern Med. 2014;161:270–80.

22. Mühlbauer V, Prinz R, Mühlhauser I, Wegwarth O. Alternative package leaflets improve people's understanding of drug side effects—A randomized controlled exploratory survey. PLoS One. 2018;13:1–19.

23. Bansback N, Bell M, Spooner L, Pompeo A, Han PKJ, Harrison M. Communicating Uncertainty in Benefits and Harms: A Review of Patient Decision Support Interventions. Patient. Springer International Publishing; 2017;10:311–9.

24. Colligan E, Metzler A, Tiryaki E. Shared decision-making in multiple sclerosis : A review. Mult. Scler. J. 2017;23:185–90.

25. Hay MC, Strathmann C, Lieber E, Wick K, Giesser B. Why Patients Go Online: Multiple Sclerosis, the Internet, and Physician-Patient Communication. Neurologist. 2008;14:374–81.

26. Trojano M, Tintore M, Montalban X, Hillert J, Kalincik T, Iaffaldano P, et al. Treatment decisions in multiple sclerosis — insights from real-world observational studies. Nat. Rev. Neurol. Nature Publishing Group; 2017;

27. Stanca CO, Birgit P, Diego B, Giambastiani CM. Joint Healthcare Professional and Patient Development of Communication Tools to Improve the Standard of MS Care. 2019;

28. Reen GK, Silber E, Langdon DW. Interventions to support risk and benefit understanding of disease-modifying drugs in Multiple Sclerosis patients: A systematic review. Patient Educ. Couns. Elsevier Ireland Ltd; 2017;100:1031–48.

29. Rath L, Vijiaratnam N, Skibina O. Assessing understanding: Patients prescribed natalizumab for multiple sclerosis individual risk and symptoms of progressive multifocal leukoencephalopathy. 2016;194–9.

30. Kopke S, Kasper J, Flachenecker P, Meissner H, Brandt A, Hauptmann B, et al. Patient education programme on immunotherapy in multiple sclerosis (PEPIMS): A controlled rater-blinded study. Clin. Rehabil. England; 2016;

31. Greiner P, Sawka A, Imison E. Patient and Physician Perspectives on MSdialog, an Electronic PRO Diary in Multiple Sclerosis. Patient. Springer International Publishing; 2015;8:541–50.

32. Köpke S, Kern S, Ziemssen T, Berghoff M, Kleiter I, Marziniak M, et al. Evidence-based

patient information programme in early multiple sclerosis: a randomised controlled trial. J. Neurol. Neurosurg. Psychiatry. Köpke, Sascha, University of Lubeck, Institute for Social Medicine and Epidemiology, Ratzeburger Allee 160, D-23538, Lubeck, Germany: BMJ Publishing Group; 2014;85:411–8.

33. Köpke S, Kasper J, Mühlhauser I, Nübling M, Heesen C. Patient education program to enhance decision autonomy in multiple sclerosis relapse management: a randomized-controlled trial. Mult. Scler. 2009;15:96–104.

34. Kasper J, Köpke S, Mühlhauser I, Nübling M, Heesen C. Informed shared decision making about immunotherapy for patients with multiple sclerosis (ISDIMS): A randomized controlled trial. Eur. J. Neurol. Kasper, J., Unit of Health Sciences and Education, University of Hamburg, Martin-Luther-King-Platz 6, D-20146, Hamburg, Germany: Wiley-Blackwell Publishing Ltd.; 2008;15:1345–52.

35. Rahn AC, Köpke S, Backhus I, Kasper J, Anger K, Untiedt B, et al. Nurse-led immunotreatment DEcision Coaching In people with Multiple Sclerosis (DECIMS) – Feasibility testing, pilot randomised controlled trial and mixed methods process evaluation. Int. J. Nurs. Stud. Elsevier; 2018;78:26–36.

36. Dwan K, Li T, Altman DG, Elbourne D. CONSORT 2010 statement: Extension to randomised crossover trials. BMJ. 2019;366.

37. Keeney A, Duerson H. Collated near-vision test card. Am. J. opthalomology. 1958;46:592–4.

38. Reen GK, Silber E, Langdon DW. Best Methods of Communicating Clinical Trial Data to Improve Understanding of Treatments for Patients with Multiple Sclerosis. Value Heal. [Internet]. Elsevier Inc.; 2018;21:762–6. Available from:

http://dx.doi.org/10.1016/j.jval.2017.12.015

39. Reen GK, Silber E, Langdon DW. Multiple sclerosis patients' understanding and preferences for risks and benefits of disease-modifying drugs: A systematic review. J. Neurol. Sci. Elsevier B.V.; 2017;375:107–22.

40. Senn S. Cross-over Trials in Clinical Research. 2002.

41. Hamstra D a., Johnson SB, Daignault S, Zikmund-Fisher BJ, Taylor JMG, Larkin K, et al. The Impact of Numeracy on Verbatim Knowledge of the Longitudinal Risk for Prostate Cancer Recurrence following Radiation Therapy. Med. Decis. Mak. 2014;35:27–36.

42. Hawley ST, Zikmund-Fisher B, Ubel P, Jancovic A, Lucas T, Fagerlin A. The impact of the format of graphical presentation on health-related knowledge and treatment choices. Patient Educ. Couns. 2008;73:448–55.

43. O'Connor AM. Validation of a Decisional Conflict Scale. Med. Decis. Mak. 1995;15:25–30.

44. Garvelink MM, Boland L, Klein K, Nguyen DV, Menear M, Bekker HL, et al. Decisional Conflict Scale Use over 20 Years: The Anniversary Review. Med. Decis. Mak. 2019;39:301–14.

45. Bass PF, Wilson JF, Griffith CH. A shortened instrument for literacy screening. J. Gen. Intern. Med. 2003;18:1036–8.

46. Langdon DW, Warrington EK. VESPAR: Verbal and Spatial Reasoning Test. Psychology Press; 1995.

47. Wechsler D. Wechsler Test of Adult Reading. Psychological Corporation; 2001.

48. Zigmond a S, Snaith RP. The hospital anxiety and depression scale. Acta Psychiatr Scand. 1983;67:361–70.

49. Litster B, Fiest KM, Patten SB, Fisk JD, Walker JR, Graff LA, et al. Screening Tools for Anxiety in Persons with Multiple Sclerosis: A Systematic Review. Int. J. MS Care. 2016;1537-2073.2016-004.

50. Krupp LB, Alvarez LA, LaRocca NG, Scheinberg LC. The fatigue severity scale. Application to patients with multiple sclerosis and systemic lupus erythematosus. Arch Neurol. 1989;46:1121–3.

51. Langdon D, Amato M, Boringa J, Brochet B, Foley F, Fredrikson S, et al. Recommendations for a Brief International Cognitive Assessment for Multiple Sclerosis (BICAMS). Mult. Scler. J. 2012;18:891–8.

52. Protheroe J, Bower P, Chew-Graham C, Peters TJ, Fahey T. Effectiveness of a computerized decision aid in primary care on decision making and quality of life in menorrhagia: results of the MENTIP randomized controlled trial. Med. Decis. Making. 2007;27:575–84.

53. Colombo C, Mosconi P, Confalonieri P, Baroni I, Traversa S, Hill SJ, et al. Web Search Behavior and Information Needs of People With Multiple Sclerosis: Focus Group Study and Analysis of Online Postings. Interact. J. Med. Res. 2014;3:e12.

Appendix

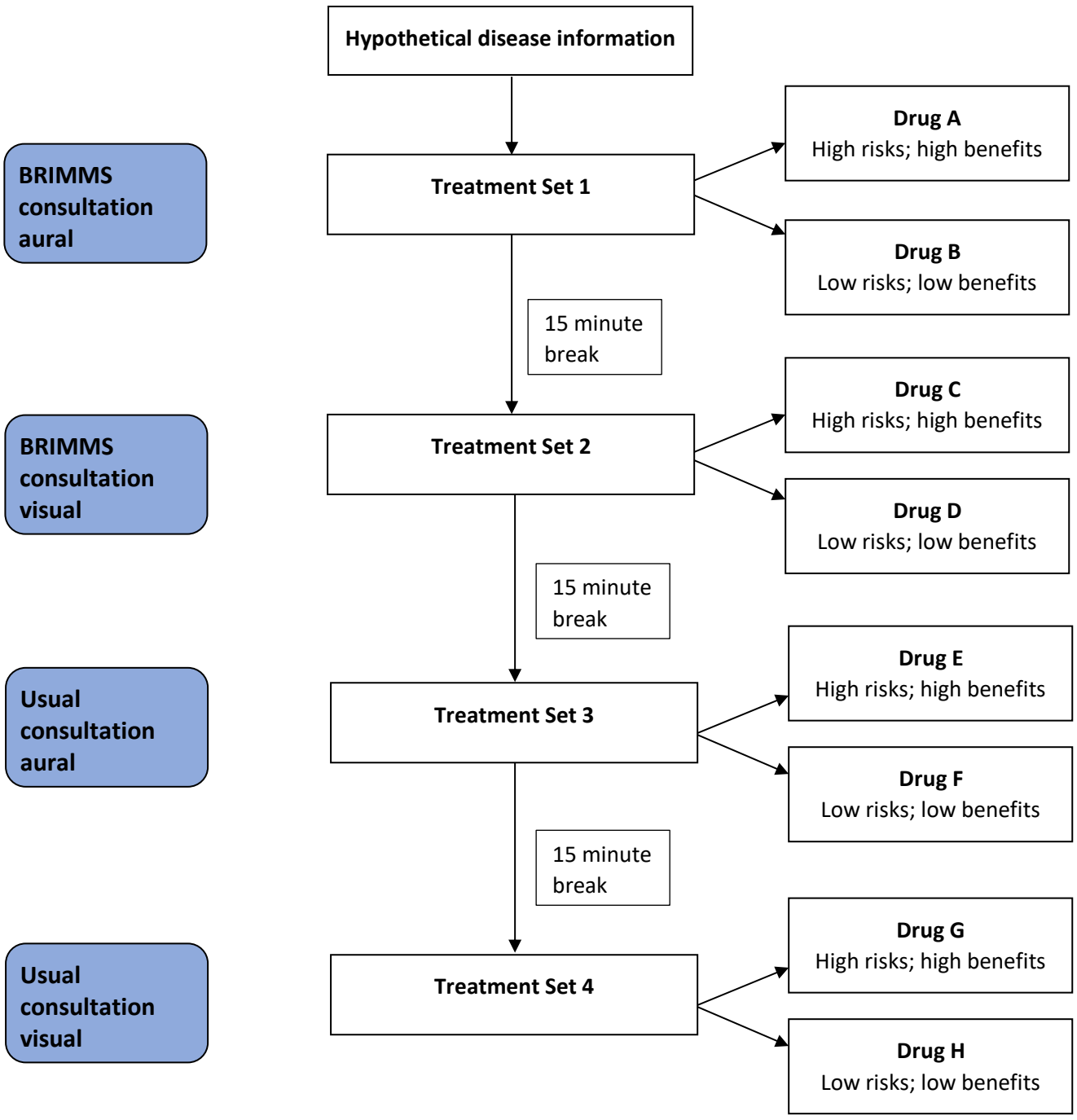

Fig 1 An example of the order of materials presented to patients. The four consultation styles and treatment sets were all given in a random order (e.g. BRIMMS consultation visual could be presented last with Treatment set 2). The order of the two drugs in a treatment set were also randomised. Hypothetical drug names not shown for simplicity.