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Study protocol for a randomised controlled trial of a web-based behavioural lifestyle programme for emPOWERment in early Multiple Sclerosis (POWER@MS1)

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ABSTRACT

Introduction Multiple sclerosis (MS) is an inflammatory and degenerative disease of the central nervous system that mainly affects young adults. Uncertainty is a major psychological burden of the disease from diagnosis to prognosis, enhanced by the pressure to make early decisions on a diverse set of immunotherapies. Watchful waiting for 1-2 years while adapting goals and lifestyle habits to life with a chronic disease represents another reasonable option for persons with MS (PwMS). A behaviour change programme based on evidence-based patient information (EBPI) is not available in standard care. This randomised controlled trial (RCT) investigates the hypothesis that such a programme can change patient behaviour and reduce inflammatory disease activity in PwMS.

Methods and analysis A multiphase mixed methods study will be conducted. The web-based behavioural intervention will be evaluated and revised in a feasibility and pilot phase with experts and PwMS. The intervention will be evaluated in a RCT aiming to recruit 328 patients with clinically isolated syndrome (CIS), suspected MS or confirmed MS for less than one year, who have not yet started immunotherapy. Moreover, a mixed-methods process evaluation and a health economic evaluation will be carried out. Participants will be recruited in at least 16 MS centres across Germany and randomised to an intervention group with 12 months of access to EBPI about lifestyle factors in MS, combined with a complex behaviour change programme, or to a control group (optimised standard care). The combined primary endpoint is the incidence of new T2 lesions on magnetic resonance imaging or confirmed relapses.

Ethics and dissemination The study has been approved by the Ethics Committee of the Hamburg Medical Council (PV6015) and all relevant local ethics boards. It was prospectively registered at ClinicalTrials.gov (NCT03968172).

Keywords Multiple sclerosis, Complex intervention, Lifestyle intervention, Randomised controlled trial, Evidence-based medicine

Strengths and limitations of this study

- Patients are actively involved in the development process of the intervention group programme in order to address the complex needs of newly diagnosed PwMS.
- This study has the chance to show that lifestyle interventions can influence molecular processes in an immunological disease, which could considerably strengthen the importance of lifestyle management in healthcare.
- The intervention does not include personal consultation, which may limit the extent and sustainability of changes in lifestyle habits.

INTRODUCTION

Multiple Sclerosis (MS) is an inflammatory and degenerative disease of the central nervous system (CNS) that affects about 240,000 people in Germany, typically first diagnosed during early adulthood (1). Over the past decade, new diagnostic criteria (2) enabled earlier diagnosis of the disease and magnetic resonance imaging (MRI) has become a crucial diagnostic and prognostic instrument. Moreover, MRI is used for the evaluation of treatment success despite considerable limitations (3). However, there is still no highly specific diagnostic marker and diagnosis may remain unclear for years. In addition, reliable prognosis remains difficult and it

is hardly possible to estimate the long-term expected disability, especially when based on disease development during the first 1-2 years after onset. For this reason, diagnostic information about MS is often experienced as traumatising and can cause disappointment and distrust in the medical system at an early stage (4). Although available immunotherapies reduce relapse rates, the long-term benefit on disability progression remains unclear (5, 6). Nevertheless, early therapy directly after MS diagnosis is recommended (7), while adherence to immunotherapy in the first two years may be as low as 30-50% (8). These manifold uncertainties and the resulting psychological stress may have a negative effect on MS disease activity (9).

Surveys have shown that PwMS are a patient group that frequently uses internet sources to gather information (10). However, these sources often provide contradictory and poorly curated advice on lifestyle-related matters (11). The existing care structures cannot meet the complex information needs of PwMS, although the potential of stress management and lifestyle measures, especially exercise and nutrition, in neurodegenerative diseases as MS is high (12, 13). Rigorous studies are largely missing and systematic, evidence-based patient information about lifestyle factors in MS combined with a behaviour change programme is not available. Training and empowerment interventions in MS have so far mainly been studied in face-to-face or group programmes (14). Online interventions in MS have mainly been investigated for the management of symptoms such as depression and fatigue (15, 16). POWER@MS1 aims to encourage patients with MS to find the best way of dealing with the disease on the basis of evidence-based patient information (EBPI) and a complex behaviour change intervention. The goal of this programme is a more targeted immunotherapy initiation, and consequently, better adherence and optimisation of lifestyle habits.

Objectives

This study investigates the hypothesis that EBPI about lifestyle factors in MS combined with a complex behaviour change programme (EBBC programme) can reduce inflammatory disease activity in MS and change patient behaviour.

Primary objective

To determine if the EBBC programme can reduce inflammatory disease activity in MS as measured clinically by relapses or by new T2 lesions on MRI.

Secondary objectives

The secondary objectives are to determine if the EBBC programme can

- strengthen patient autonomy and empowerment,
- promote informed decisions on immunotherapy,
- improve quality of life,
- reduce anxiety and depression,
- increase physical activity and a healthy dietary behaviour,
- increase effectiveness of neurologist consultations,
- fit with users and contextual factors,
- and save health care costs.

METHODS AND ANALYSIS

Study design

A 'multiphase-mixed-methods-study' covering the first three phases of the Medical Research Council (MRC) Framework for the development and evaluation of complex interventions (17) will be conducted:

1. Development: A web-based behavioural intervention programme will be adapted and designed as a highly individualized system based on simulated dialogues. This programme will provide MS patients with EBPI partly based on previous work of the research team (13). In addition, a web-based control group programme will be developed based on information material available from the German Multiple Sclerosis Society (DMSG).

2. Feasibility: Feasibility testing involves several aspects, such as examination of practicability and acceptance. At an early stage of development, the intervention programme will be presented to expert PwMS and evaluated using qualitative methods (think-aloud, teach-back) and closed questions. Subsequently, it will be presented to and discussed with medical MS experts in a pre-test phase. The outcome instruments as well as the tool will then be piloted with PwMS in order to assess comprehensibility, user-friendliness and acceptance, followed by a final revision of the programme.

3. Evaluation: The intervention will be evaluated in a superiority, rater-blinded, randomised controlled, parallel group trial. Study participants will be randomised to the intervention group (IG) with access to the EBBC programme in addition to standard of care or to the control group (CG) with optimised standard care using an allocation ratio of 1:1. In addition, a mixed-methods process evaluation (see Appendix I) and a health economic evaluation will be carried out.

Study setting

Recruitment and neurological encounters will take place in community clinics, private practises, and academic hospitals with a specialisation in MS across Germany.

Eligibility criteria

Patients aged between 18 and 65 years with CIS, suspected or confirmed MS for less than 12 months, who signed informed consent, will be included. Furthermore, they must have at least two MS-typical lesions on T2-weighted images on MRI scans and an MS typical cerebrospinal fluid finding with detection of oligoclonal bands. Internet access is mandatory for participation. Patients who are not able to provide informed consent or have a substantial psychiatric disorder or substantial cognitive deficit based on clinical impression will be excluded. Patients who have been treated with glatiramer acetate, teriflunomide, dimethylfumarate or interferons within the last six months prior to study inclusion or have received corticosteroid therapy within 4 weeks prior to study inclusion will also be excluded. Patients with a planned treatment start within three months after inclusion or patients who had received any other MS-specific immunotherapy at any time in the past will not be eligible. Pregnancy and claustrophobia are also exclusion criteria.

Interventions

Eligible patients will be randomised to the IG programme or the CG programme. Both programmes will be offered online on the same platform with a similar design.

Intervention group (IG): EBBC programme

The IG programme is an MS-specific adaptation of the earlier developed "Optimmune®" tool by GAIA (https://gaia-group.com/en/). Based on current research and theory of the field (18-20), it was developed for lifestyle management in cancer patients based on empowerment (21) and cognitive behavioural therapy (CBT) approaches, including acceptance and mindfulness oriented techniques (22-24). Furthermore, EBPI, autonomy supportive intervention concepts based on self-determination theory (25), the principles of responsiveness (26) and individual content-tailoring (27, 28) are crucial components of the intervention format. The programme specifically attempts to avoid fear appeals and simple information provision (e.g. 'lecturing').

The system is based on the AI-based software platform broca®, which is the basis for several effective therapy support systems evaluated in earlier RCTs, e.g. (15, 22, 29-31). An optional email and SMS reminder system aims to enhance involvement. Usage of the IG programme will be monitored and reacted on to ensure patient adherence.

Disease management and lifestyle techniques as well as exercises will be taught in sequentially active interactive learning units ("simulated dialogues") focusing on the following topics:

1. Diagnosis, prognosis and immunotherapy decision making
2. Support in coping
3. Techniques for coping with stress / depressive symptoms and developing positive emotions
4. Optimisation of dietary behaviour
5. Optimisation of physical activity behaviour
6. Sleep hygiene and methods for dealing with insomnia

Altogether, the IG programme will consist of 16 modules and accompany each patient over a period of 12 months with initial 2-3 weekly modules, later only weekly reminders and modules every 2 weeks and booster sessions in the end.

Control group (CG): Information from self-help societies

CG participants will receive access to an information platform with optimised standard care consisting of information compiled from DMSG information material to reflect current practice. It will also accompany participants over a period of 12 months and cover similar topics as in the IG. A reminder function as well as usage monitoring and adherence promotion will be applied as in the IG.

Patient and public involvement

Patients were involved in the development phase of the intervention and also participated in the feasibility and piloting testing of the IG programme (see "Study design").

Criteria for discontinuation and relevant concomitant care

In case of new events (relapse or T2 lesion), formally the primary endpoint will be reached. However, study participants will be asked to stay in the study. Immunotherapy may be started during the trial period.

Outcomes

Data will be collected over a period of 12 months, with a flexible follow-up of up to 24 months in early recruited patients. A list of outcomes including measurement time points is provided in Table 1.

Instrument	Measurement time points								
	t_{-1}	t_0	V_1	V_2	V_3	V_4	V_5*	V_6*	t_X
Month	-1	0	1	3	6	12	18*	24*	X
Eligibility screen	X								
Informed consent	X								
Demographic data	X								
MRI		X		X	X	X	X	X	
Clinical visit		X	X	X	X	X	X	X	
Relapse history		X	X	X	X	X	X	X	X
Immunotherapy status		X	X	X	X	X	X	X	X
EDSS		X				X			
RIKNO10				X					
CPS						X			X
Decision satisfaction									X
Patient activation		X				X			
Emotional coping		X				X			
Changes in empowerment						X			
Expectancy			X						
Readiness to change		X		X		X			
HAQUAMS		X				X			
EQ-5D-5L		X			X	X	X	X	
HADS		X				X			
GLTEQ		X				X			
BSA		X				X			
QHOD2		X		X		X			
myfood24		X				X			
Process evaluation	X	X	X	X	X	X	X	X	
Health economic parameters		X			X	X	X	X	

t_{-1} = before enrolment; t_0 = before allocation; $V_1 – V_6$ = post allocation (V_1 = Visit in month 1; V_2 = Visit in month 3; V_3 = Visit in month 6; V_4 = Visit in month 12; V_5 = Visit in month 18; V_6 = Visit in month 24); * = only in early recruited patients; t_x = after reaching the primary endpoint.
BSA: Bewegungs- und Sportaktivität Fragebogen (Physical Activity, Exercise, and Sport Questionnaire); CPS: Control Preference Scale; EDSS: Expanded Disability Status Scale; GLTEQ: Godin Leisure-Time Exercise Questionnaire; HADS: Hospital Anxiety and Depression Scale; HAPA: Health Action Process Approach; HAQUAMS: Hamburg Quality of Life in MS Scale; MRI: Magnetic Resonance Imaging; QHOD2: Questionnaire of Healthy Diet; RIKNO: Risk Knowledge in Relapsing Multiple Sclerosis.

Table 1: Assessments and measurement time points

Primary outcome

The primary endpoint is the time to a new relapse or, as a surrogate for inflammatory disease activity, a new lesion on T2-weighted images on MRI scans, whatever first occurs. Occurrence of new T2 lesions will be assessed according to an MRI protocol (Localizer, 3D FLAIR sagittal e.g. 3x3mmm, 3D image T1w native sagittal, 1-3mm, PD/T2w axial 3mm, protocol duration approx. 20 min.). MRI scans will be read centrally by an experienced rater, blinded to subject identity and group assignment.

Relapses will be clinically evaluated by participating neurologists. In case of a relapse, duration of complaints/impairment, relapse symptoms (worsened or newly occurred), degree of impairment due to the relapse and the degree of certainty with regard to the classification of the worsening as a relapse will be assessed.

Secondary outcomes

To assess risk knowledge, an abbreviated 10-item version of the MS risk knowledge questionnaire (RIKNO 2.0 (32)) will be used.

As a surrogate of decision quality, preferred and realized role preference in decision discussions for or against immunotherapy based on the Control Preference Scale (CPS) (33) will be assessed. Immunotherapy status will be assessed to determine whether an immunotherapy was newly started, aborted or changed.

The extent of patient activation (i.e. expressed in the confidence and knowledge to take action, as well as actually taking health-related action) based on the Patient Activation Measure, PAM (34) and the coping capability, based on selected items of the coping self-efficacy scale, CSES (35) will be measured. In addition, patient expectancies based on the credibility/expectancy questionnaire (36) will be assessed. Based on selected items of the Health Action Process Approach, HAPA (37), readiness to change will be estimated in order to determine the interventions impact on willingness to change lifestyle habits. Moreover, changes in perceived empowerment (based on (38), selected items) will be measured.

Impairment in the Expanded Disability Status Scale (EDSS) (39) will be determined by the treating neurologist.

Ideally, the lifestyle intervention leads to more general satisfaction with life but may also alleviate symptoms such as depression, anxiety, fatigue. Quality of life will be measured with the Hamburg Quality of Life in MS Scale, HAQUAMS (40) and the generic EQ-5D-5L (41). The Hospital anxiety and distress scale, HADS (42) will be used as a measures for depression and anxiety.

Physical activity behaviour will be measured with the Godin Leisure-Time Exercise Questionnaire (GLTEQ) (43) and the Physical Activity, Exercise, and Sport Questionnaire (Bewegungs- und Sportaktivität (BSA)) (44).

The Questionnaire of Healthy Diet (QHOD2), an adapted version of the Mediterranean Diet Screener (aMDS) as used in (45) that was developed by the German Institute of Human Nutrition (DIfE), will be used to measure the frequency of intake of characteristic food groups

in the last seven days. To provide nutrient intake data, the 24-h dietary recall myfood24 (46) will be used, in each case three times within a time period of two to three weeks (two weekdays, one weekend day).

Health economic outcomes

Health economic parameters will be assessed to determine the efficiency of the intervention by comparing the cost and outcome of the IG to the CG. All direct costs associated with the intervention as well as costs resulting from the consumption of health-related goods and services (47) and indirect costs due to productivity losses will be considered from the perspective of the German statutory health insurance and the society.
To determine efficiency of the intervention, a cost-effectiveness analysis will be performed in terms of additional costs per additional relapse or T2 lesion (clinical endpoint) averted and a cost-utility analysis, which aims to calculate the additional costs required for an additional improvement in quality-adjusted life years (QALYs). Incremental cost-effectiveness ratio and incremental cost-utility ratio will be calculated as the ratio of the difference in mean costs and difference in mean outcomes between IG and CG. QALYs will be measured by a well-established preference based quality of life instrument (EQ-5D-5L) and evaluated by a German tariff to generate utilities (41). A standardised instrument (48) will be used to record the healthcare consumption of study participants focusing mainly on outpatient doctor visits, visits to other health service providers, sick days, hospital stays and MS immune medication. Productivity losses will be estimated using the human capital approach (49). 95% confidence intervals for the outcome of the analyses will be determined non-parametrically based on the distribution characteristics of costs using bootstrap procedures (50). Univariate and probabilistic sensitivity analyses will be performed and cost-effectiveness acceptance curves will be executed to take into account uncertainty (51).

Participant timeline

The time schedule is depicted in Figure 1.

Figure 1: Participant timeline

Sample size

Based on effect sizes resulting from an RCT for a stress management intervention (13) as well as data from cohorts on lesion development after an initial clinical event ((52), personal communication Michael Scheel, Charité Berlin), one event (relapse or at least one new T2 lesion) is expected in every second patient within 12 months in the CG. 100 events result in a statistical power of 85% for a two-way significance level test of 5% and an assumed hazard ratio of 0.55, i.e. a reduction of 45% by IG compared to the CG. Thus, with a mean observation time of 12 months, the 100 events required can be expected to be observed in 262 patients (131 per group). Assuming about 20% dropouts over one year, 328 patients will be randomised (164 per group, 20% dropout = 33 = 131 per group). A sample size recalculation will be performed after 12 months to review the assumptions on event rates and dropouts (53). If necessary, the number of cases will be increased to a maximum of 450 patients.

Recruitment

Eligible MS centres will be recruited by the coordinating centre in Hamburg (University Medical Center Hamburg-Eppendorf, UKE). Recruitment and inclusion of MS patients will

take place in the participating MS centres through neurologists. In addition, POWER@MS1 will be advertised on the website of the DMSG. Overall, a recruitment period of 12 months is assumed with approx. 20 patients per centre, with one to two patients per month. Reasons for rejection will be documented.

Allocation

Group assignment will be undertaken externally and in a concealed manner through the electronic data capture system secuTrial® to prevent any manipulation of persons involved in the study. Eligible study participants will be randomised into the IG or to the CG in blocks (1:1 allocation ratio) through a computer-generated system in secuTrial®. After baseline documentation and subsequent randomisation, patients will be provided with access (login) details to the IG or CG programme by an unblinded member of the study team.

Blinding

The study will be conducted as an investigator blinded trial and participating MS centres will not be provided with any information about group assignment of a given patient. Blinding of the trial participants is pursued, but only possible to a limited extent. Participants and neurologists might realize their participation in the IG during encounters.

Data collection methods

Data will be obtained at different time points using paper-based and web-based questionnaires (see Table 1). In case of missing data, participants will be contacted by a member of the UKE. All study relevant data will be entered into secuTrial® and provided online. Results of MRI scans (image data) will be saved on CD and sent to the study centre by mail. They will be quality-checked, pseudonymised and uploaded in a protected reading centre database. Data obtained with regard to nutrition behaviour will be collected via secured online-platforms of the Humanstudienzentrum of the DIfE and Dietary Assessment Limited (University of Leeds spinout company), which act in accordance with EU General Data Protection Regulation (Datenschutz-Grundverordnung, DSGVO). Data obtained through myfood24 will be stored on a server in the Netherlands, with a backup in the UK. After data collection, data will be transferred to secuTrial® and connected with the existing datasets. In addition, usage of the web-based programmes will be monitored.

Data management

The IG and CG programme will be provided via a secure online platform that meets all legal requirements (SSL Encryption). All study data will be used and evaluated pseudonymously. However, all participating MS centres will have a list with names and assigned pseudonyms. All electronic and paper-based data material will be stored at the UKE for a maximum period of ten years and will be destroyed subsequently. Stored CDs containing MRI images will be destroyed directly after analysis of the study data. In case of withdrawn consent, pseudonymised data will be anonymised. A deletion of already anonymized data is not possible.

Statistical methods

The effect on the primary endpoint will be estimated in a Cox proportional hazards regression that, in addition to treatment, also includes study centre as a factor; it will be reported as hazard ratio (HR) with 95% confidence interval and p-value testing the null hypothesis H0: HR=1.

Kaplan-Meier curves of the primary endpoint for both groups will be used to illustrate the treatment effect.

Secondary endpoints will be analysed using mean comparisons between IG and CG with adjustment for the baseline assessments and centre in analysis of covariance (ANCOVA) models. Least squares group differences will be reported with 95% confidence intervals and p-values testing the null hypothesis of no intervention effect. The number of portions/day or week for different food groups will be analysed, evaluated and compared to current recommendations. Data obtained through the 24h recall (myfood24) will be used to analyse intake of selected nutrients of interest comparing mean changes in intake from baseline to post intervention between IG and CG, adjusting for baseline intake. MRI lesion counts will be analysed using negative binomial regression models adjusting for baseline MRI and centre. Adverse events will be summarized as frequencies and percentages by treatment group.

In addition, subgroup and moderator variable analysis is planned to be performed (e.g. early therapy vs no therapy and women vs men).

Reasons for study withdrawal will be reported. In case of missing data, all patients will be analysed in the group they were randomised to (intention-to-treat analysis). Early study discontinuations will be treated as independent right censoring in the primary analysis. In case of substantial or differential study discontinuations, the validity of the independent censoring assumption will be explored in shared random effects models of the primary endpoint and time to study discontinuation. To handle missing data in baseline variables or follow-up assessments, multiple imputation models will be applied.

All details of the statistical analyses including definitions of analysis populations will be prespecified in a statistical analysis plan.

Monitoring

As part of a risk-based quality management, external independent data monitoring including onsite visits at the UKE and remote data checks in secuTrial® will be performed by the contract research organization CTC North GmbH & Co. KG.

Safety and adverse events

As no significant harms (side effects, risks or complications) are to be expected, no stopping guidelines are planned. The performance of six MRIs over two years is close to clinical standard and can be regarded as harmless. Contrast media will not be used in order to minimize the risk of possible contrast media deposition in the basal ganglia, although no information on depositions is available for the contrast media currently used (54). No auditing trials are planned or expected.

ETHICS AND DISSEMINATION

Informed consent will be obtained by the participating MS centres and sent to the study centre by fax. Participants may withdraw their consent at any time. In case of reaching the primary endpoint, patients are requested to remain in the study and continued access to the web tools will be guaranteed until the study end. Only the study team (investigators) and Alexander Stahmann (medical information scientist at the German MS Registry) will have access to the final trial dataset. For publications, an anonymized data set will be used. If possible, an

anonymized data set will be made available in the publication process in order to disseminate the study results.

Trial results will be communicated at scientific conferences and meetings (e.g. at the yearly German Neurologists Society, the RIMS network) by the investigators and presented on the DMSG website and other relevant patient websites. Authorship will be shared between persons involved in the study following the current guidelines of the International Committee of Medical Journal Editors (ICMJE). Professional writers and persons not directly involved in the study will not be granted authorship.

CONCLUSION

This will be the first study assessing the impact of a lifestyle management programme combined with EBPI on inflammatory activity in MS. If successful, POWER@MS1 has a groundbreaking potential to change guidelines on MS care enabling lifestyle management a firm place as active MS treatment.

Current trial status

Patient recruitment has started in July 2019.

Abbreviations aMDS: adapted Mediterranean Diet Screener; BSA: Bewegungs- und Sportaktivität Fragebogen (Physical Activity, Exercise, and Sport Questionnaire); CBT: cognitive behavioural therapy; CG: control group; CIS: clinically isolated syndrome; CNS: central nervous system; CPS: Control Preference Scale; CSES: Coping Self-efficacy Scale; DIfE: Deutsches Institut für Ernährungsforschung (German Institute of Human Nutrition); DMSG: Deutsche Multiple Sklerose Gesellschaft (German Multiple Sclerosis Society); DSGVO: Datenschutz-Grundverordnung; EBBC: evidence-based behaviour change; EBPI: evidence-based patient information; EDSS: Expanded-Disability-Status-Scale; GLTEQ: Godin Leisure-Time Exercise Questionnaire; HADS: Hospital Anxiety and Depression Scale; HAPA: Health Action Process Approach; HAQUAMS: Hamburg Quality of Life in MS Scale; ICER: incremental cost-effectiveness ratio; HR: hazard ratio; ICMJE: International Committee of Medical Journal Editors; ICUR: incremental cost-utility ratio; IG: intervention group; MRC: Medical Research Council; MRI: magnetic resonance imaging; MS: multiple sclerosis; PAM: Patient Activation Measure; QALY: quality-adjusted life year; PwMS: persons with multiple sclerosis; RCT: randomised controlled trial; UKE: Universitätsklinikum Hamburg-Eppendorf (University Medical Center Hamburg-Eppendorf)

Contributors CH is the principal investigator and led the planning and development of the full study with support from NK, KRL, TS, AR, JP, JS, SK, TF, SMG and HT. NK and CH wrote the first draft of the paper. TF specifically revised the statistical analyses sections of this paper. AI provided health economic expertise. MVDL contributed as a patient expert. All authors conceived the study, revised the manuscript for relevant scientific content, and approved the final version.

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Competing interests CH has received research grants, speaker honoraria and travel grants from Biogen, Celgene, Genzyme, Merck, Roche. JPS receives research funding from Deutsche

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Patient consent Not required.

Ethics approval and trial registration The study has been approved by the Ethics Committee of the Hamburg Medical Council (PV6015) and all relevant local ethics boards. The trial was prospectively registered at Clinicaltrials.gov (NCT03968172). Important and major protocol modifications and amendments will have to be approved and reported to all relevant ethical committees. In addition, all changes will be noted in the study registration.

Provenance and peer review Not commissioned; externally peer reviewed.

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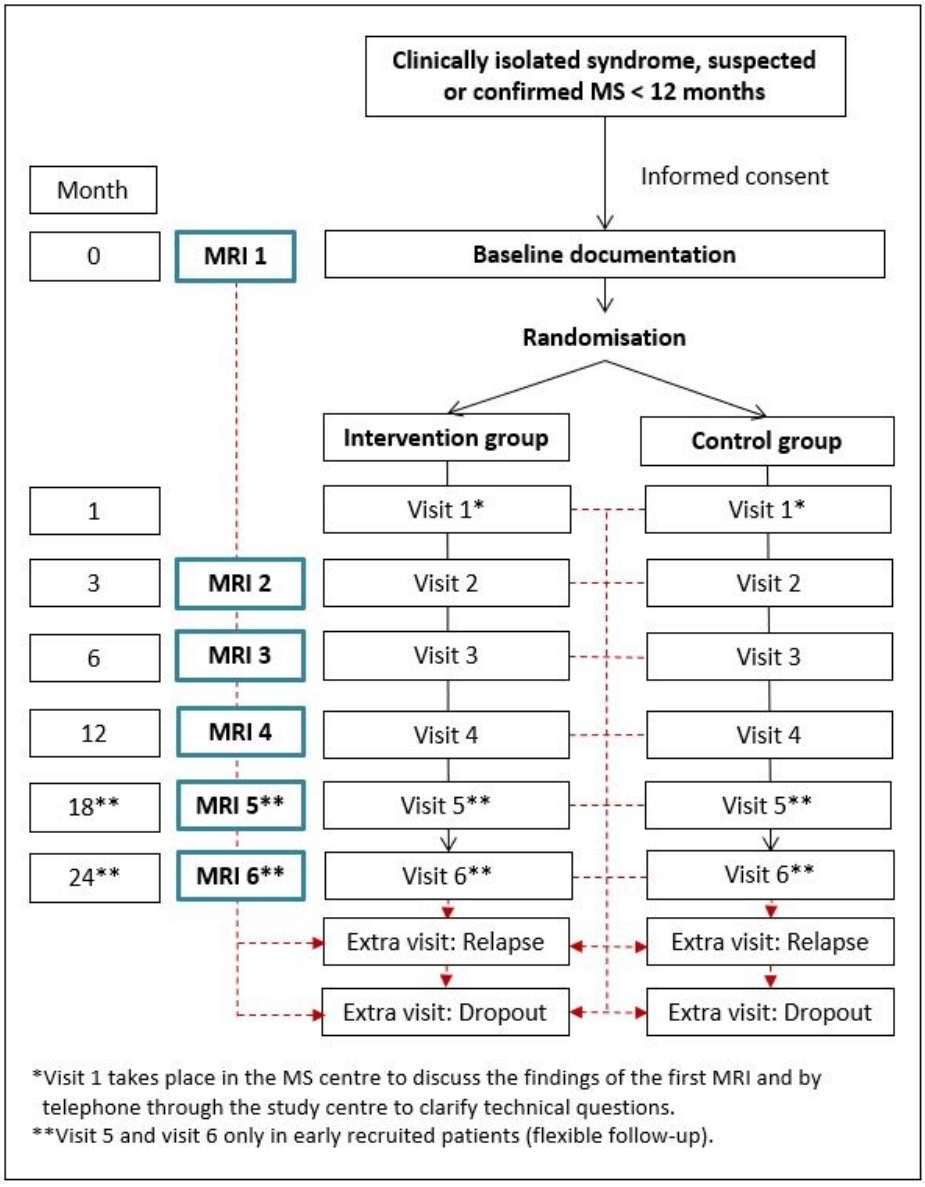

Figure 1: Participant timeline

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Appendix I: Process evaluation

A mixed methods approach (1) is used for the process evaluation based on standardised questionnaires and telephone interviews (see Table 2, Figure 2). Further, the outcome assessments of the main study are an important data source for the process evaluation. The process evaluation aims to clarify whether the intervention was delivered as intended (fidelity) and in which quantity (dose) the intervention was implemented (2, 3). Moreover, implementation barriers and facilitators will be explored. As shown in Table 2 and Figure 2, we will assess contextual factors, components associated with recruitment, delivery, responses and maintenance of centres and individuals (PwMS) as well as unintended consequences using different methods.

Sampling

Questionnaires will be provided to all participants. Interviews will be performed with 10 to 20 with PwMS from each study group until information saturation is reached. Of the healthcare providers, up to 10 neurologists and 5 radiologists will be interviewed based on a purposeful sampling strategy, i.e. aiming for a diversity of centres in organisational structure and size.

Timing

The process evaluation will be conducted in parallel to the main trial (see Table 2 for specific timing of assessments).

Data analysis

First, the process evaluation and trial data will be analysed separately. Afterwards, data will be combined and used to determine post-trial interview questions. Quantitative process evaluation data (questionnaires and evaluation forms) will be analysed descriptively using SPSS (International Business Machines Corporation (IBM), Armonk, United States of America) or R (R Development Core Team) software. Subgroup analyses considering study outcomes and patient characteristics will be performed (for example, start of immunotherapy and decision type) in order to explore the impact of the intervention on different groups. Interviews will be analysed by thematic analysis (4) using MAXQDA (5).

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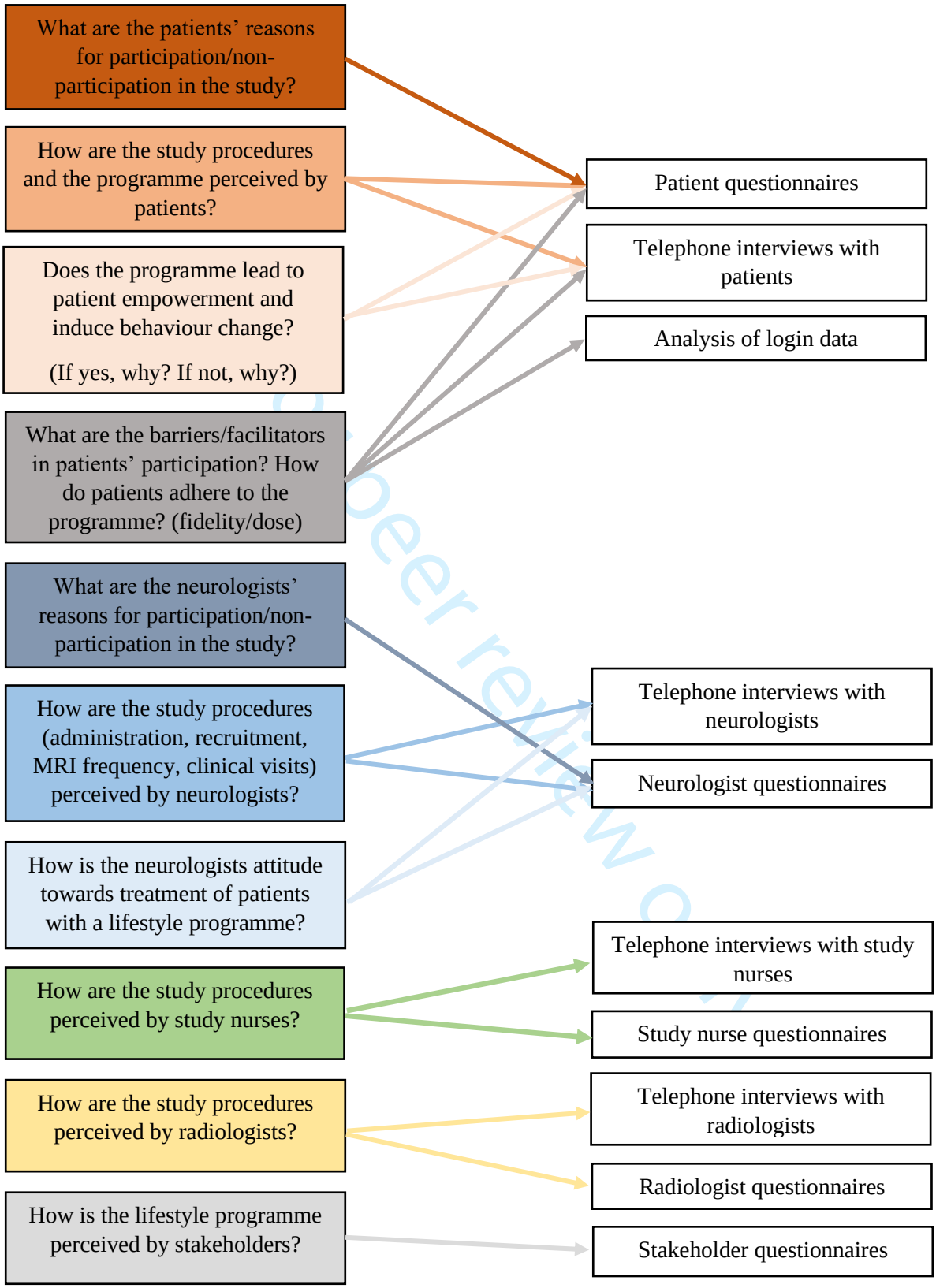
Overview process evaluation POWER@MS1			
Domain	**Objects of investigation**	**Ascertainment/Data collection tool**	**Time point**
Context	Context factors in Germany (health system)	Description	Pre-intervention
	Centre-specific structures and processes	Questionnaire, interviews	Pre-intervention
Recruitment of centres	Centre recruitment	Documentation of recruited centres, phone calls or visits in interested centres	Pre-intervention
	Reason for study participation/ for non-participation (promoting factors and barriers)	Questionnaire (neurologists)	Pre- and during intervention
Delivery to centres	Delivery of information (study management) to neurologists, study nurses and radiologists (participation, reach)	Provision of study materials about the intervention programme, initiation of study centres	Pre-intervention
	Delivery of the study monitoring platform access to all centres	Provision of access data	Pre-intervention
Response of centres	Attitude (neurologists, study nurses and radiologists) regarding the study procedures (e.g. administration, recruitment, clinical visits, MRI frequency) and the intervention	Evaluation forms, interviews	During and post-intervention
Maintenance of centres	Study centres: recruitment of patients	Documentation of recruited patients, evaluation forms, interviews	During and post-intervention
Recruitment of individuals	Recruitment of PwMS	Information video (provided online via YouTube and stakeholder websites/ social media/ network distributors/ magazines), study information leaflets, recruitment in the centres (screening lists, baseline questionnaires)	Pre-intervention
Delivery to individuals	Intervention group: delivery of the intervention to individuals (EBPI about lifestyle factors in MS combined with a complex behaviour change programme)	Provision of access (login) data, e-mail and text message reminders, monitoring of programme usage, evaluation forms, interviews	During and post-intervention

	Control group: delivery of the control intervention to individuals (web-based information on lifestyle factors consisting of optimised standard care material)	Provision of access (login) data, e-mail and text message reminders, monitoring of programme usage, evaluation forms, interviews	During and post-intervention
Response of individuals	E.g.: Satisfaction with the study procedures (e.g. frequency of MRIs and clinical visits) and the intervention, knowledge, attitude, empowerment, change in behaviour, barriers and facilitators	Questionnaires (primary and secondary endpoints RCT), evaluation forms, interviews	Post-intervention, after reaching the primary endpoint
Maintenance of individuals	PwMS (users of the programme): knowledge, empowerment, change in behaviour and reasons for usage	Questionnaires (primary and secondary endpoints RCT), evaluation forms, interviews	During and post-intervention
	PwMS (non-user of the programme): knowledge, empowerment, change in behaviour and reasons for non-usage	Contacting participants via e-mail or telephone, questionnaire, interviews	During and post-intervention
Unintended consequences	Patients: anxiety, depression, negative impact on disease specific quality of life	Evaluation form, interviews, secondary outcome measurement	During and post-intervention
	Neurologists: professional relationship to patients, barriers for implementation	Evaluation form, interviews	During and post-intervention
	Study nurses: stress, professional relationship to patients, barriers for implementation	Evaluation form, interviews	During and post-intervention
Theory	EBPI, TDF, TPB, Empowerment	Application during study planning and the development of study materials, used in evaluation forms, in the programme and in secondary outcome measurement	Pre-, during and post-intervention

EBPI = evidence-based patient information; MRI = magnetic resonance imaging; MS = Multiple Sclerosis; PwMS = Persons with Multiple Sclerosis; RCT = randomised controlled trial; TDF = Theoretical Domains Framework; TPB = Theory of Planned Behavior

Table 2: Overview process evaluation POWER@MS1

Figure 2: Process evaluation POWER@MS1: questions and methods



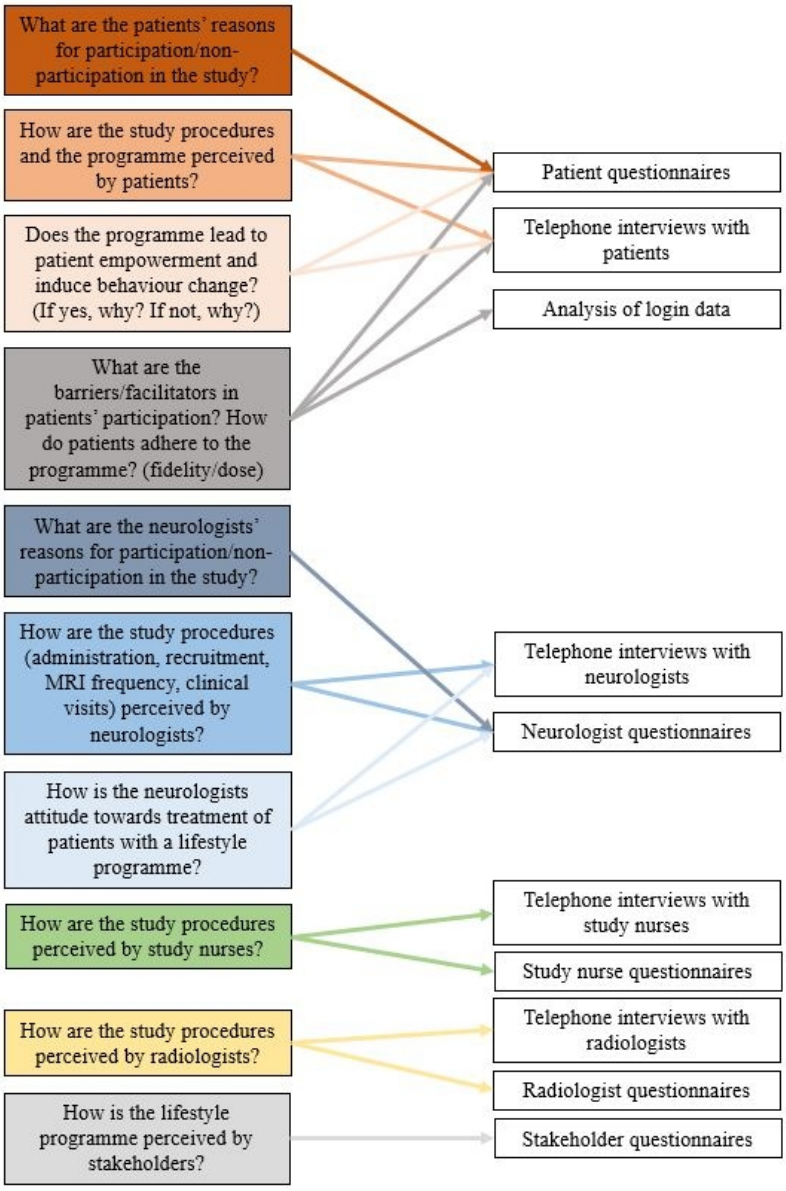


Figure 2: Process evaluation POWER@MS1: questions and methods

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SPIRIT

STANDARD PROTOCOL ITEMS: RECOMMENDATIONS FOR INTERVENTIONAL TRIALS

SPIRIT 2013 Checklist: Recommended items to address in a clinical trial protocol and related documents*

Section/item	Item No	Description	Addressed on page number
Administrative information			
Title	1	Descriptive title identifying the study design, population, interventions, and, if applicable, trial acronym	1
Trial registration	2a	Trial identifier and registry name. If not yet registered, name of intended registry	1
	2b	All items from the World Health Organization Trial Registration Data Set	N/A
Protocol version	3	Date and version identifier	1
Funding	4	Sources and types of financial, material, and other support	11
Roles and responsibilities	5a	Names, affiliations, and roles of protocol contributors	1
	5b	Name and contact information for the trial sponsor	11
	5c	Role of study sponsor and funders, if any, in study design; collection, management, analysis, and interpretation of data; writing of the report; and the decision to submit the report for publication, including whether they will have ultimate authority over any of these activities	11
	5d	Composition, roles, and responsibilities of the coordinating centre, steering committee, endpoint adjudication committee, data management team, and other individuals or groups overseeing the trial, if applicable (see Item 21a for data monitoring committee)	10

Introduction			
Background and rationale	6a	Description of research question and justification for undertaking the trial, including summary of relevant studies (published and unpublished) examining benefits and harms for each intervention	2-3
	6b	Explanation for choice of comparators	5
Objectives	7	Specific objectives or hypotheses	3
Trial design	8	Description of trial design including type of trial (eg, parallel group, crossover, factorial, single group), allocation ratio, and framework (eg, superiority, equivalence, noninferiority, exploratory)	3-4
Methods: Participants, interventions, and outcomes			
Study setting	9	Description of study settings (eg, community clinic, academic hospital) and list of countries where data will be collected. Reference to where list of study sites can be obtained	4
Eligibility criteria	10	Inclusion and exclusion criteria for participants. If applicable, eligibility criteria for study centres and individuals who will perform the interventions (eg, surgeons, psychotherapists)	4
Interventions	11a	Interventions for each group with sufficient detail to allow replication, including how and when they will be administered	4-5
	11b	Criteria for discontinuing or modifying allocated interventions for a given trial participant (eg, drug dose change in response to harms, participant request, or improving/worsening disease)	5
	11c	Strategies to improve adherence to intervention protocols, and any procedures for monitoring adherence (eg, drug tablet return, laboratory tests)	4
	11d	Relevant concomitant care and interventions that are permitted or prohibited during the trial	5
Outcomes	12	Primary, secondary, and other outcomes, including the specific measurement variable (eg, systolic blood pressure), analysis metric (eg, change from baseline, final value, time to event), method of aggregation (eg, median, proportion), and time point for each outcome. Explanation of the clinical relevance of chosen efficacy and harm outcomes is strongly recommended	5-8
Participant timeline	13	Time schedule of enrolment, interventions (including any run-ins and washouts), assessments, and visits for participants. A schematic diagram is highly recommended (see Figure)	8

Sample size	14	Estimated number of participants needed to achieve study objectives and how it was determined, including clinical and statistical assumptions supporting any sample size calculations	8
Recruitment	15	Strategies for achieving adequate participant enrolment to reach target sample size	8

Methods: Assignment of interventions (for controlled trials)

Allocation:			
Sequence generation	16a	Method of generating the allocation sequence (eg, computer-generated random numbers), and list of any factors for stratification. To reduce predictability of a random sequence, details of any planned restriction (eg, blocking) should be provided in a separate document that is unavailable to those who enrol participants or assign interventions	8
Allocation concealment mechanism	16b	Mechanism of implementing the allocation sequence (eg, central telephone; sequentially numbered, opaque, sealed envelopes), describing any steps to conceal the sequence until interventions are assigned	8
Implementation	16c	Who will generate the allocation sequence, who will enrol participants, and who will assign participants to interventions	8
Blinding (masking)	17a	Who will be blinded after assignment to interventions (eg, trial participants, care providers, outcome assessors, data analysts), and how	8
	17b	If blinded, circumstances under which unblinding is permissible, and procedure for revealing a participant's allocated intervention during the trial	N/A

Methods: Data collection, management, and analysis

Data collection methods	18a	Plans for assessment and collection of outcome, baseline, and other trial data, including any related processes to promote data quality (eg, duplicate measurements, training of assessors) and a description of study instruments (eg, questionnaires, laboratory tests) along with their reliability and validity, if known. Reference to where data collection forms can be found, if not in the protocol	8-9
	18b	Plans to promote participant retention and complete follow-up, including list of any outcome data to be collected for participants who discontinue or deviate from intervention protocols	8-9

Data management	19	Plans for data entry, coding, security, and storage, including any related processes to promote data quality (eg, double data entry; range checks for data values). Reference to where details of data management procedures can be found, if not in the protocol	9
Statistical methods	20a	Statistical methods for analysing primary and secondary outcomes. Reference to where other details of the statistical analysis plan can be found, if not in the protocol	9-10
	20b	Methods for any additional analyses (eg, subgroup and adjusted analyses)	9
	20c	Definition of analysis population relating to protocol non-adherence (eg, as randomised analysis), and any statistical methods to handle missing data (eg, multiple imputation)	9
Methods: Monitoring			
Data monitoring	21a	Composition of data monitoring committee (DMC); summary of its role and reporting structure; statement of whether it is independent from the sponsor and competing interests; and reference to where further details about its charter can be found, if not in the protocol. Alternatively, an explanation of why a DMC is not needed	10
	21b	Description of any interim analyses and stopping guidelines, including who will have access to these interim results and make the final decision to terminate the trial	10
Harms	22	Plans for collecting, assessing, reporting, and managing solicited and spontaneously reported adverse events and other unintended effects of trial interventions or trial conduct	10
Auditing	23	Frequency and procedures for auditing trial conduct, if any, and whether the process will be independent from investigators and the sponsor	10
Ethics and dissemination			
Research ethics approval	24	Plans for seeking research ethics committee/institutional review board (REC/IRB) approval	2, 11
Protocol amendments	25	Plans for communicating important protocol modifications (eg, changes to eligibility criteria, outcomes, analyses) to relevant parties (eg, investigators, REC/IRBs, trial participants, trial registries, journals, regulators)	11

Consent or assent	26a	Who will obtain informed consent or assent from potential trial participants or authorised surrogates, and how (see Item 32)	10
	26b	Additional consent provisions for collection and use of participant data and biological specimens in ancillary studies, if applicable	N/A
Confidentiality	27	How personal information about potential and enrolled participants will be collected, shared, and maintained in order to protect confidentiality before, during, and after the trial	9-10
Declaration of interests	28	Financial and other competing interests for principal investigators for the overall trial and each study site	11
Access to data	29	Statement of who will have access to the final trial dataset, and disclosure of contractual agreements that limit such access for investigators	10
Ancillary and post-trial care	30	Provisions, if any, for ancillary and post-trial care, and for compensation to those who suffer harm from trial participation	N/A
Dissemination policy	31a	Plans for investigators and sponsor to communicate trial results to participants, healthcare professionals, the public, and other relevant groups (eg, via publication, reporting in results databases, or other data sharing arrangements), including any publication restrictions	10
	31b	Authorship eligibility guidelines and any intended use of professional writers	10
	31c	Plans, if any, for granting public access to the full protocol, participant-level dataset, and statistical code	10
Appendices			
Informed consent materials	32	Model consent form and other related documentation given to participants and authorised surrogates	Appendix°
Biological specimens	33	Plans for collection, laboratory evaluation, and storage of biological specimens for genetic or molecular analysis in the current trial and for future use in ancillary studies, if applicable	N/A

*It is strongly recommended that this checklist be read in conjunction with the SPIRIT 2013 Explanation & Elaboration for important clarification on the items. Amendments to the protocol should be tracked and dated.

°Available in German.

BMJ Open

Study protocol for a randomised controlled trial of a web-based behavioural lifestyle programme for emPOWERment in early Multiple Sclerosis (POWER@MS1)

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Manuscript ID	bmjopen-2020-041720.R1
Article Type:	Protocol
Date Submitted by the Author:	05-Oct-2020
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Primary Subject Heading:	Neurology
Secondary Subject Heading:	Evidence based practice, Patient-centred medicine, Public health, Communication

Keywords:	Multiple sclerosis < NEUROLOGY, PUBLIC HEALTH, Clinical trials < THERAPEUTICS, Information technology < BIOTECHNOLOGY & BIOINFORMATICS, Magnetic resonance imaging < RADIOLOGY & IMAGING

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Study protocol for a randomised controlled trial of a web-based behavioural lifestyle programme for emPOWERment in early Multiple Sclerosis (POWER@MS1)

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ABSTRACT

Introduction Multiple sclerosis (MS) is an inflammatory and degenerative disease of the central nervous system that mainly affects young adults. Uncertainty is a major psychological burden of the disease from diagnosis to prognosis, enhanced by the pressure to make early decisions on a diverse set of immunotherapies. Watchful waiting for 1-2 years while adapting goals and lifestyle habits to life with a chronic disease represents another reasonable option for persons with MS (PwMS). A behaviour change programme based on evidence-based patient information (EBPI) is not available in standard care. This randomised controlled trial (RCT) investigates the hypothesis that such a programme can change patient behaviour and reduce inflammatory disease activity in PwMS.

Methods and analysis A multiphase-mixed-methods study will be conducted. The web-based behavioural intervention was evaluated and revised in a feasibility and pilot phase with experts and PwMS. The intervention will be evaluated in a RCT aiming to recruit 328 persons with clinically isolated syndrome (CIS), suspected MS or confirmed MS for less than one year, who have not yet started immunotherapy. Moreover, a mixed-methods process evaluation and a health economic evaluation will be carried out. Participants will be recruited in at least 16 MS centres across Germany and randomised to an intervention group with 12 months of access to EBPI about lifestyle factors in MS, combined with a complex behaviour change programme or to a control group (optimised standard care). The combined primary endpoint is the incidence of new T2 lesions on magnetic resonance imaging or confirmed relapses.

Ethics and dissemination The study has been approved by the Ethics Committee of the Hamburg Chamber of Physicians (PV6015) and prospectively registered at ClinicalTrials.gov (NCT03968172). Trial results will be communicated at scientific conferences and meetings and presented on relevant patient websites and in patient education seminars.

Keywords Multiple sclerosis, Complex intervention, Lifestyle intervention, Randomised controlled trial, Evidence-based medicine

Strengths and limitations of this study

- Patients are actively involved in the development process of the intervention group programme in order to address the complex needs of newly diagnosed PwMS.
- This study provides an opportunity to test if lifestyle interventions can influence surrogate measures of disease activity in an immune-mediated disease.
- Evidence for benefits of lifestyle interventions beyond general wellbeing could considerably strengthen the importance of lifestyle management in healthcare.
- The intervention does not include personal consultation, which may limit the extent and sustainability of changes in lifestyle habits.
- Designing a pragmatic trial, we chose predominantly patient reported secondary clinical outcomes while more sophisticated instruments, as e.g. accelerometry, might yield more accurate estimates.

INTRODUCTION

Multiple Sclerosis (MS) is an inflammatory and degenerative disease of the central nervous system (CNS) that affects about 240,000 people in Germany, typically first diagnosed during

early adulthood (1). Over the past decade, new diagnostic criteria (2) enabled earlier diagnosis of the disease and magnetic resonance imaging (MRI) has become a crucial diagnostic and prognostic instrument. Moreover, MRI is used for the evaluation of treatment success despite considerable limitations (3). However, there is still no highly specific diagnostic marker and diagnosis may remain unclear for years. In addition, reliable prognosis remains difficult and it is hardly possible to estimate the long-term expected disability, especially when based on disease development during the first 1-2 years after onset. For this reason, diagnostic information about MS is often experienced as traumatising and can cause disappointment and distrust in the medical system at an early stage (4). Although available immunotherapies reduce relapse rates, the long-term benefit on disability progression remains unclear (5, 6). Nevertheless, early therapy directly after MS diagnosis is recommended (7), while adherence to immunotherapy in the first two years may be as low as 30-50% (8). These manifold uncertainties and the resulting psychological stress may have a negative effect on MS disease activity (9).

Surveys have shown that PwMS are a patient group that frequently uses internet sources to gather information (10). However, these sources often provide contradictory and poorly curated advice on lifestyle-related matters (11). The existing care structures cannot meet the complex information needs of PwMS. There is a high potential of lifestyle management with regard to improved quality of life and a reduction of inflammatory disease activity as well as reduced neurodegeneration in MS (12, 13). Rigorous studies are largely missing and systematic, evidence-based patient information (EBPI) about lifestyle factors in MS combined with a behaviour change programme is not available. Training and empowerment interventions in MS have so far mainly been studied in face-to-face or group programmes (14). Despite few examples on change of physical activity behaviour in MS, such as Motl et al. (15), online interventions in MS have mainly been investigated for the management of symptoms such as depression and fatigue (16, 17), but not for change of overall lifestyle behaviour. POWER@MS1 aims to encourage PwMS to find the best way of dealing with the disease on the basis of EBPI and a complex behaviour change intervention. The goal of this programme is a more targeted immunotherapy initiation. Moreover, the programme aims to optimise coping strategies and lifestyle habits, such as stress management, sleeping behaviour, physical activity and dietary behaviour.

Objectives

This study investigates the hypothesis that EBPI about lifestyle factors in MS combined with a complex behaviour change programme (EBBC programme) can reduce inflammatory disease activity in MS and change patient behaviour.

Primary objective

To determine if the EBBC programme can reduce inflammatory disease activity in MS as measured clinically by relapses or by new T2 lesions on MRI.

Secondary objectives

The secondary objectives are to determine if the EBBC programme can

- strengthen patient autonomy and empowerment
- promote informed decisions on immunotherapy,
- improve quality of life,

- reduce anxiety and depression,
- increase physical activity and a healthy dietary behaviour,
- increase effectiveness of neurologist consultations,
- fit with users and contextual factors,
- and save health care costs.

METHODS AND ANALYSIS

Study design

A 'multiphase-mixed-methods-study' covering the first three phases of the Medical Research Council (MRC) Framework for the development and evaluation of complex interventions (18) will be conducted:

1. Development: A web-based behavioural intervention programme was adapted and designed as a highly individualized system based on simulated dialogues (coordinated information provision based on the existing health beliefs and interests). The theoretical models used to develop the intervention are shortly outlined in the "Interventions" section. This programme provides PwMS with EBPI partly based on previous work of the research team (13). In addition, a web-based control group programme was developed based on information material available from the German Multiple Sclerosis Society (DMSG). Details with regard to the development and adaptation process will be reported in a separate publication.

2. Feasibility: Feasibility testing involved several aspects, such as examination of practicability and acceptance. At an early stage of development, the intervention programme was presented to expert PwMS (e.g. PwMS who are deeply involved in information strategies or in exchange with other PwMS as well as PwMS who have responsible roles in self-help organisations or advocacy roles) and evaluated using qualitative methods (think-aloud, teach-back) and closed questions. Subsequently, it was presented to and discussed with medical MS experts in a pre-test phase. The outcome instruments as well as the tool were then piloted with PwMS in order to assess comprehensibility, user-friendliness and acceptance, followed by a final revision of the programme. Results of feasibility testing and piloting, including revisions of the programme, will be published separately.

3. Evaluation: The intervention will be evaluated in a superiority, rater-blinded, randomised controlled, parallel group trial. This protocol is focusing purely on the RCT. Study participants will be randomised to the intervention group (IG) with access to the EBBC programme in addition to standard of care or to the control group (CG) with optimised standard care using an allocation ratio of 1:1. In addition, a mixed-methods process evaluation (see Appendix I) and a health economic evaluation will be carried out.

Study setting

Recruitment and neurological encounters will take place in community clinics, private practises, and academic hospitals with a specialisation in MS across Germany.

Eligibility criteria

Persons aged between 18 and 65 years with CIS, suspected or confirmed MS for less than 12 months, who signed informed consent, will be included. Furthermore, they must have at least two MS-typical lesions on T2-weighted images on MRI scans and an MS typical cerebrospinal fluid finding with detection of oligoclonal bands. Internet access is mandatory for participation.

PwMS who are not able to provide informed consent or have a substantial psychiatric disorder or substantial cognitive deficit based on clinical impression will be excluded. PwMS who have been treated with glatiramer acetate, teriflunomide, dimethylfumarate or interferons within the last six months prior to study inclusion or have received corticosteroid therapy within 4 weeks prior to study inclusion will also be excluded. PwMS with a planned treatment start within three months after inclusion or PwMS who had received any other MS-specific immunotherapy at any time in the past will not be eligible. Pregnancy and claustrophobia are also exclusion criteria.

Interventions

Eligible PwMS will be randomised to the IG programme or the CG programme. Both programmes will be offered online on the same platform with a similar design.

Intervention group (IG): EBBC programme

The IG programme is an MS-specific adaptation of the earlier developed "Optimmune®" tool by GAIA (https://gaia-group.com/en/). Based on current research and theory of the field (19-21), it was developed for lifestyle management in cancer patients based on empowerment (22) and cognitive behavioural therapy (CBT) approaches, including acceptance and mindfulness oriented techniques (23-25). These techniques influence different theoretical domains as outlined in the theoretical domains framework (21) and thereby the participants' ability, motivation and opportunity to change their physical activity, stress management attitudes and dietary behaviour. For example, CBT techniques such as behavioural activation and identifying and refuting unhelpful automatic thoughts and cognitive distortions, goal setting, goal review, agreeing on behavioural contracts, setting graded tasks, planning social support, action planning, weighing of pros and cons, preparing for/dealing with setbacks, self-motivational statements, constructing if-then plans and formulating implementation intentions and positive emotion induction are incorporated throughout. Mental imagery exercises and mindfulness/acceptance exercises are integrated both in text format and as audio recording. Furthermore, EBPI, autonomy supportive intervention concepts based on self-determination theory (26), the principles of responsiveness (27) and individual content-tailoring (28, 29) are crucial components of the intervention format. The programme specifically attempts to avoid fear appeals and simple information provision (e.g. 'lecturing'). The programme does not provide drug specific information about available immunotherapies. The programme aims to translate evidence in the MS treatment and lifestyle management area in order to illustrate that decisions can be made. It follows the concept that every PwMS can develop an individual approach towards the disease, which might be a targeted immunotherapy initiation in one case or the development of a sophisticated food concept in the other.

The system is based on the AI-based software platform broca®, which is the basis for several effective therapy support systems evaluated in earlier RCTs, e.g. (16, 23, 30-32). An optional email and SMS reminder system (e.g. with lifestyle-related stimuli or reminders regarding programme usage and newly activated modules) aims to enhance involvement. Usage of the IG programme will be monitored biweekly and reacted on after four weeks of non-usage to ensure patient adherence.

The programme is designed as a highly individualized, dialogue-based system that provides PwMS with narrative and coordinated information based on their existing health beliefs, interests, etc. Each text passage ends with a set of pre-programmed response options in

multiple-choice format reflecting possible reader's feedback, such as "Yes. That makes sense." or "I do not quite understand this yet." The participant is invited to tick the matching response and will be guided to the next page referring to the choice, e.g. "I'm glad that you can understand it." or "No problem. Then let me explain it in a little more detail." More precisely, disease management and lifestyle techniques as well as exercises will be taught in sequentially active interactive learning units ("simulated dialogues") focusing on the following topics:

1. Diagnosis, prognosis and immunotherapy decision making
2. Support in coping
3. Techniques for coping with stress / depressive symptoms and developing positive emotions
4. Optimisation of dietary behaviour
5. Optimisation of physical activity behaviour
6. Sleep hygiene and methods for dealing with insomnia

The modules are not ordered by priority. Altogether, the IG programme will consist of 16 modules and accompany each participant over a period of 12 months with initial 2-3 weekly modules, later only weekly reminders and modules every 2 weeks and booster sessions in the end.

Control group (CG): Information from self-help societies

CG participants will receive access to an information platform with optimised standard care consisting of information compiled from DMSG information material to reflect current practice. It will also accompany participants over a period of 12 months and cover similar topics as in the IG. A reminder function as well as usage monitoring and adherence promotion will be applied as in the IG.

Patient and public involvement

PwMS were involved in the development phase of the intervention and also participated in the feasibility and piloting testing of the IG programme (see "Study design"). They were given access to the programme and invited to evaluate content, practicability, user-friendliness and comprehensibility of the programme, also considering the needs of newly diagnosed PwMS. The programme was revised based on the acquired feedback (e.g. technical adjustments, inclusion of more break possibilities and a progress bar in the modules). In addition, suggestions for prospective adjustments, which were not possible due to technical limitations, such as the embedding of video material, were gathered. Details regarding the feedback and resulting programme changes will be communicated in a separate publication.

Criteria for discontinuation and relevant concomitant care

In case of new events (relapse or T2 lesion), formally the primary endpoint will be reached. However, study participants will be asked to stay in the study. Immunotherapy may be started during the trial period. Immunotherapy type, use, and adherence rates will be collected during the clinical visits throughout the study.

Outcomes

Data will be collected over a period of 12 months, with a flexible follow-up of up to 24 months in early recruited PwMS. A list of outcomes including measurement time points is provided in Table 1.

Instrument	Measurement time points								
	t_{-1}	t_0	V_1	V_2	V_3	V_4	V_5*	V_6*	t_X
Month	-1	0	1	3	6	12	18*	24*	X
Eligibility screen	X								
Informed consent	X								
Demographic data	X								
MRI		X		X	X	X	X	X	
Clinical visit		X	X	X	X	X	X	X	
Relapse history		X	X	X	X	X	X	X	X
Immunotherapy status		X	X	X	X	X	X	X	X
EDSS		X				X			
RIKNO10				X					
CPS						X			X
Decision satisfaction									X
Patient activation		X				X			
Emotional coping		X				X			
Changes in empowerment						X			
Expectancy			X						
Readiness to change		X		X		X			
HAQUAMS		X				X			
EQ-5D-5L		X			X	X	X	X	
HADS		X				X			
GLTEQ		X				X			
BSA		X				X			
QHOD2		X		X		X			
myfood24		X				X			
Process evaluation	X	X	X	X	X	X	X	X	
Health economic parameters		X			X	X	X	X	

t_{-1} = before enrolment; t_0 = before allocation; $V_1 – V_6$ = post allocation (V_1 = Visit in month 1; V_2 = Visit in month 3; V_3 = Visit in month 6; V_4 = Visit in month 12; V_5 = Visit in month 18; V_6 = Visit in month 24); * = only in early recruited PwMS; t_x = after reaching the primary endpoint.
BSA: Bewegungs- und Sportaktivität Fragebogen (Physical Activity, Exercise, and Sport Questionnaire); CPS: Control Preference Scale; EDSS: Expanded Disability Status Scale; GLTEQ: Godin Leisure-Time Exercise Questionnaire; HADS: Hospital Anxiety and Depression Scale; HAPA: Health Action Process Approach; HAQUAMS: Hamburg Quality of Life in MS Scale; MRI: Magnetic Resonance Imaging; QHOD2: Questionnaire of Healthy Diet; RIKNO: Risk Knowledge in Relapsing Multiple Sclerosis.

Table 1: Assessments and measurement time points

Primary outcome

The primary endpoint is the time to a new relapse or, as a surrogate for inflammatory disease activity, a new lesion on T2-weighted images on MRI scans, whatever first occurs. Occurrence of new T2 lesions will be assessed according to an MRI protocol (Localizer, 3D FLAIR sagittal e.g. 3x3mmm, 3D image T1w native sagittal, 1-3mm, PD/T2w axial 3mm, protocol duration approx. 20 min.). MRI scans will be read centrally by an experienced rater, blinded to subject identity and group assignment.

Relapses will be clinically evaluated by participating neurologists. In case of a relapse, duration of complaints/impairment, relapse symptoms (worsened or newly occurred), degree of impairment due to the relapse and the degree of certainty with regard to the classification of the worsening as a relapse will be assessed.

Secondary outcomes

To assess risk knowledge, an abbreviated 10-item version of the MS risk knowledge questionnaire (RIKNO 2.0 (33)) will be used.

As a surrogate of decision quality, preferred and realized role preference in decision discussions for or against immunotherapy based on the Control Preference Scale (CPS) (34) will be assessed. Immunotherapy status will be assessed to determine whether an immunotherapy was newly started, aborted or changed.

The extent of patient activation (i.e. expressed in the confidence and knowledge to take action, as well as actually taking health-related action) based on the Patient Activation Measure, PAM (35) and the coping capability, based on two items (item 10 and 24) of the coping self-efficacy scale, CSES (36) will be measured. In addition, patient expectancies based on items 1-3 of the credibility/expectancy questionnaire (37) will be assessed. Based on principles of the Health Action Process Approach, HAPA (38), readiness to change (39) will be estimated in order to determine the interventions impact on willingness to change lifestyle habits. Moreover, changes in perceived empowerment (based on (40), items 1, 3 and 4) will be measured.

Impairment in the Expanded Disability Status Scale (EDSS) (41) will be determined by the treating neurologist.

Ideally, the lifestyle intervention leads to more general satisfaction with life but may also alleviate symptoms such as depression, anxiety, fatigue. Quality of life will be measured with the Hamburg Quality of Life in MS Scale, HAQUAMS (42) and the generic EQ-5D-5L (43). The Hospital anxiety and distress scale, HADS (44) will be used as a measures for depression and anxiety.

Physical activity behaviour will be measured with the Godin Leisure-Time Exercise Questionnaire (GLTEQ) (45) and the Physical Activity, Exercise, and Sport Questionnaire (Bewegungs- und Sportaktivität (BSA)) (46).

The Questionnaire of Healthy Diet (QHOD2), an adapted version of the Mediterranean Diet Screener (aMDS) as used in (47) that was developed by the German Institute of Human Nutrition (DIfE), will be used to measure the frequency of intake of characteristic food groups

in the last seven days. To provide nutrient intake data, the 24-h dietary recall myfood24 (48) will be used, in each case three times within a time period of two to three weeks (two weekdays, one weekend day).

Health economic outcomes

Health economic parameters will be assessed to determine the efficiency of the intervention by comparing the cost and outcome of the IG to the CG. All direct costs associated with the intervention as well as costs resulting from the consumption of health-related goods and services (49) and indirect costs due to productivity losses will be considered from the perspective of the German statutory health insurance and the society.
To determine efficiency of the intervention, a cost-effectiveness analysis will be performed in terms of additional costs per additional relapse or T2 lesion (clinical endpoint) averted and a cost-utility analysis, which aims to calculate the additional costs required for an additional improvement in quality-adjusted life years (QALYs). Incremental cost-effectiveness ratio and incremental cost-utility ratio will be calculated as the ratio of the difference in mean costs and difference in mean outcomes between IG and CG. QALYs will be measured by a well-established preference based quality of life instrument (EQ-5D-5L) and evaluated by a German tariff to generate utilities (43). A standardised instrument (50) will be used to record the healthcare consumption of study participants focusing mainly on outpatient doctor visits, visits to other health service providers, sick days, hospital stays and MS immune medication. Productivity losses will be estimated using the human capital approach (51). 95% confidence intervals for the outcome of the analyses will be determined non-parametrically based on the distribution characteristics of costs using bootstrap procedures (52). Univariate and probabilistic sensitivity analyses will be performed and cost-effectiveness acceptance curves will be executed to take into account uncertainty (53).

Participant timeline

The time schedule is depicted in Figure 1.

Figure 1: Participant timeline

Sample size

Based on effect sizes resulting from an RCT for a stress management intervention (13) as well as data from cohorts on lesion development after an initial clinical event ((54), personal communication Michael Scheel, Charité Berlin), one event (relapse or at least one new T2 lesion) is expected in every second PwMS within 12 months in the CG. 100 events result in a statistical power of 85% for a two-way significance level test of 5% and an assumed hazard ratio of 0.55, i.e. a reduction of 45% by IG compared to the CG. Thus, with a mean observation time of 12 months, the 100 events required can be expected to be observed in 262 PwMS (131 per group). Assuming about 20% dropouts over one year, 328 PwMS will be randomised (164 per group, 20% dropout = 33 = 131 per group). A sample size recalculation will be performed after 12 months to review the assumptions on event rates and dropouts (55). If necessary, the number of cases will be increased to a maximum of 450 PwMS.

Recruitment

Eligible MS centres will be recruited by the coordinating centre in Hamburg (University Medical Center Hamburg-Eppendorf, UKE). Recruitment and inclusion of PwMS will take

place in the participating MS centres through neurologists. In addition, POWER@MS1 will be advertised on the website of the DMSG. Overall, a recruitment period of 12 months is assumed with approx. 20 PwMS per centre, with one to two PwMS per month. Reasons for rejection will be documented.

Allocation

Group assignment will be undertaken externally and in a concealed manner through the electronic data capture system secuTrial® to prevent any manipulation of persons involved in the study. Eligible study participants will be randomised into the IG or to the CG in blocks (1:1 allocation ratio) through a computer-generated system in secuTrial®. After baseline documentation and subsequent randomisation, PwMS will be provided with access (login) details to the IG or CG programme by an unblinded member of the study team.

Blinding

The study will be conducted as an investigator blinded trial and participating MS centres will not be provided with any information about group assignment of a given PwMS. Blinding of the trial participants is pursued, but only possible to a limited extent. Participants and neurologists might realize their participation in the IG during encounters.

Data collection methods

Data will be obtained at different time points using paper-based and web-based questionnaires (see Table 1). In case of missing data, participants will be contacted by a member of the UKE. All study relevant data will be entered into secuTrial® and provided online. Results of MRI scans (image data) will be saved on CD and sent to the study centre by mail. They will be quality-checked, pseudonymised and uploaded in a protected reading centre database. Data obtained with regard to nutrition behaviour will be collected via secured online-platforms of the Humanstudienzentrum of the DIfE and Dietary Assessment Limited (University of Leeds spinout company), which act in accordance with EU General Data Protection Regulation (Datenschutz-Grundverordnung, DSGVO). Data obtained through myfood24 will be stored on a server in the Netherlands, with a backup in the UK. After data collection, data will be transferred to secuTrial® and connected with the existing datasets. In addition, usage of the web-based programmes will be monitored.

Data management

The IG and CG programme will be provided via a secure online platform that meets all legal requirements (SSL Encryption). All study data will be used and evaluated pseudonymously. However, all participating MS centres will have a list with names and assigned pseudonyms. All electronic and paper-based data material will be stored at the UKE for a maximum period of ten years and will be destroyed subsequently. Stored CDs containing MRI images will be destroyed directly after analysis of the study data. In case of withdrawn consent, pseudonymised data will be anonymised. A deletion of already anonymized data is not possible.

Statistical methods

The effect on the primary endpoint will be estimated in a Cox proportional hazards regression that, in addition to treatment, also includes study centre as a factor; it will be reported as hazard ratio (HR) with 95% confidence interval and p-value testing the null hypothesis H0: HR=1.

Kaplan-Meier curves of the primary endpoint for both groups will be used to illustrate the treatment effect.

Secondary endpoints will be analysed using mean comparisons between IG and CG with adjustment for the baseline assessments and centre in analysis of covariance (ANCOVA) models. Least squares group differences will be reported with 95% confidence intervals and p-values testing the null hypothesis of no intervention effect. The number of portions/day or week for different food groups will be analysed, evaluated and compared to current recommendations. Data obtained through the 24h recall (myfood24) will be used to analyse intake of selected nutrients of interest comparing mean changes in intake from baseline to post intervention between IG and CG, adjusting for baseline intake. MRI lesion counts will be analysed using negative binomial regression models adjusting for baseline MRI and centre. Adverse events will be summarized as frequencies and percentages by treatment group.

In addition, subgroup and moderator variable analysis is planned to be performed (e.g. early therapy vs no therapy and women vs men).

Reasons for study withdrawal will be reported. In case of missing data, all PwMS will be analysed in the group they were randomised to (intention-to-treat analysis). Early study discontinuations will be treated as independent right censoring in the primary analysis. In case of substantial or differential study discontinuations, the validity of the independent censoring assumption will be explored in shared random effects models of the primary endpoint and time to study discontinuation. To handle missing data in baseline variables or follow-up assessments, multiple imputation models will be applied.

All details of the statistical analyses including definitions of analysis populations will be prespecified in a statistical analysis plan.

Monitoring

As part of a risk-based quality management, external independent data monitoring including onsite visits at the UKE and remote data checks in secuTrial® will be performed by the contract research organization CTC North GmbH & Co. KG.

Safety and adverse events

As no significant harms (side effects, risks or complications) are to be expected, no stopping guidelines are planned. The performance of six MRIs over two years is close to clinical standard and can be regarded as harmless. Contrast media will not be used in order to minimize the risk of possible contrast media deposition in the basal ganglia, although no information on depositions is available for the contrast media currently used (56). No auditing trials are planned or expected.

ETHICS AND DISSEMINATION

The study has been approved by the Ethics Committee of the Hamburg Chamber of Physicians (PV6015) and the ethics committees of participating study centres. The trial was registered at ClinicalTrials.gov (NCT03968172).

Informed consent (see Appendix II) will be obtained by the participating MS centres and a copy will be sent to the study centre in Hamburg. Participants may withdraw their consent at any time. A financial compensation for participation in this study cannot be granted. In case of

reaching the primary endpoint, PwMS are requested to remain in the study and continued access to the web tools will be guaranteed until the study end. Only the study team (investigators) and Alexander Stahmann (medical information scientist at the German MS Registry) will have access to the final trial dataset. For publications, an anonymized data set will be used. If possible, an anonymized data set will be made available in the publication process in order to disseminate the study results.

Trial results will be communicated at scientific conferences and meetings (e.g. at the yearly German Neurologists Society, the RIMS network) by the investigators and presented on the DMSG website and other relevant patient websites. Authorship will be shared between persons involved in the study following the current guidelines of the International Committee of Medical Journal Editors (ICMJE). Professional writers and persons not directly involved in the study will not be granted authorship.

DISCUSSION

This will be the first study assessing the impact of a lifestyle management programme combined with EBPI on inflammatory activity in MS. If successful, POWER@MS1 has a paradigm shifting potential. If successful, the trial could give lifestyle management a label as putative disease-modifying. This can impact guideline development.

Current trial status

Recruitment of PwMS has started in July 2019.

Abbreviations aMDS: adapted Mediterranean Diet Screener; BSA: Bewegungs- und Sportaktivität Fragebogen (Physical Activity, Exercise, and Sport Questionnaire); CBT: cognitive behavioural therapy; CG: control group; CIS: clinically isolated syndrome; CNS: central nervous system; CPS: Control Preference Scale; CSES: Coping Self-efficacy Scale; DIfE: Deutsches Institut für Ernährungsforschung (German Institute of Human Nutrition); DMSG: Deutsche Multiple Sklerose Gesellschaft (German Multiple Sclerosis Society); DSGVO: Datenschutz-Grundverordnung; EBBC: evidence-based behaviour change; EBPI: evidence-based patient information; EDSS: Expanded-Disability-Status-Scale; GLTEQ: Godin Leisure-Time Exercise Questionnaire; HADS: Hospital Anxiety and Depression Scale; HAPA: Health Action Process Approach; HAQUAMS: Hamburg Quality of Life in MS Scale; ICER: incremental cost-effectiveness ratio; HR: hazard ratio; ICMJE: International Committee of Medical Journal Editors; ICUR: incremental cost-utility ratio; IG: intervention group; MRC: Medical Research Council; MRI: magnetic resonance imaging; MS: multiple sclerosis; PAM: Patient Activation Measure; QALY: quality-adjusted life year; PwMS: persons with multiple sclerosis; RCT: randomised controlled trial; UKE: Universitätsklinikum Hamburg-Eppendorf (University Medical Center Hamburg-Eppendorf)

Contributors CH is the principal investigator and led the planning and development of the full study with support from NK, KRL, TS, AR, JP, JS, SK, TF, SMG and HT. NK and CH wrote the first draft of the paper. TF specifically revised the statistical analyses sections of this paper. AI provided health economic expertise. MVDL contributed as a PwMS expert. All authors conceived the study, revised the manuscript for relevant scientific content, and approved the final version.

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Patient consent Not required.

Ethics approval and trial registration The study has been approved by the Ethics Committee of the Hamburg Chamber of Physicians (PV6015) and all relevant local ethics boards. The trial was prospectively registered at Clinicaltrials.gov (NCT03968172). Important and major protocol modifications and amendments will have to be approved and reported to all relevant ethical committees. In addition, all changes will be noted in the study registration.

Provenance and peer review Not commissioned; externally peer reviewed.

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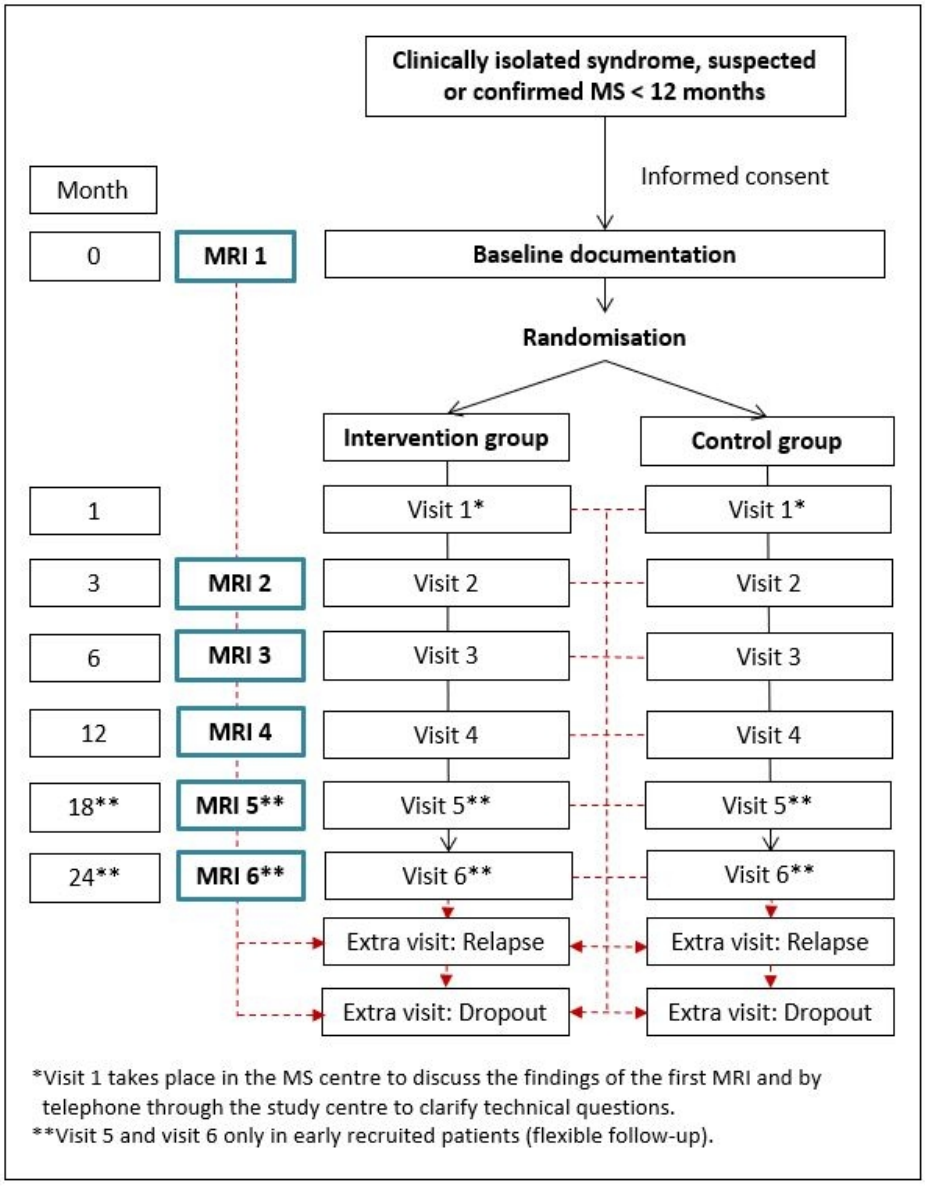

Figure 1: Participant timeline

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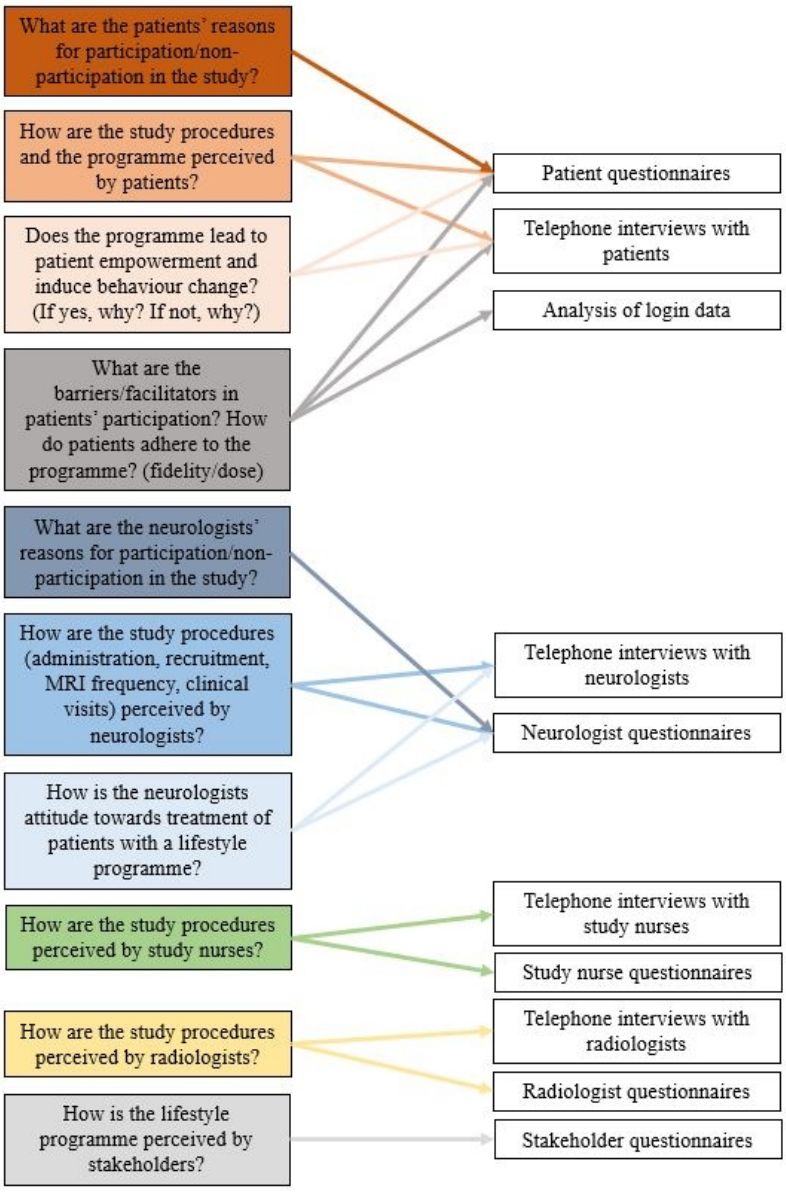

Figure 2: Process evaluation POWER@MS1: questions and methods

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Appendix I: Process evaluation

A mixed methods approach (1) is used for the process evaluation based on standardised questionnaires and telephone interviews (see Table 2, Figure 2). Further, the outcome assessments of the main study are an important data source for the process evaluation. The process evaluation aims to clarify whether the intervention was delivered as intended (fidelity) and in which quantity (dose) the intervention was implemented (2, 3). Moreover, implementation barriers and facilitators will be explored. As shown in Table 2 and Figure 2, we will assess contextual factors, components associated with recruitment, delivery, responses and maintenance of centres and individuals (PwMS) as well as unintended consequences using different methods.

Sampling

Questionnaires will be provided to all participants. Interviews will be performed with 10 to 20 with PwMS from each study group until information saturation is reached. Of the healthcare providers, up to 10 neurologists and 5 radiologists will be interviewed based on a purposeful sampling strategy, i.e. aiming for a diversity of centres in organisational structure and size.

Timing

The process evaluation will be conducted in parallel to the main trial (see Table 2 for specific timing of assessments).

Data analysis

First, the process evaluation and trial data will be analysed separately. Afterwards, data will be combined and used to determine post-trial interview questions. Quantitative process evaluation data (questionnaires and evaluation forms) will be analysed descriptively using SPSS (International Business Machines Corporation (IBM), Armonk, United States of America) or R (R Development Core Team) software. Subgroup analyses considering study outcomes and patient characteristics will be performed (for example, start of immunotherapy and decision type) in order to explore the impact of the intervention on different groups. Interviews will be analysed by thematic analysis (4) using MAXQDA (5).

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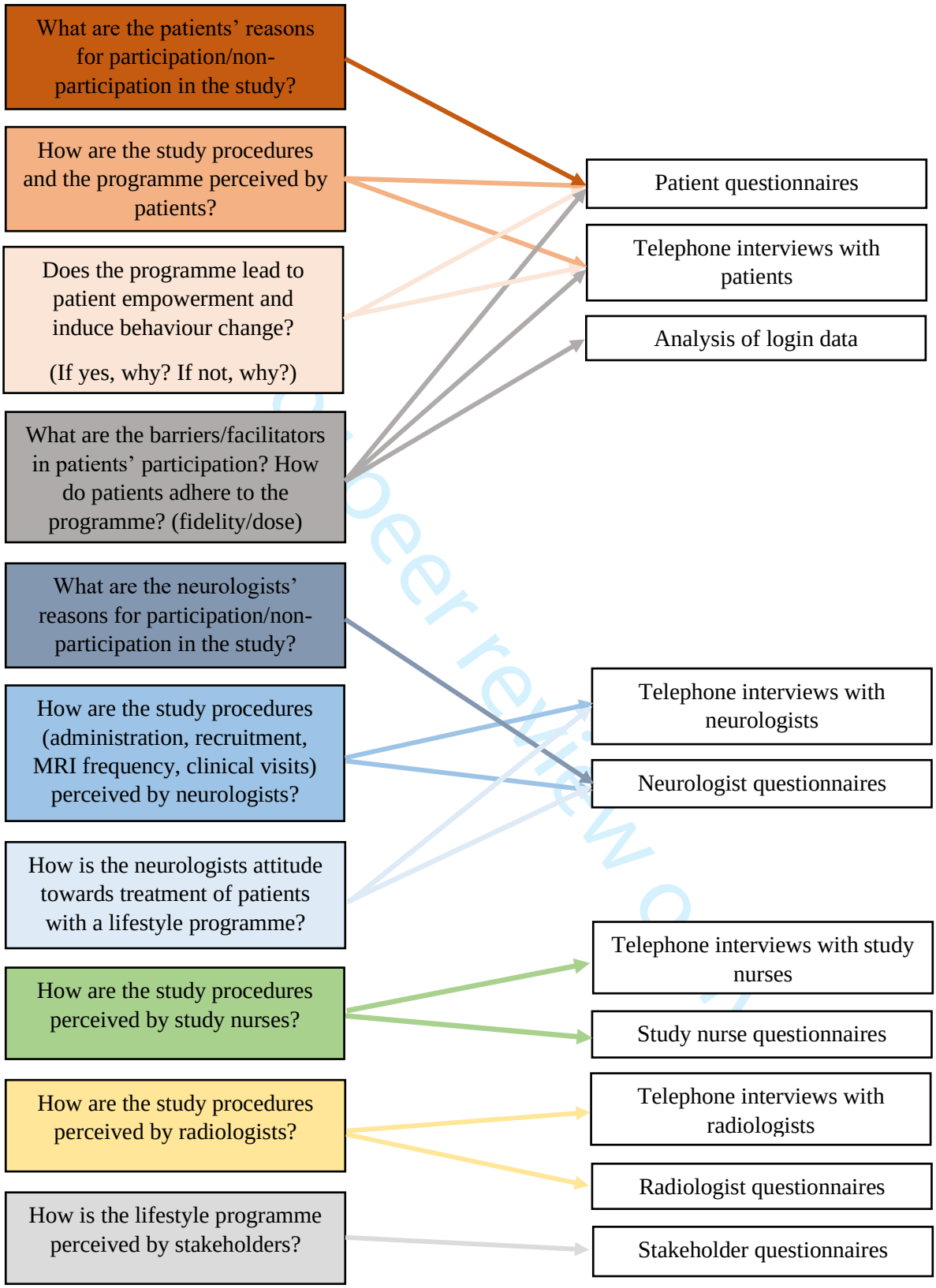
Overview process evaluation POWER@MS1			
Domain	**Objects of investigation**	**Ascertainment/Data collection tool**	**Time point**
Context	Context factors in Germany (health system)	Description	Pre-intervention
	Centre-specific structures and processes	Questionnaire, interviews	Pre-intervention
Recruitment of centres	Centre recruitment	Documentation of recruited centres, phone calls or visits in interested centres	Pre-intervention
	Reason for study participation/ for non-participation (promoting factors and barriers)	Questionnaire (neurologists)	Pre- and during intervention
Delivery to centres	Delivery of information (study management) to neurologists, study nurses and radiologists (participation, reach)	Provision of study materials about the intervention programme, initiation of study centres	Pre-intervention
	Delivery of the study monitoring platform access to all centres	Provision of access data	Pre-intervention
Response of centres	Attitude (neurologists, study nurses and radiologists) regarding the study procedures (e.g. administration, recruitment, clinical visits, MRI frequency) and the intervention	Evaluation forms, interviews	During and post-intervention
Maintenance of centres	Study centres: recruitment of patients	Documentation of recruited patients, evaluation forms, interviews	During and post-intervention
Recruitment of individuals	Recruitment of PwMS	Information video (provided online via YouTube and stakeholder websites/ social media/ network distributors/ magazines), study information leaflets, recruitment in the centres (screening lists, baseline questionnaires)	Pre-intervention
Delivery to individuals	Intervention group: delivery of the intervention to individuals (EBPI about lifestyle factors in MS combined with a complex behaviour change programme)	Provision of access (login) data, e-mail and text message reminders, monitoring of programme usage, evaluation forms, interviews	During and post-intervention

	Control group: delivery of the control intervention to individuals (web-based information on lifestyle factors consisting of optimised standard care material)	Provision of access (login) data, e-mail and text message reminders, monitoring of programme usage, evaluation forms, interviews	During and post-intervention
Response of individuals	E.g.: Satisfaction with the study procedures (e.g. frequency of MRIs and clinical visits) and the intervention, knowledge, attitude, empowerment, change in behaviour, barriers and facilitators	Questionnaires (primary and secondary endpoints RCT), evaluation forms, interviews	Post-intervention, after reaching the primary endpoint
Maintenance of individuals	PwMS (users of the programme): knowledge, empowerment, change in behaviour and reasons for usage	Questionnaires (primary and secondary endpoints RCT), evaluation forms, interviews	During and post-intervention
	PwMS (non-user of the programme): knowledge, empowerment, change in behaviour and reasons for non-usage	Contacting participants via e-mail or telephone, questionnaire, interviews	During and post-intervention
Unintended consequences	Patients: anxiety, depression, negative impact on disease specific quality of life	Evaluation form, interviews, secondary outcome measurement	During and post-intervention
	Neurologists: professional relationship to patients, barriers for implementation	Evaluation form, interviews	During and post-intervention
	Study nurses: stress, professional relationship to patients, barriers for implementation	Evaluation form, interviews	During and post-intervention
Theory	EBPI, TDF, TPB, Empowerment	Application during study planning and the development of study materials, used in evaluation forms, in the programme and in secondary outcome measurement	Pre-, during and post-intervention

EBPI = evidence-based patient information; MRI = magnetic resonance imaging; MS = Multiple Sclerosis; PwMS = Persons with Multiple Sclerosis; RCT = randomised controlled trial; TDF = Theoretical Domains Framework; TPB = Theory of Planned Behavior

Table 2: Overview process evaluation POWER@MS1

Figure 2: Process evaluation POWER@MS1: questions and methods



Appendix II: Model consent form

Klinik und Poliklinik für Neurologie
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Patienteninformation zur Studie „POWER@MS1“ – RCT (Version 1.3)

Ansprechpartnerinnen: Nicole Krause, Tanja Steffen
Kontakt: powerms1@uke.de

Hamburg, 15.06.2020

Information und Einwilligung zur Studie:

Interaktive Webplattform zum EmPOWERment bei früher Multipler Sklerose (POWER@MS1) – Randomisiert kontrollierte Studie (RCT)

Sehr geehrte Studieninteressent*innen,

das Institut für Neuroimmunologie und Multiple Sklerose sowie der Bundesverband der Selbsthilfe (DMSG) danken Ihnen für Ihr Interesse an unserer Studie zum webbasierten Empowerment für Menschen mit Multipler Sklerose (MS). Die Studie wird öffentlich durch den Innovationsfond beim gemeinsamen Bundesausschuss (G-BA) gefördert.

Bitte lesen Sie diese Studieninformation sorgfältig durch. Ihre Ärztin oder ihr Arzt wird mit Ihnen auch direkt über die Studie sprechen. Bitte fragen Sie diesen oder diese oder kontaktieren Sie den unten genannten Studienleiter Prof. Dr. med. Christoph Heesen oder die Studienkoordinatorinnen Nicole Krause und Tanja Steffen, wenn Sie etwas nicht verstehen oder wenn Sie zusätzlich etwas wissen möchten.

Was ist das Ziel dieser Studie?

Bei Ihnen ist kürzlich ein MS Verdacht geäußert oder auch eine MS Diagnose gestellt worden. Diese Diagnose stellt für viele Patienten eine erhebliche Verunsicherung dar. Fragen die viele umtreiben sind zum Beispiel:

Wie sicher ist die Diagnose?

Werde ich einen eher gutartigen oder aktiveren Verlauf haben?

Brauche ich eine ganz frühe Immuntherapie?

Was kann ich tun, außer Medikamente zu nehmen?

Diese Fragen können im Rahmen von Arztbesuchen, beim Neurologen, nur begrenzt diskutiert werden. Im Internet gibt es eine Fülle von Informationen, deren Qualität oft zweifelhaft ist. Um Sie im ersten Jahr Ihrer MS Diagnose zu begleiten, haben wir verschiedene Materialien entwickelt, die Sie darin unterstützen sollen, einen eigenen Weg mit der Erkrankung zu finden.

Das Ziel dieser Studie ist es zu klären, ob diese von uns entwickelten und über das Internet bereit gestellten Materialien hilfreich sind. Im Verlauf von bis zu 2 Jahren wird insbesondere die Aktivität der MS im MRT (=Magnetresonanztomografie), mit Untersuchungen alle 6 Monate, sehr genau untersucht werden. Darüber hinaus erhalten Sie mehrmals Fragebögen zu möglichen Beeinträchtigungen, zu Ihrer Stimmungslage, aber auch zu Lebensstilfaktoren wie Ihrer sportlichen Aktivität und Ihren Ernährungsgewohnheiten.

Auf was müssen Sie sich als Teilnehmer/in einstellen?

In der Studie werden, in zwei Gruppen, unterschiedliche Informationsstrategien zu Lebensstilfaktoren verglichen. Die Zuordnung zu einer der Gruppen erfolgt zufällig (randomisiert). Wenn Sie sich für die Teilnahme entscheiden, erhalten Sie einen Zugangscode (Login) für eine Internetseite mit Informationen und Schulungsmaterialien. Dort melden Sie sich mit einer E-Mail-Adresse und einem selbst gewählten Passwort an. Die Webseite wird Ihnen über einen neutralen E-Mailabsender (ohne Bezug zur MS), in zeitlichen Abständen, immer wieder Informationen und Erinnerungen schicken. Auch per SMS können Sie auf eigenen Wunsch angesprochen werden. In diese Kontaktaufnahmen müssen Sie einwilligen. Dabei müssen Sie bedenken, dass jegliche Kommunikation über das Internet möglicherweise von Unbefugten abgehört werden kann und ein nicht sicher kalkulierbares Risiko besteht, dass bei der Nutzung von Internetplattformen Dritte an die eingegebenen Informationen gelangen können. Die Wahrscheinlichkeit, dass Ihnen damit jemand schadet ist jedoch sehr gering.

Wenn Sie innerhalb von 3 Monaten vor Studienbeginn ein geeignetes MRT bekommen haben, kann dieses für die Studie genutzt werden. Sollte kein geeignetes MRT vorliegen, erfolgt ein MRT zu Studienbeginn und nach 3, 6 und 12 Monaten. Für einen Teil der Patienten, die sehr früh eingeschlossen werden, erfolgen weitere MRTs zu Monat 18 und 24. Hier sollten die Aufnahmen bestenfalls immer am gleichen Gerät, in der gleichen Praxis erfolgen. Eine Kopie der Bilder wird an die Studienzentrale in Hamburg gesendet werden. Aufgrund der Anzahl an studienbedingten MRT-Untersuchungen entsteht durch die Teilnahme an der POWER@MS1 Studie ein zusätzlicher Zeitaufwand für Sie. Da das Verwenden von Kontrastmittel im Rahmen der Studie nicht notwendig ist, bestehen für Sie aber keine Risiken aufgrund der zusätzlichen MRT-Untersuchungen.

Zu Beginn der Studie und nach 12 Monaten erfolgt eine umfangreichere Erhebung mit Fragebogenmaterialien, aber auch im Verlauf der Studie (maximal 2 Jahre) benötigen wir Ihre Mitarbeit in Form der Bearbeitung von Fragebogenmaterial. Dies stellen wir entweder in Papierform mit Rücksendeumschlag zur Verfügung oder über ein persönliches Login im Internet für die gesicherte Forschungsdatenbank des MS-Registers der Deutschen Multiple Sklerose Gesellschaft (DSMG, Bundesverband e.V.), welche zur elektronischen Abbildung dieser Studie genutzt wird. Die Forschungsdatenbank wird von der MS Forschungs- und Projektentwicklungs-gGmbH in Hannover, einer 100%igen Tochter der DMS-Stiftung der DMSG, auf Servern in Deutschland betrieben. Das Ernährungsverhalten untersuchen wir mit zwei internetbasierten Erhebungsinstrumenten. Eines dieser Instrumente wird über eine gesicherte Online-Platt-

form des Humanstudienzentrums des Deutschen Instituts für Ernährungsforschung (DIfE) verwaltet. Das zweite Instrument wird von der Dietary Assessment Ltd (ein Spin-Out-Unternehmen der Universität Leeds) verwaltet, welche die erhaltenen Daten auf einem Server in den Niederlanden, mit einem Backup in England speichert. Beide Einrichtungen handeln in Übereinstimmung mit der Datenschutz-Grundverordnung (DSGVO) der EU und verarbeiten die Daten in pseudonymisierter Form (das heißt mit einem Code, ohne direkte Verbindung zu Ihrem Namen). Die Links zu den Ernährungserhebungen werden Ihnen über die Studien-E-Mail (powerms1@uke.de) von Mitarbeitern/innen der Studienzentrale in Hamburg zugesendet. Zum Schluss der Studie möchten wir noch mit einigen Teilnehmerinnen und Teilnehmern Interviews durchführen, die aufgezeichnet und verschriftlicht werden. Nach Beendigung der Studie werden die Tonaufnahmen der Interviews vernichtet. Hierzu werden Sie gesondert angesprochen und es erfolgt eine extra Einwilligung dafür.

Wer kann teilnehmen?

Sie können an der Studie teilnehmen, wenn:

1. Bei Ihnen im letzten Jahr eine MS Verdachtsdiagnose oder definitive Diagnose einer schubförmigen MS gestellt wurde.
2. Sie seit mindestens 6 Monaten keine Immuntherapie erhalten und in den nächsten 3 Monaten keine Immuntherapie geplant ist.
3. In den letzten 4 Wochen keine Cortisontherapie erfolgte und sie nicht schwanger sind.
4. Im Kernspin des Kopfes und Rückens mindestens 2 Entzündungsherde zu sehen sind.
5. Sie einen Internetzugang und ein internetfähiges Gerät (z.B. Laptop oder Tablet) haben.
6. Sie zwischen 18 und 65 Jahre alt sind.

Gibt es Risiken?

Risiken, jenseits der oben genannten zur Datensicherheit, liegen nicht vor.

Was passiert, wenn ich einen Schub habe oder neue Herde im MRT erscheinen?

Im Falle eines Schubes müssen Sie Ihren behandelnden Arzt aufsuchen. Dieser wird mit Ihnen zum einen über eine Schubtherapie und zum anderen über eine MS Immuntherapie entscheiden. Genauso liegt, bei Nachweis neuer Herde im MRT, eine Immuntherapieentscheidung an. Dabei kann die Entscheidung auch vertagt werden oder auch eine Entscheidung gegen eine Therapie gefällt werden. Direkt nach diesem Entscheidungsgespräch erfolgt, arzt- und patientenseitig, eine Bewertung. Zusätzlich möchten wir in diesem Fall aus der Studienzentrale eine kurze telefonische Befragung, innerhalb von 4 Wochen, mit Ihnen durchführen.

Was passiert mit meinen Daten?

Ihre Kontaktdaten werden an die Studienzentrale in Hamburg übermittelt. Ihre E-Mail-Adresse und Mobilfunknummer werden im Programm POWER@MS1 hinterlegt. Das Programm erinnert Sie regelmäßig, wenn neue Materialien für Sie bereit liegen. Dieser Kontakt erfolgt primär per E-Mail oder SMS. Ferner kann es sein, dass Sie kurze Verhaltenstipps per E-Mail oder SMS erhalten. Aus Datenschutzgründen sind E-Mail-Absender über das Programm so allgemein gehalten, dass nicht auf die MS rückgeschlossen werden kann. Hier müssen Sie darauf achten, dass die Nachrichten nicht im Spam-Ordner verschwinden. Zusätzlich kann es sein, dass Sie über die Studien-E-Mail (powerms1@uke.de) von Mitarbeitern/innen der Studien-

zentrale in Hamburg kontaktiert werden, mit der Bitte, bestimmte Studienfragen zu beantworten. Alle Patientendaten werden bis zum Studienende pseudonymisiert in einer Datenbank des deutschen MS-Registers gesammelt. Parallel dazu werden die Kernspindaten in Hamburg pseudonymisiert ausgewertet. Beide Datenbanken werden am Studienende verbunden und zusammen ausgewertet.

Zusätzlich werden die Zugriffszeiten auf der Studienwebsite erfasst, sodass wir abschätzen können, wie intensiv Sie sich mit den Materialien befasst haben. Diese Daten werden, wie alle anderen Daten, pseudonymisiert ausgewertet.

Nach Abschluss der Auswertung werden die Daten (inklusive Audiodaten) in Hamburg am INIMS auf einem geschützten Computer, über einen Zeitraum von 10 Jahren, sicher gelagert und anschließend vernichtet. Mit Ihrer Einwilligung werden darüber hinaus Ihre MS-bezogenen Daten in der Forschungsplattform des MS-Registers gespeichert (siehe Extraeinwilligung MS-Register). Ihre Einwilligung und die Teilnahme Ihres Zentrums am MS-Register vorausgesetzt, werden Ihre Daten gemeinsam mit dem Gesamtdatenbestand des MS-Registers, entsprechend Ihrer Einwilligung, ausgewertet. Die Daten können darüber hinaus der wissenschaftlichen Öffentlichkeit zugänglich gemacht werden, damit unsere Ergebnisse überprüft und gegebenenfalls auch mit anderen Ergebnissen verglichen werden können. Dazu werden die Daten anonymisiert, sodass keine Identifizierung mehr möglich ist. Stimmen Sie im Falle des Widerrufs Ihrer Einwilligungserklärung einer Weiterverwendung Ihrer sicher anonymisierten Daten nicht zu, ist eine Teilnahme an der Studie nicht möglich.

Teilnahme, Haftung, Versicherung, Aufwandsentschädigung

Die Teilnahme an der Studie ist freiwillig. Sie können Ihre Einwilligung jederzeit und ohne Angabe von Gründen widerrufen, ohne dass dadurch Nachteile für Sie entstehen.

Da es sich nicht um eine Studie zur Prüfung eines neuen Arzneimittels oder Medizinproduktes oder eines neuen Anwendungsgebietes handelt, ist keine besondere Studienversicherung (Probandenversicherung) zur Gefährdungshaftung vorgesehen. Es gelten die allgemeinen Haftungsgrundsätze.

Die wissenschaftliche Leitung hat Prof. Dr. med. Christoph Heesen (Telefon: 040-7410-53776). Die Studienkoordinatorin ist Nicole Krause (Telefon: 040-7410-54077). Sollten Sie noch weitere Fragen haben, stehen Ihnen der Versuchsleiter und die Studienkoordinatorin zur Beantwortung gerne zur Verfügung.

Für die Teilnahme an dieser Studie können keinerlei finanzielle Aufwandsentschädigungen gewährt werden.

Wir würden uns sehr freuen, wenn Sie dieses Projekt durch Ihre Teilnahme unterstützen.

Mit freundlichen Grüßen

Prof. Dr. med. Christoph Heesen Nicole Krause

Datenschutzerklärung

Die erhobenen Daten unterliegen der Schweigepflicht und den datenschutzgesetzlichen Bestimmungen. Die Daten werden ausschließlich für wissenschaftliche Zwecke verwendet. Zugriff auf diese Daten haben die Projektleiter/Innen. Die Datenauswertung erfolgt durch Prof. Dr. Heesen und seine explizit autorisierten Mitarbeiter ohne Bezug zu den persönlichen Daten der Studienteilnehmer. Die in den Studien erhobenen Daten werden in pseudonymisierter[1] Form ausgewertet und für die Dauer von 10 Jahren gespeichert. Bei der Pseudonymisierung wird dem richtigen Namen ein Pseudonym (also ein Nummern- und Buchstabencode, z.B. A01, B01) zugeordnet. In den Dokumenten wird nur auf das Pseudonym und nicht auf den Namen verwiesen, sodass personenbezogene Daten nicht oder nur durch einen unverhältnismäßig großen Aufwand einer bestimmten Person zugeordnet werden können. Die personenbezogenen Daten sind gegen unbefugten Zugriff gesichert. Nach Beendigung der Studie werden die Tonaufnahmen der Interviews vernichtet. Ein individueller Widerruf der Erlaubnis zur Verwendung Ihrer Daten ist jederzeit möglich.

Eine Weitergabe der erhobenen Daten im Rahmen der Studie erfolgt nur in anonymisierter[2] Form. Die beteiligten Personen sind zur Verschwiegenheit verpflichtet. Gleiches gilt für die Veröffentlichung der Studienergebnisse.

Die Studienteilnehmer/innen haben das Recht, über die von Ihnen erhobenen personenbezogenen Daten Auskunft zu verlangen und über möglicherweise anfallende personenbezogene Ergebnisse der Studie ggf. informiert zu werden.
Diese Studie ist auch durch die zuständige Ethik-Kommission der Ärztekammer Hamburg beraten worden. Der zuständigen Landesbehörde kann ggf. Einsichtnahme in die Studienunterlagen gewährt werden. Im Falle des Widerrufs Ihrer Einwilligungserklärung werden die bereits erhobenen anonymisiert[2] und in dieser Form weiter genutzt.

[1] *Pseudonymisieren ist das Ersetzen des Namens und anderer Identifikationsmerkmale durch ein Kennzeichen zu dem Zweck, die Identifizierung des Betroffenen auszuschließen oder wesentlich zu erschweren (§ 3 Abs. 6a Bundesdatenschutzgesetz).*

[2] *Anonymisieren ist das Verändern personenbezogener Daten derart, dass die Einzelangaben über persönliche oder sachliche Verhältnisse nicht mehr oder nur mit einem unverhältnismäßig großen Aufwand an Zeit, Kosten und Arbeitskraft einer bestimmten oder bestimmbaren natürlichen Person zugeordnet werden können (§ 3 Abs. 6 Bundesdatenschutzgesetz).*

Ergänzende Information für Studienteilnehmer gemäß Europäischer Datenschutz-Grundverordnung[3]:

Hiermit informieren wir Sie über die in der DSGVO festgelegten Rechte (Artikel 12 ff. DSGVO)**:**

Rechtsgrundlage: Die Rechtsgrundlage zur Verarbeitung der Sie betreffenden personenbezogenen Daten bildet bei klinischen Studien Ihre freiwillige schriftliche Einwilligung gemäß DSGVO sowie der Deklaration von Helsinki (Erklärung des Weltärztebundes zu den ethischen Grundsätzen für die medizinische Forschung am Menschen) und der Leitlinie für Gute Klinische Praxis. Zeitgleich mit der DSGVO tritt in Deutschland das überarbeitete Bundesdatenschutzgesetz (BDSG-neu) in Kraft.

Für die Datenverarbeitung verantwortliche Person: Der Studienleiter des Universitätsklinikums Hamburg-Eppendorf: **Prof. Dr. Christoph Heesen**

Recht auf Auskunft: Sie haben das Recht auf Auskunft über die Sie betreffenden personenbezogenen Daten, die im Rahmen der klinischen Studie erhoben, verarbeitet oder ggf. an Dritte übermittelt werden (Aushändigen einer kostenfreien Kopie) (Artikel 15 DSGVO, §34 BDSG-neu).

Recht auf Berichtigung: Sie haben das Recht, Sie betreffende unrichtige personenbezogene Daten berichtigen zu lassen (Artikel 16 und 19 DSGVO).

Recht auf Löschung: Sie haben das Recht auf Löschung Sie betreffender personenbezogener Daten, z. B. wenn diese Daten für den Zweck, für den sie erhoben wurden, nicht mehr notwendig sind (Artikel 17 und 19 DSGVO, §35 BDSG-neu).

Recht auf Einschränkung der Verarbeitung: Unter bestimmten Voraussetzungen haben Sie das Recht, eine Einschränkung der Verarbeitung zu verlangen, d.h. die Daten dürfen nur gespeichert, aber nicht verarbeitet werden. Dies müssen Sie beantragen. Wenden Sie sich hierzu bitte an Ihren Studienleiter oder an den Datenschutzbeauftragten des Prüfzentrums (Artikel 18 und 19 DSGVO).

Recht auf Datenübertragbarkeit: Sie haben das Recht, die Sie betreffenden personenbezogenen Daten, die Sie dem Verantwortlichen für die klinische Studie bereitgestellt haben, zu erhalten. Damit können Sie beantragen, dass diese Daten entweder Ihnen oder, soweit technisch möglich, einer anderen von Ihnen benannten Stelle übermittelt werden (Artikel 20 DSGVO).

Widerspruchsrecht: Sie haben das Recht, jederzeit gegen konkrete Entscheidungen oder Maßnahmen zur Verarbeitung der Sie betreffenden personenbezogenen Daten Widerspruch einzulegen (Art 21 DSGVO, § 36BDSG-neu). Eine solche Verarbeitung findet anschließend grundsätzlich nicht mehr statt.

Einwilligung zur Verarbeitung personenbezogener Daten und Recht auf Widerruf dieser Einwilligung: Die Verarbeitung Ihrer personenbezogenen Daten ist nur mit Ihrer Einwilligung rechtmäßig (Artikel 6 DSGVO). Sie haben das Recht, Ihre Einwilligung zur Verarbeitung personenbezogener Daten jederzeit zu widerrufen. Im Falle des Widerrufs müssen Ihre personenbezogenen Daten grundsätzlich gelöscht werden (Artikel 7, Absatz 3 DSGVO). Es gibt allerdings Ausnahmen, nach denen die bis zum Zeitpunkt des Widerrufs erhobenen Daten

[3] Verordnung (EU) 2016/679 des Europäischen Parlaments und des Rates vom 27. April 2016 zum Schutz natürlicher Personen bei der Verarbeitung personenbezogener Daten, zum freien Datenverkehr und zur Aufhebung der Richtlinie 95/46/EG (Datenschutz-Grundverordnung)

weiter verarbeitet werden dürfen, z.B. wenn die weitere Datenverarbeitung zur Erfüllung einer rechtlichen Verpflichtung erforderlich ist (Art. 17 Abs. 3 b DSGVO).

Möchten Sie eines dieser Rechte in Anspruch nehmen, wenden Sie sich bitte an den Studienleiter Ihres Prüfzentrums.

Außerdem haben Sie das **Recht, Beschwerde bei einer Aufsichtsbehörde/n einzulegen,** wenn Sie der Ansicht sind, dass die Verarbeitung der Sie betreffenden personenbezogenen Daten gegen die DSGVO verstößt. Wenn Sie Bedenken hinsichtlich des Umgangs mit Ihren personenbezogenen Datenhaben, können Sie sich an die für Sie zuständige Datenschutzbehörde wenden:

Die für das UKE beauftragte Behörde	**Datenschutz-Aufsichtsbehörde**
Datenschutzbeauftragter des Universitätsklinikums Hamburg-Eppendorf	Hamburgische Beauftragte für Datenschutz und Informationsfreiheit
Matthias Jaster	
Martinistraße 52 20246 Hamburg 040 / 7410 - 56890	Ludwig-Erhard-Str. 22 20459 Hamburg 040 / 42854 - 4040
m.jaster@uke.de	mailbox@datenschutz.hamburg.de

Einwilligungserklärung zur Teilnahme an der Studie POWER@MS1

Teilnehmer, Teilnehmerin (Name in Druckbuchstaben):

……..

Bitte ankreuzen und unterschreiben

O Hiermit willige ich zur freiwilligen Teilnahme an der Studie ein.

Ich wurde mündlich ausführlich und verständlich über das Anliegen, die Bedeutung und die Tragweite der Studie aufgeklärt. Das Informationsschreiben zur Studie und zum Umgang mit den erfassten Daten habe ich gelesen und verstanden. Meine Fragen zur Studie wurden erläutert und beantwortet.

Zur Einwilligung hatte ich ausreichend Zeit. Meine Teilnahme ist freiwillig und kann jederzeit ohne Angaben von Gründen widerrufen werden, ohne dass für mich Nachteile entstehen. Ich habe keinerlei Kosten oder finanziellen Nutzen durch die Teilnahme an dieser Studie. Es gelten die Richtlinien des Datenschutzes.

Eine Kopie der Einwilligungserklärung habe ich erhalten und erkläre hiermit meine freiwillige Teilnahme an dieser Studie.

Ort, Datum	Unterschrift des Teilnehmers / der Teilnehmerin
……	……
Ort, Datum	Unterschrift des Arztes
……	……

SPIRIT
STANDARD PROTOCOL ITEMS: RECOMMENDATIONS FOR INTERVENTIONAL TRIALS

SPIRIT 2013 Checklist: Recommended items to address in a clinical trial protocol and related documents*

Section/item	Item No	Description	Addressed on page number
Administrative information			
Title	1	Descriptive title identifying the study design, population, interventions, and, if applicable, trial acronym	1
Trial registration	2a	Trial identifier and registry name. If not yet registered, name of intended registry	2
	2b	All items from the World Health Organization Trial Registration Data Set	N/A
Protocol version	3	Date and version identifier	1
Funding	4	Sources and types of financial, material, and other support	12
Roles and responsibilities	5a	Names, affiliations, and roles of protocol contributors	1
	5b	Name and contact information for the trial sponsor	12
	5c	Role of study sponsor and funders, if any, in study design; collection, management, analysis, and interpretation of data; writing of the report; and the decision to submit the report for publication, including whether they will have ultimate authority over any of these activities	12
	5d	Composition, roles, and responsibilities of the coordinating centre, steering committee, endpoint adjudication committee, data management team, and other individuals or groups overseeing the trial, if applicable (see Item 21a for data monitoring committee)	11

Introduction			
Background and rationale	6a	Description of research question and justification for undertaking the trial, including summary of relevant studies (published and unpublished) examining benefits and harms for each intervention	2-3
	6b	Explanation for choice of comparators	6
Objectives	7	Specific objectives or hypotheses	3
Trial design	8	Description of trial design including type of trial (eg, parallel group, crossover, factorial, single group), allocation ratio, and framework (eg, superiority, equivalence, noninferiority, exploratory)	3-4
Methods: Participants, interventions, and outcomes			
Study setting	9	Description of study settings (eg, community clinic, academic hospital) and list of countries where data will be collected. Reference to where list of study sites can be obtained	4
Eligibility criteria	10	Inclusion and exclusion criteria for participants. If applicable, eligibility criteria for study centres and individuals who will perform the interventions (eg, surgeons, psychotherapists)	4
Interventions	11a	Interventions for each group with sufficient detail to allow replication, including how and when they will be administered	4-6
	11b	Criteria for discontinuing or modifying allocated interventions for a given trial participant (eg, drug dose change in response to harms, participant request, or improving/worsening disease)	6
	11c	Strategies to improve adherence to intervention protocols, and any procedures for monitoring adherence (eg, drug tablet return, laboratory tests)	5
	11d	Relevant concomitant care and interventions that are permitted or prohibited during the trial	6
Outcomes	12	Primary, secondary, and other outcomes, including the specific measurement variable (eg, systolic blood pressure), analysis metric (eg, change from baseline, final value, time to event), method of aggregation (eg, median, proportion), and time point for each outcome. Explanation of the clinical relevance of chosen efficacy and harm outcomes is strongly recommended	6-9
Participant timeline	13	Time schedule of enrolment, interventions (including any run-ins and washouts), assessments, and visits for participants. A schematic diagram is highly recommended (see Figure)	9

Sample size	14	Estimated number of participants needed to achieve study objectives and how it was determined, including clinical and statistical assumptions supporting any sample size calculations	9
Recruitment	15	Strategies for achieving adequate participant enrolment to reach target sample size	9
Methods: Assignment of interventions (for controlled trials)			
Allocation:			
Sequence generation	16a	Method of generating the allocation sequence (eg, computer-generated random numbers), and list of any factors for stratification. To reduce predictability of a random sequence, details of any planned restriction (eg, blocking) should be provided in a separate document that is unavailable to those who enrol participants or assign interventions	9
Allocation concealment mechanism	16b	Mechanism of implementing the allocation sequence (eg, central telephone; sequentially numbered, opaque, sealed envelopes), describing any steps to conceal the sequence until interventions are assigned	9
Implementation	16c	Who will generate the allocation sequence, who will enrol participants, and who will assign participants to interventions	9
Blinding (masking)	17a	Who will be blinded after assignment to interventions (eg, trial participants, care providers, outcome assessors, data analysts), and how	9
	17b	If blinded, circumstances under which unblinding is permissible, and procedure for revealing a participant's allocated intervention during the trial	N/A
Methods: Data collection, management, and analysis			
Data collection methods	18a	Plans for assessment and collection of outcome, baseline, and other trial data, including any related processes to promote data quality (eg, duplicate measurements, training of assessors) and a description of study instruments (eg, questionnaires, laboratory tests) along with their reliability and validity, if known. Reference to where data collection forms can be found, if not in the protocol	10
	18b	Plans to promote participant retention and complete follow-up, including list of any outcome data to be collected for participants who discontinue or deviate from intervention protocols	10

Data management	19	Plans for data entry, coding, security, and storage, including any related processes to promote data quality (eg, double data entry; range checks for data values). Reference to where details of data management procedures can be found, if not in the protocol	10
Statistical methods	20a	Statistical methods for analysing primary and secondary outcomes. Reference to where other details of the statistical analysis plan can be found, if not in the protocol	10-11
	20b	Methods for any additional analyses (eg, subgroup and adjusted analyses)	10
	20c	Definition of analysis population relating to protocol non-adherence (eg, as randomised analysis), and any statistical methods to handle missing data (eg, multiple imputation)	10-11
Methods: Monitoring			
Data monitoring	21a	Composition of data monitoring committee (DMC); summary of its role and reporting structure; statement of whether it is independent from the sponsor and competing interests; and reference to where further details about its charter can be found, if not in the protocol. Alternatively, an explanation of why a DMC is not needed	11
	21b	Description of any interim analyses and stopping guidelines, including who will have access to these interim results and make the final decision to terminate the trial	11
Harms	22	Plans for collecting, assessing, reporting, and managing solicited and spontaneously reported adverse events and other unintended effects of trial interventions or trial conduct	11
Auditing	23	Frequency and procedures for auditing trial conduct, if any, and whether the process will be independent from investigators and the sponsor	11
Ethics and dissemination			
Research ethics approval	24	Plans for seeking research ethics committee/institutional review board (REC/IRB) approval	2, 11, 12
Protocol amendments	25	Plans for communicating important protocol modifications (eg, changes to eligibility criteria, outcomes, analyses) to relevant parties (eg, investigators, REC/IRBs, trial participants, trial registries, journals, regulators)	12

Consent or assent	26a	Who will obtain informed consent or assent from potential trial participants or authorised surrogates, and how (see Item 32)	11
	26b	Additional consent provisions for collection and use of participant data and biological specimens in ancillary studies, if applicable	N/A
Confidentiality	27	How personal information about potential and enrolled participants will be collected, shared, and maintained in order to protect confidentiality before, during, and after the trial	10, 11
Declaration of interests	28	Financial and other competing interests for principal investigators for the overall trial and each study site	12
Access to data	29	Statement of who will have access to the final trial dataset, and disclosure of contractual agreements that limit such access for investigators	11
Ancillary and post-trial care	30	Provisions, if any, for ancillary and post-trial care, and for compensation to those who suffer harm from trial participation	N/A
Dissemination policy	31a	Plans for investigators and sponsor to communicate trial results to participants, healthcare professionals, the public, and other relevant groups (eg, via publication, reporting in results databases, or other data sharing arrangements), including any publication restrictions	2, 11
	31b	Authorship eligibility guidelines and any intended use of professional writers	11
	31c	Plans, if any, for granting public access to the full protocol, participant-level dataset, and statistical code	11
Appendices			
Informed consent materials	32	Model consent form and other related documentation given to participants and authorised surrogates	Appendix II°
Biological specimens	33	Plans for collection, laboratory evaluation, and storage of biological specimens for genetic or molecular analysis in the current trial and for future use in ancillary studies, if applicable	N/A

*It is strongly recommended that this checklist be read in conjunction with the SPIRIT 2013 Explanation & Elaboration for important clarification on the items. Amendments to the protocol should be tracked and dated. The SPIRIT checklist is copyrighted by the SPIRIT Group under the Creative Commons "Attribution-NonCommercial-NoDerivs 3.0 Unported" license.

°Available in German.

BMJ Open

Study protocol for a randomised controlled trial of a web-based behavioural lifestyle programme for emPOWERment in early Multiple Sclerosis (POWER@MS1)

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Primary Subject Heading:	Neurology
Secondary Subject Heading:	Evidence based practice, Patient-centred medicine, Public health, Communication

Keywords:	Multiple sclerosis < NEUROLOGY, PUBLIC HEALTH, Clinical trials < THERAPEUTICS, Information technology < BIOTECHNOLOGY & BIOINFORMATICS, Magnetic resonance imaging < RADIOLOGY & IMAGING

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Study protocol for a randomised controlled trial of a web-based behavioural lifestyle programme for emPOWERment in early Multiple Sclerosis (POWER@MS1)

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ABSTRACT

Introduction Multiple sclerosis (MS) is an inflammatory and degenerative disease of the central nervous system that mainly affects young adults. Uncertainty is a major psychological burden of the disease from diagnosis to prognosis, enhanced by the pressure to make early decisions on a diverse set of immunotherapies. Watchful waiting for 1-2 years while adapting goals and lifestyle habits to life with a chronic disease represents another reasonable option for persons with MS (PwMS). A behaviour change programme based on evidence-based patient information (EBPI) is not available in standard care. This randomised controlled trial (RCT) with an embedded process evaluation investigates the efficacy and cost-effectiveness of a web-based behavioural lifestyle programme to change lifestyle behaviour and reduce inflammatory disease activity in PwMS.

Methods and analysis A web-based behavioural intervention will be evaluated in a RCT aiming to recruit 328 persons with clinically isolated syndrome (CIS), suspected MS or confirmed MS for less than one year, who have not yet started immunotherapy. Moreover, a mixed-methods process evaluation and a health economic evaluation will be carried out. Participants will be recruited in at least 16 MS centres across Germany and randomised to an intervention group with 12 months of access to EBPI about lifestyle factors in MS, combined with a complex behaviour change programme or to a control group (optimised standard care). The combined primary endpoint is the incidence of new T2 lesions on magnetic resonance imaging or confirmed relapses.

Ethics and dissemination The study has been approved by the Ethics Committee of the Hamburg Chamber of Physicians (PV6015) and prospectively registered at ClinicalTrials.gov (NCT03968172). Trial results will be communicated at scientific conferences and meetings and presented on relevant patient websites and in patient education seminars.

Keywords Multiple sclerosis, Complex intervention, Lifestyle intervention, Randomised controlled trial, Evidence-based medicine

Strengths and limitations of this study

- Patients are actively involved in the development process of the intervention group programme in order to address the complex needs of newly diagnosed PwMS.
- This study provides an opportunity to test if lifestyle interventions can influence surrogate measures of disease activity in an immune-mediated disease.
- The intervention does not include personal consultation, which may limit the extent and sustainability of changes in lifestyle habits.
- We aimed to design a patient-centred pragmatic trial and thus selected patient reported outcomes as secondary endpoints, however, objective measures, as e.g. accelerometry, are not included.

INTRODUCTION

Multiple Sclerosis (MS) is an inflammatory and degenerative disease of the central nervous system (CNS) that affects about 240,000 people in Germany, typically first diagnosed during early adulthood (1). Over the past decade, new diagnostic criteria (2) enabled earlier diagnosis of the disease and magnetic resonance imaging (MRI) has become a crucial diagnostic and

prognostic instrument. Moreover, MRI is used for the evaluation of treatment success despite considerable limitations (3). However, there is still no highly specific diagnostic marker and diagnosis may remain unclear for years. In addition, reliable prognosis remains difficult and it is hardly possible to estimate the long-term expected disability, especially when based on disease development during the first 1-2 years after onset. For this reason, diagnostic information about MS is often experienced as traumatising and can cause disappointment and distrust in the medical system at an early stage (4). Although available immunotherapies reduce relapse rates, the long-term benefit on disability progression remains unclear (5, 6). Nevertheless, early therapy directly after MS diagnosis is recommended (7), while adherence to immunotherapy in the first two years may be as low as 30-50% (8). These manifold uncertainties and the resulting psychological stress may have a negative effect on MS disease activity (9).

Surveys have shown that PwMS are a patient group that frequently uses internet sources to gather information (10). However, these sources often provide contradictory and poorly curated advice on lifestyle-related matters (11). The existing care structures cannot meet the complex information needs of PwMS. Experimental research as well as several clinical studies have suggested that improved lifestyle management may have the potential to impact inflammatory and neurodegenerative processes in MS (12, 13). Rigorous studies are largely missing and systematic, evidence-based patient information (EBPI) about lifestyle factors in MS combined with a behaviour change programme is not available. Training and empowerment interventions in MS have so far mainly been studied in face-to-face or group programmes (14). There are only very few examples for interventions that effectively change physical activity behaviour in MS. Motl et al. (15) have demonstrated in a pilot study that an internet-based intervention may change walking behaviour as assessed by self-report. However, online interventions in MS have mainly been investigated for the management of symptoms such as depression and fatigue (16, 17), but not for change of overall lifestyle behaviour. POWER@MS1 aims to encourage PwMS to find the best way of dealing with the disease on the basis of EBPI and a complex behaviour change intervention. The goal of the web-based behavioural lifestyle programme evaluated in this RCT is to optimise coping strategies and lifestyle habits, such as stress management, sleeping behaviour, physical activity and dietary behaviour. This may lead to decreased disease activity and lower distress to make an early treatment decision. Together with the careful MRI monitoring of the disease dynamics in the study, this procedure might enable a more targeted immunotherapy initiation.

Objectives

This study investigates the hypothesis that EBPI about lifestyle factors in MS combined with a complex behaviour change programme (EBBC programme) can reduce inflammatory disease activity in MS and change patient behaviour.

Primary objective

To determine if the EBBC programme can reduce inflammatory disease activity in MS as measured clinically by relapses or by new T2 lesions on MRI.

Secondary objectives

The secondary objectives are to determine if the EBBC programme can

- strengthen patient autonomy and empowerment

- promote informed decisions on immunotherapy,
- improve quality of life,
- reduce anxiety and depression,
- increase physical activity and a healthy dietary behaviour,
- increase effectiveness of neurologist consultations,
- fit with users and contextual factors,
- and save health care costs.

METHODS AND ANALYSIS

Study design

Based on developmental work following the Medical Research Council (MRC) Framework for the development and evaluation of complex interventions (18), a web-based behavioural intervention programme on lifestyle adaptation in MS was developed (for details see below). In addition, a web-based control group programme was developed based on information material available from the German Multiple Sclerosis Society (DMSG). Details with regard to the development and adaptation process will be reported in a separate publication.

The intervention will be evaluated in a superiority, rater-blinded, randomised controlled, parallel group trial. This protocol is focusing purely on the RCT. Study participants will be randomised to the intervention group (IG) with access to the EBBC programme in addition to standard of care or to the control group (CG) with optimised standard care using an allocation ratio of 1:1. In addition, a mixed-methods process evaluation (see Appendix I) and a health economic evaluation will be carried out.

Study setting

Recruitment and neurological encounters will take place in community clinics, private practises, and academic hospitals with a specialisation in MS across Germany.

Eligibility criteria

Persons aged between 18 and 65 years with CIS, suspected or confirmed MS for less than 12 months, who signed informed consent, will be included. Furthermore, they must have at least two MS-typical lesions on T2-weighted images on MRI scans and an MS typical cerebrospinal fluid finding with detection of oligoclonal bands. Internet access is mandatory for participation. PwMS who are not able to provide informed consent or have a substantial psychiatric disorder or substantial cognitive deficit based on clinical impression will be excluded. PwMS who have been treated with glatiramer acetate, teriflunomide, dimethylfumarate or interferons within the last six months prior to study inclusion or have received corticosteroid therapy within 4 weeks prior to study inclusion will also be excluded. PwMS with a planned treatment start within three months after inclusion or PwMS who had received any other MS-specific immunotherapy at any time in the past will not be eligible. Pregnancy and claustrophobia are also exclusion criteria.

Interventions

Eligible PwMS will be randomised to the IG programme or the CG programme. Both programmes will be offered online on the same platform with a similar design.

Intervention group (IG): EBBC programme

The IG programme is an MS-specific adaptation of the earlier developed "Optimune®" tool by GAIA (https://gaia-group.com/en/). Based on current research and theory of the field (19-21), it was developed for lifestyle management in cancer patients based on empowerment (22) and cognitive behavioural therapy (CBT) approaches, including acceptance and mindfulness oriented techniques (23-25). These techniques influence different theoretical domains as outlined in the theoretical domains framework (21) and thereby the participants' ability, motivation and opportunity to change their physical activity, stress management attitudes and dietary behaviour. For example, CBT techniques such as behavioural activation and identifying and refuting unhelpful automatic thoughts and cognitive distortions, goal setting, goal review, agreeing on behavioural contracts, setting graded tasks, planning social support, action planning, weighing of pros and cons, preparing for/dealing with setbacks, self-motivational statements, constructing if-then plans and formulating implementation intentions and positive emotion induction are incorporated throughout. Mental imagery exercises and mindfulness/acceptance exercises are integrated both in text format and as audio recording. Furthermore, EBPI, autonomy supportive intervention concepts based on self-determination theory (26), the principles of responsiveness (27) and individual content-tailoring (28, 29) are crucial components of the intervention format. The programme specifically attempts to avoid fear appeals and simple information provision (e.g. 'lecturing'). The programme does not provide drug specific information about available immunotherapies. The programme aims to translate evidence in the MS treatment and lifestyle management area in order to illustrate that decisions can be made. It follows the concept that every PwMS can develop an individual approach towards the disease, which might be a targeted immunotherapy initiation in one case or the development of a sophisticated food concept in the other.

The system is based on the AI-based software platform broca®, which is the basis for several effective therapy support systems evaluated in earlier RCTs, e.g. (16, 23, 30-32). An optional email and SMS reminder system (e.g. with lifestyle-related stimuli or reminders regarding programme usage and newly activated modules) aims to enhance involvement. Usage of the IG programme will be monitored biweekly and reacted on after four weeks of non-usage to ensure patient adherence.

The programme is designed as a highly individualised system that provides PwMS with narrative and coordinated information based on their existing health beliefs, interests, etc. Each text passage ends with a set of pre-programmed response options in multiple-choice format reflecting possible reader's feedback, such as "Yes. That makes sense." or "I do not quite understand this yet." The participant is invited to tick the matching response and will be guided to the next page referring to the choice, e.g. "I'm glad that you can understand it." or "No problem. Then let me explain it in a little more detail." These simulated dialogues lead to a highly individualised way through the intervention, while on the other hand, the programme makes sure that every important area is touched. More precisely, disease management and lifestyle techniques as well as exercises will be taught in sequentially active interactive learning units ("simulated dialogues") focusing on the following topics:

1. Diagnosis, prognosis and immunotherapy decision making
2. Support in coping
3. Techniques for coping with stress / depressive symptoms and developing positive emotions
4. Optimisation of dietary behaviour
5. Optimisation of physical activity behaviour
6. Sleep hygiene and methods for dealing with insomnia

The modules are not ordered by priority. Altogether, the IG programme will consist of 16 modules and accompany each participant over a period of 12 months with initial 2-3 weekly modules, later only weekly reminders and modules every 2 weeks and 4 booster sessions at the end.

Control group (CG): Information from self-help societies

CG participants will receive access to an information platform with optimised standard care consisting of information compiled from DMSG information material to reflect current practice. It will also accompany participants over a period of 12 months and cover similar topics as in the IG. A reminder function as well as usage monitoring and adherence promotion will be applied as in the IG.

Patient and public involvement

PwMS were involved in the development phase of the intervention and also participated in the feasibility and piloting testing of the IG programme (see "Study design"). They were given access to the programme and invited to evaluate content, practicability, user-friendliness and comprehensibility of the programme, also considering the needs of newly diagnosed PwMS. The programme was revised based on the acquired feedback (e.g. technical adjustments, inclusion of more break possibilities and a progress bar in the modules). In addition, suggestions for prospective adjustments, which were not possible due to technical limitations, such as the embedding of video material, were gathered. Details regarding the feedback and resulting programme changes will be communicated in a separate publication.

Criteria for discontinuation and relevant concomitant care

In case of new events (relapse or T2 lesion), formally the primary endpoint will be reached. However, study participants will be asked to stay in the study. Immunotherapy may be started during the trial period. Immunotherapy type, use, and adherence rates will be collected during the clinical visits throughout the study.

Outcomes

Data will be collected over a period of 12 months, with a flexible follow-up of up to 24 months in early recruited PwMS. A list of outcomes including measurement time points is provided in Table 1.

Instrument	**Measurement time points**								
	t_{-1}	**t_0**	**V_1**	**V_2**	**V_3**	**V_4**	**V_5***	**V_6***	**t_X**
Month	-1	0	1	3	6	12	18*	24*	X
Eligibility screen	X								
Informed consent	X								
Demographic data	X								
MRI		X		X	X	X	X	X	
Clinical visit		X	X	X	X	X	X	X	
Relapse history		X	X	X	X	X	X	X	X

Immunotherapy status		X	X	X	X	X	X	X	X
EDSS		X				X			
RIKNO10				X					
CPS						X			X
Decision satisfaction									X
Patient activation		X				X			
Emotional coping		X				X			
Changes in empowerment						X			
Expectancy			X						
Readiness to change		X		X		X			
HAQUAMS		X				X			
EQ-5D-5L		X			X	X	X	X	
HADS		X				X			
GLTEQ		X				X			
BSA		X				X			
QHOD2		X		X		X			
myfood24		X				X			
Process evaluation	X	X	X	X	X	X	X	X	
Health economic parameters		X			X	X	X	X	

t_{-1} = before enrolment; t_0 = before allocation; $V_1 – V_6$ = post allocation (V_1 = Visit in month 1; V_2 = Visit in month 3; V_3 = Visit in month 6; V_4 = Visit in month 12; V_5 = Visit in month 18; V_6 = Visit in month 24); * = only in early recruited PwMS; t_x = after reaching the primary endpoint.
BSA: Bewegungs- und Sportaktivität Fragebogen (Physical Activity, Exercise, and Sport Questionnaire); CPS: Control Preference Scale; EDSS: Expanded Disability Status Scale; GLTEQ: Godin Leisure-Time Exercise Questionnaire; HADS: Hospital Anxiety and Depression Scale; HAPA: Health Action Process Approach; HAQUAMS: Hamburg Quality of Life in MS Scale; MRI: Magnetic Resonance Imaging; QHOD2: Questionnaire of Healthy Diet; RIKNO: Risk Knowledge in Relapsing Multiple Sclerosis.

Table 1: Assessments and measurement time points

Primary outcome

The primary endpoint is the time to a new relapse or, as a surrogate for inflammatory disease activity, a new lesion on T2-weighted images on MRI scans, whatever first occurs. Occurrence of new T2 lesions will be assessed according to an MRI protocol (Localizer, 3D FLAIR sagittal e.g. 3x3mmm, 3D image T1w native sagittal, 1-3mm, PD/T2w axial 3mm, protocol duration approx. 20 min.). MRI scans will be read centrally by an experienced rater, blinded to subject identity and group assignment.

Relapses will be clinically evaluated by participating neurologists. In case of a relapse, duration of complaints/impairment, relapse symptoms (worsened or newly occurred), degree of impairment due to the relapse and the degree of certainty with regard to the classification of the worsening as a relapse will be assessed.

Secondary outcomes

To assess risk knowledge, an abbreviated 10-item version of the MS risk knowledge questionnaire (RIKNO 2.0 (33)) will be used.

As a surrogate of decision quality, preferred and realized role preference in decision discussions for or against immunotherapy based on the Control Preference Scale (CPS) (34) will be assessed. Immunotherapy status will be assessed to determine whether an immunotherapy was newly started, aborted or changed.

The extent of patient activation (i.e. expressed in the confidence and knowledge to take action, as well as actually taking health-related action) based on the Patient Activation Measure, PAM (35) and the coping capability, based on two items (item 10 and 24) of the coping self-efficacy scale, CSES (36) will be measured. In addition, patient expectancies based on items 1-3 of the credibility/expectancy questionnaire (37) will be assessed. Based on principles of the Health Action Process Approach, HAPA (38), readiness to change (39) will be estimated in order to determine the interventions impact on willingness to change lifestyle habits. Moreover, changes in perceived empowerment (based on (40), items 1, 3 and 4) will be measured.

Impairment in the Expanded Disability Status Scale (EDSS) (41) will be determined by the treating neurologist.

Ideally, the lifestyle intervention leads to more general satisfaction with life but may also alleviate symptoms such as depression, anxiety, fatigue. Quality of life will be measured with the Hamburg Quality of Life in MS Scale, HAQUAMS (42) and the generic EQ-5D-5L (43). The Hospital anxiety and distress scale, HADS (44) will be used as a measures for depression and anxiety.

Physical activity behaviour will be measured with the Godin Leisure-Time Exercise Questionnaire (GLTEQ) (45) and the Physical Activity, Exercise, and Sport Questionnaire (Bewegungs- und Sportaktivität (BSA)) (46).

The Questionnaire of Healthy Diet (QHOD2), an adapted version of the Mediterranean Diet Screener (aMDS) as used in (47) that was developed by the German Institute of Human Nutrition (DIfE), will be used to measure the frequency of intake of characteristic food groups in the last seven days. To provide nutrient intake data, the 24-h dietary recall myfood24 (48) will be used, in each case three times within a time period of two to three weeks (two weekdays, one weekend day).

Health economic outcomes

Health economic parameters will be assessed to determine the efficiency of the intervention by comparing the cost and outcome of the IG to the CG. All direct costs associated with the intervention as well as costs resulting from the consumption of health-related goods and services (49) and indirect costs due to productivity losses will be considered from the perspective of the German statutory health insurance and the society.
To determine efficiency of the intervention, a cost-effectiveness analysis will be performed in terms of additional costs per additional relapse or T2 lesion (clinical endpoint) averted and a cost-utility analysis, which aims to calculate the additional costs required for an additional improvement in quality-adjusted life years (QALYs). Incremental cost-effectiveness ratio and

incremental cost-utility ratio will be calculated as the ratio of the difference in mean costs and difference in mean outcomes between IG and CG. QALYs will be measured by a well-established preference based quality of life instrument (EQ-5D-5L) and evaluated by a German tariff to generate utilities (43). A standardised instrument (50) will be used to record the healthcare consumption of study participants focusing mainly on outpatient doctor visits, visits to other health service providers, sick days, hospital stays and MS immune medication. Productivity losses will be estimated using the human capital approach (51). 95% confidence intervals for the outcome of the analyses will be determined non-parametrically based on the distribution characteristics of costs using bootstrap procedures (52). Univariate and probabilistic sensitivity analyses will be performed and cost-effectiveness acceptance curves will be executed to take into account uncertainty (53).

Participant timeline

The time schedule is depicted in Figure 1.

Figure 1: Participant timeline

Sample size

Based on effect sizes resulting from an RCT for a stress management intervention (13) as well as data from cohorts on lesion development after an initial clinical event ((54), personal communication Michael Scheel, Charité Berlin), one event (relapse or at least one new T2 lesion) is expected in every second PwMS within 12 months in the CG. 100 events result in a statistical power of 85% for a two-way significance level test of 5% and an assumed hazard ratio of 0.55, i.e. a reduction of 45% by IG compared to the CG. Thus, with a mean observation time of 12 months, the 100 events required can be expected to be observed in 262 PwMS (131 per group). Assuming about 20% dropouts over one year, 328 PwMS will be randomised (164 per group, 20% dropout = 33 = 131 per group). A sample size recalculation will be performed after 12 months to review the assumptions on event rates and dropouts (55). If necessary, the number of cases will be increased to a maximum of 450 PwMS.

Recruitment

Eligible MS centres will be recruited by the coordinating centre in Hamburg (University Medical Center Hamburg-Eppendorf, UKE). Recruitment and inclusion of PwMS will take place in the participating MS centres through neurologists. In addition, POWER@MS1 will be advertised on the website of the DMSG. Overall, a recruitment period of 12 months is assumed with approx. 20 PwMS per centre, with one to two PwMS per month. Reasons for rejection will be documented.

Allocation

Group assignment will be undertaken externally and in a concealed manner through the electronic data capture system secuTrial® to prevent any manipulation of persons involved in the study. Eligible study participants will be randomised into the IG or to the CG in blocks (1:1 allocation ratio) through a computer-generated system in secuTrial®. After baseline documentation and subsequent randomisation, PwMS will be provided with access (login) details to the IG or CG programme by an unblinded member of the study team.

Blinding

The study will be conducted as an investigator blinded trial and participating MS centres will not be provided with any information about group assignment of a given PwMS. Blinding of the trial participants is pursued, but only possible to a limited extent. Participants and neurologists might realize their participation in the IG during encounters.

Data collection methods

Data will be obtained at different time points using paper-based and web-based questionnaires (see Table 1). In case of missing data, participants will be contacted by a member of the UKE. All study relevant data will be entered into secuTrial® and provided online. Results of MRI scans (image data) will be saved on CD. In accordance with current procedures implemented in medical practice, CDs with MRI data will be sent to the study centre in sealed envelopes via regular mail. This has been reviewed and accepted by the reviewing ethics committees and is in compliance with current data protection rules and regulations in Germany. They will be quality-checked, pseudonymised and uploaded in a protected reading centre database. Data obtained with regard to nutrition behaviour will be collected via secured online-platforms of the Humanstudienzentrum of the DIfE and Dietary Assessment Limited (University of Leeds spinout company), which act in accordance with EU General Data Protection Regulation (Datenschutz-Grundverordnung, DSGVO). Data obtained through myfood24 will be stored on a server in the Netherlands, with a backup in the UK. After data collection, data will be transferred to secuTrial® and connected with the existing datasets. In addition, usage of the web-based programmes will be monitored.

Data management

The IG and CG programme will be provided via a secure online platform that meets all legal requirements (SSL Encryption). All study data will be used and evaluated pseudonymously. However, all participating MS centres will have a list with names and assigned pseudonyms. All electronic and paper-based data material will be stored at the UKE for a maximum period of ten years and will be destroyed subsequently. Stored CDs containing MRI images will be destroyed directly after analysis of the study data. In case of withdrawn consent, pseudonymised data will be anonymised. A deletion of already anonymized data is not possible.

Statistical methods

The effect on the primary endpoint will be estimated in a Cox proportional hazards regression that, in addition to treatment, also includes study centre as a factor; it will be reported as hazard ratio (HR) with 95% confidence interval and p-value testing the null hypothesis H0: HR=1. Kaplan-Meier curves of the primary endpoint for both groups will be used to illustrate the treatment effect.

Secondary endpoints will be analysed using mean comparisons between IG and CG with adjustment for the baseline assessments and centre in analysis of covariance (ANCOVA) models. Least squares group differences will be reported with 95% confidence intervals and p-values testing the null hypothesis of no intervention effect. The number of portions/day or week for different food groups will be analysed, evaluated and compared to current recommendations. Data obtained through the 24h recall (myfood24) will be used to analyse intake of selected nutrients of interest comparing mean changes in intake from baseline to post intervention between IG and CG, adjusting for baseline intake. MRI lesion counts will be

analysed using negative binomial regression models adjusting for baseline MRI and centre. Adverse events will be summarized as frequencies and percentages by treatment group.

In addition, subgroup and moderator variable analysis is planned to be performed (e.g. early therapy vs no therapy and women vs men).

Reasons for study withdrawal will be reported. In case of missing data, all PwMS will be analysed in the group they were randomised to (intention-to-treat analysis). Early study discontinuations will be treated as independent right censoring in the primary analysis. In case of substantial or differential study discontinuations, the validity of the independent censoring assumption will be explored in shared random effects models of the primary endpoint and time to study discontinuation. To handle missing data in baseline variables or follow-up assessments, multiple imputation models will be applied.

All details of the statistical analyses including definitions of analysis populations will be prespecified in a statistical analysis plan.

Monitoring

As part of a risk-based quality management, external independent data monitoring including onsite visits at the UKE and remote data checks in secuTrial® will be performed by the contract research organization CTC North GmbH & Co. KG.

Safety and adverse events

As no significant harms (side effects, risks or complications) are to be expected, no stopping guidelines are planned. The performance of six MRIs over two years is close to clinical standard and can be regarded as harmless. Contrast media will not be used in order to minimize the risk of possible contrast media deposition in the basal ganglia, although no information on depositions is available for the contrast media currently used (56). No auditing trials are planned or expected.

ETHICS AND DISSEMINATION

The study has been approved by the Ethics Committee of the Hamburg Chamber of Physicians (PV6015) and the ethics committees of participating study centres. The trial was registered at ClinicalTrials.gov (NCT03968172).

Informed consent (see Appendix II) will be obtained by the participating MS centres and a copy will be sent to the study centre in Hamburg. Participants may withdraw their consent at any time. A financial compensation for participation in this study cannot be granted. In case of reaching the primary endpoint, PwMS are requested to remain in the study and continued access to the web tools will be guaranteed until the study end. Only the study team (investigators) and Alexander Stahmann (medical information scientist at the German MS Registry) will have access to the final trial dataset. For publications, an anonymized data set will be used. If possible, an anonymized data set will be made available in the publication process in order to disseminate the study results.

Trial results will be communicated at scientific conferences and meetings (e.g. at the yearly German Neurologists Society, the RIMS network) by the investigators and presented on the DMSG website and other relevant patient websites. Authorship will be shared between persons involved in the study following the current guidelines of the International Committee of

Medical Journal Editors (ICMJE). Professional writers and persons not directly involved in the study will not be granted authorship.

DISCUSSION

This will be the first study assessing the impact of a lifestyle management programme combined with EBPI on inflammatory activity in MS. If successful, POWER@MS1 has a paradigm shifting potential. If successful, the trial could give lifestyle management a label as putative disease-modifying. This can impact guideline development.

Current trial status

Recruitment of PwMS has started in July 2019.

Abbreviations aMDS: adapted Mediterranean Diet Screener; BSA: Bewegungs- und Sportaktivität Fragebogen (Physical Activity, Exercise, and Sport Questionnaire); CBT: cognitive behavioural therapy; CG: control group; CIS: clinically isolated syndrome; CNS: central nervous system; CPS: Control Preference Scale; CSES: Coping Self-efficacy Scale; DIfE: Deutsches Institut für Ernährungsforschung (German Institute of Human Nutrition); DMSG: Deutsche Multiple Sklerose Gesellschaft (German Multiple Sclerosis Society); DSGVO: Datenschutz-Grundverordnung; EBBC: evidence-based behaviour change; EBPI: evidence-based patient information; EDSS: Expanded-Disability-Status-Scale; GLTEQ: Godin Leisure-Time Exercise Questionnaire; HADS: Hospital Anxiety and Depression Scale; HAPA: Health Action Process Approach; HAQUAMS: Hamburg Quality of Life in MS Scale; ICER: incremental cost-effectiveness ratio; HR: hazard ratio; ICMJE: International Committee of Medical Journal Editors; ICUR: incremental cost-utility ratio; IG: intervention group; MRC: Medical Research Council; MRI: magnetic resonance imaging; MS: multiple sclerosis; PAM: Patient Activation Measure; QALY: quality-adjusted life year; PwMS: persons with multiple sclerosis; RCT: randomised controlled trial; UKE: Universitätsklinikum Hamburg-Eppendorf (University Medical Center Hamburg-Eppendorf)

Contributors CH is the principal investigator and led the planning and development of the full study with support from NK, KRL, TS, AR, JP, JS, SK, TF, SMG and HT. NK and CH wrote the first draft of the paper. TF specifically revised the statistical analyses sections of this paper. AI and MV provided health economic expertise. MVDL contributed as a PwMS expert. All authors conceived the study, revised the manuscript for relevant scientific content, and approved the final version.

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Patient consent Not required.

Ethics approval and trial registration The study has been approved by the Ethics Committee of the Hamburg Chamber of Physicians (PV6015) and all relevant local ethics boards. The trial was prospectively registered at Clinicaltrials.gov (NCT03968172). Important and major protocol modifications and amendments will have to be approved and reported to all relevant ethical committees. In addition, all changes will be noted in the study registration.

Provenance and peer review Not commissioned; externally peer reviewed.

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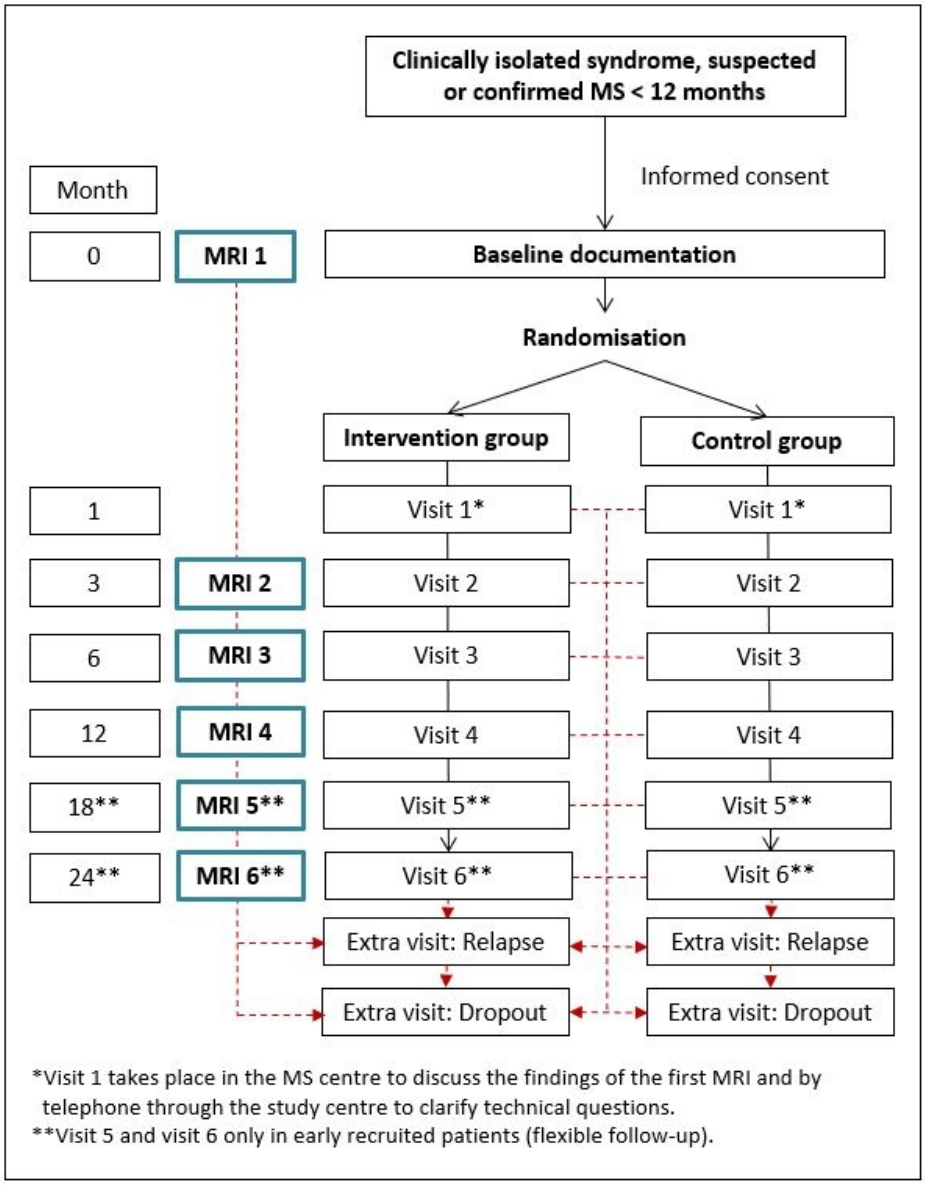

Figure 1: Participant timeline

106x135mm (144 x 144 DPI)

Appendix I: Process evaluation

A mixed methods approach (1) is used for the process evaluation based on standardised questionnaires and telephone interviews (see Table 2, Figure 2). Further, the outcome assessments of the main study are an important data source for the process evaluation. The process evaluation aims to clarify whether the intervention was delivered as intended (fidelity) and in which quantity (dose) the intervention was implemented (2, 3). Moreover, implementation barriers and facilitators will be explored. As shown in Table 2 and Figure 2, we will assess contextual factors, components associated with recruitment, delivery, responses and maintenance of centres and individuals (PwMS) as well as unintended consequences using different methods.

Sampling

Questionnaires will be provided to all participants. Interviews will be performed with 10 to 20 with PwMS from each study group until information saturation is reached. Of the healthcare providers, up to 10 neurologists and 5 radiologists will be interviewed based on a purposeful sampling strategy, i.e. aiming for a diversity of centres in organisational structure and size.

Timing

The process evaluation will be conducted in parallel to the main trial (see Table 2 for specific timing of assessments).

Data analysis

First, the process evaluation and trial data will be analysed separately. Afterwards, data will be combined and used to determine post-trial interview questions. Quantitative process evaluation data (questionnaires and evaluation forms) will be analysed descriptively using SPSS (International Business Machines Corporation (IBM), Armonk, United States of America) or R (R Development Core Team) software. Subgroup analyses considering study outcomes and patient characteristics will be performed (for example, start of immunotherapy and decision type) in order to explore the impact of the intervention on different groups. Interviews will be analysed by thematic analysis (4) using MAXQDA (5).

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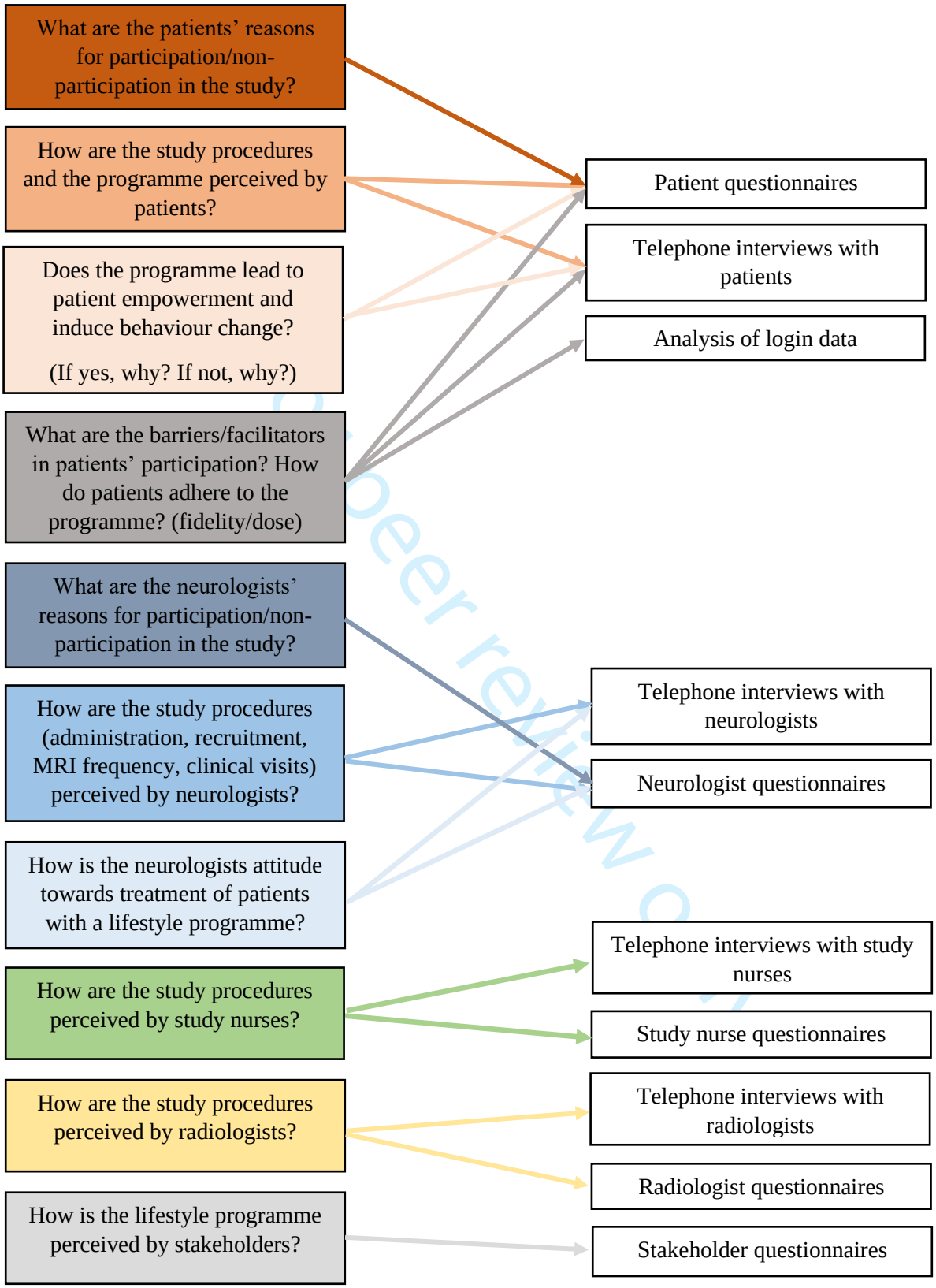
Overview process evaluation POWER@MS1			
Domain	**Objects of investigation**	**Ascertainment/Data collection tool**	**Time point**
Context	Context factors in Germany (health system)	Description	Pre-intervention
	Centre-specific structures and processes	Questionnaire, interviews	Pre-intervention
Recruitment of centres	Centre recruitment	Documentation of recruited centres, phone calls or visits in interested centres	Pre-intervention
	Reason for study participation/ for non-participation (promoting factors and barriers)	Questionnaire (neurologists)	Pre- and during intervention
Delivery to centres	Delivery of information (study management) to neurologists, study nurses and radiologists (participation, reach)	Provision of study materials about the intervention programme, initiation of study centres	Pre-intervention
	Delivery of the study monitoring platform access to all centres	Provision of access data	Pre-intervention
Response of centres	Attitude (neurologists, study nurses and radiologists) regarding the study procedures (e.g. administration, recruitment, clinical visits, MRI frequency) and the intervention	Evaluation forms, interviews	During and post-intervention
Maintenance of centres	Study centres: recruitment of patients	Documentation of recruited patients, evaluation forms, interviews	During and post-intervention
Recruitment of individuals	Recruitment of PwMS	Information video (provided online via YouTube and stakeholder websites/ social media/ network distributors/ magazines), study information leaflets, recruitment in the centres (screening lists, baseline questionnaires)	Pre-intervention
Delivery to individuals	Intervention group: delivery of the intervention to individuals (EBPI about lifestyle factors in MS combined with a complex behaviour change programme)	Provision of access (login) data, e-mail and text message reminders, monitoring of programme usage, evaluation forms, interviews	During and post-intervention

	Control group: delivery of the control intervention to individuals (web-based information on lifestyle factors consisting of optimised standard care material)	Provision of access (login) data, e-mail and text message reminders, monitoring of programme usage, evaluation forms, interviews	During and post-intervention
Response of individuals	E.g.: Satisfaction with the study procedures (e.g. frequency of MRIs and clinical visits) and the intervention, knowledge, attitude, empowerment, change in behaviour, barriers and facilitators	Questionnaires (primary and secondary endpoints RCT), evaluation forms, interviews	Post-intervention, after reaching the primary endpoint
Maintenance of individuals	PwMS (users of the programme): knowledge, empowerment, change in behaviour and reasons for usage	Questionnaires (primary and secondary endpoints RCT), evaluation forms, interviews	During and post-intervention
	PwMS (non-user of the programme): knowledge, empowerment, change in behaviour and reasons for non-usage	Contacting participants via e-mail or telephone, questionnaire, interviews	During and post-intervention
Unintended consequences	Patients: anxiety, depression, negative impact on disease specific quality of life	Evaluation form, interviews, secondary outcome measurement	During and post-intervention
	Neurologists: professional relationship to patients, barriers for implementation	Evaluation form, interviews	During and post-intervention
	Study nurses: stress, professional relationship to patients, barriers for implementation	Evaluation form, interviews	During and post-intervention
Theory	EBPI, TDF, TPB, Empowerment	Application during study planning and the development of study materials, used in evaluation forms, in the programme and in secondary outcome measurement	Pre-, during and post-intervention

EBPI = evidence-based patient information; MRI = magnetic resonance imaging; MS = Multiple Sclerosis; PwMS = Persons with Multiple Sclerosis; RCT = randomised controlled trial; TDF = Theoretical Domains Framework; TPB = Theory of Planned Behavior

Table 2: Overview process evaluation POWER@MS1

Figure 2: Process evaluation POWER@MS1: questions and methods



Appendix II: Model consent form

Klinik und Poliklinik für Neurologie
Institut für Neuroimmunologie und Multiple Sklerose (INIMS)

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Patienteninformation zur Studie „POWER@MS1“ – RCT (Version 1.3)

Ansprechpartnerinnen: Nicole Krause, Tanja Steffen
Kontakt: powerms1@uke.de

Hamburg, 15.06.2020

Information und Einwilligung zur Studie:

Interaktive Webplattform zum EmPOWERment bei früher Multipler Sklerose (POWER@MS1) – Randomisiert kontrollierte Studie (RCT)

Sehr geehrte Studieninteressent*innen,

das Institut für Neuroimmunologie und Multiple Sklerose sowie der Bundesverband der Selbsthilfe (DMSG) danken Ihnen für Ihr Interesse an unserer Studie zum webbasierten Empowerment für Menschen mit Multipler Sklerose (MS). Die Studie wird öffentlich durch den Innovationsfond beim gemeinsamen Bundesausschuss (G-BA) gefördert.

Bitte lesen Sie diese Studieninformation sorgfältig durch. Ihre Ärztin oder ihr Arzt wird mit Ihnen auch direkt über die Studie sprechen. Bitte fragen Sie diesen oder diese oder kontaktieren Sie den unten genannten Studienleiter Prof. Dr. med. Christoph Heesen oder die Studienkoordinatorinnen Nicole Krause und Tanja Steffen, wenn Sie etwas nicht verstehen oder wenn Sie zusätzlich etwas wissen möchten.

Was ist das Ziel dieser Studie?

Bei Ihnen ist kürzlich ein MS Verdacht geäußert oder auch eine MS Diagnose gestellt worden. Diese Diagnose stellt für viele Patienten eine erhebliche Verunsicherung dar. Fragen die viele umtreiben sind zum Beispiel:

Wie sicher ist die Diagnose?

Werde ich einen eher gutartigen oder aktiveren Verlauf haben?

Brauche ich eine ganz frühe Immuntherapie?

Was kann ich tun, außer Medikamente zu nehmen?

Diese Fragen können im Rahmen von Arztbesuchen, beim Neurologen, nur begrenzt diskutiert werden. Im Internet gibt es eine Fülle von Informationen, deren Qualität oft zweifelhaft ist. Um Sie im ersten Jahr Ihrer MS Diagnose zu begleiten, haben wir verschiedene Materialien entwickelt, die Sie darin unterstützen sollen, einen eigenen Weg mit der Erkrankung zu finden.

Das Ziel dieser Studie ist es zu klären, ob diese von uns entwickelten und über das Internet bereit gestellten Materialien hilfreich sind. Im Verlauf von bis zu 2 Jahren wird insbesondere die Aktivität der MS im MRT (=Magnetresonanztomografie), mit Untersuchungen alle 6 Monate, sehr genau untersucht werden. Darüber hinaus erhalten Sie mehrmals Fragebögen zu möglichen Beeinträchtigungen, zu Ihrer Stimmungslage, aber auch zu Lebensstilfaktoren wie Ihrer sportlichen Aktivität und Ihren Ernährungsgewohnheiten.

Auf was müssen Sie sich als Teilnehmer/in einstellen?

In der Studie werden, in zwei Gruppen, unterschiedliche Informationsstrategien zu Lebensstilfaktoren verglichen. Die Zuordnung zu einer der Gruppen erfolgt zufällig (randomisiert). Wenn Sie sich für die Teilnahme entscheiden, erhalten Sie einen Zugangscode (Login) für eine Internetseite mit Informationen und Schulungsmaterialien. Dort melden Sie sich mit einer E-Mail-Adresse und einem selbst gewählten Passwort an. Die Webseite wird Ihnen über einen neutralen E-Mailabsender (ohne Bezug zur MS), in zeitlichen Abständen, immer wieder Informationen und Erinnerungen schicken. Auch per SMS können Sie auf eigenen Wunsch angesprochen werden. In diese Kontaktaufnahmen müssen Sie einwilligen. Dabei müssen Sie bedenken, dass jegliche Kommunikation über das Internet möglicherweise von Unbefugten abgehört werden kann und ein nicht sicher kalkulierbares Risiko besteht, dass bei der Nutzung von Internetplattformen Dritte an die eingegebenen Informationen gelangen können. Die Wahrscheinlichkeit, dass Ihnen damit jemand schadet ist jedoch sehr gering.

Wenn Sie innerhalb von 3 Monaten vor Studienbeginn ein geeignetes MRT bekommen haben, kann dieses für die Studie genutzt werden. Sollte kein geeignetes MRT vorliegen, erfolgt ein MRT zu Studienbeginn und nach 3, 6 und 12 Monaten. Für einen Teil der Patienten, die sehr früh eingeschlossen werden, erfolgen weitere MRTs zu Monat 18 und 24. Hier sollten die Aufnahmen bestenfalls immer am gleichen Gerät, in der gleichen Praxis erfolgen. Eine Kopie der Bilder wird an die Studienzentrale in Hamburg gesendet werden. Aufgrund der Anzahl an studienbedingten MRT-Untersuchungen entsteht durch die Teilnahme an der POWER@MS1 Studie ein zusätzlicher Zeitaufwand für Sie. Da das Verwenden von Kontrastmittel im Rahmen der Studie nicht notwendig ist, bestehen für Sie aber keine Risiken aufgrund der zusätzlichen MRT-Untersuchungen.

Zu Beginn der Studie und nach 12 Monaten erfolgt eine umfangreichere Erhebung mit Fragebogenmaterialien, aber auch im Verlauf der Studie (maximal 2 Jahre) benötigen wir Ihre Mitarbeit in Form der Bearbeitung von Fragebogenmaterial. Dies stellen wir entweder in Papierform mit Rücksendeumschlag zur Verfügung oder über ein persönliches Login im Internet für die gesicherte Forschungsdatenbank des MS-Registers der Deutschen Multiple Sklerose Gesellschaft (DSMG, Bundesverband e.V.), welche zur elektronischen Abbildung dieser Studie genutzt wird. Die Forschungsdatenbank wird von der MS Forschungs- und Projektentwicklungs-gGmbH in Hannover, einer 100%igen Tochter der DMS-Stiftung der DMSG, auf Servern in Deutschland betrieben. Das Ernährungsverhalten untersuchen wir mit zwei internetbasierten Erhebungsinstrumenten. Eines dieser Instrumente wird über eine gesicherte Online-Platt-

form des Humanstudienzentrums des Deutschen Instituts für Ernährungsforschung (DIfE) verwaltet. Das zweite Instrument wird von der Dietary Assessment Ltd (ein Spin-Out-Unternehmen der Universität Leeds) verwaltet, welche die erhaltenen Daten auf einem Server in den Niederlanden, mit einem Backup in England speichert. Beide Einrichtungen handeln in Übereinstimmung mit der Datenschutz-Grundverordnung (DSGVO) der EU und verarbeiten die Daten in pseudonymisierter Form (das heißt mit einem Code, ohne direkte Verbindung zu Ihrem Namen). Die Links zu den Ernährungserhebungen werden Ihnen über die Studien-E-Mail (powerms1@uke.de) von Mitarbeitern/innen der Studienzentrale in Hamburg zugesendet. Zum Schluss der Studie möchten wir noch mit einigen Teilnehmerinnen und Teilnehmern Interviews durchführen, die aufgezeichnet und verschriftlicht werden. Nach Beendigung der Studie werden die Tonaufnahmen der Interviews vernichtet. Hierzu werden Sie gesondert angesprochen und es erfolgt eine extra Einwilligung dafür.

Wer kann teilnehmen?

Sie können an der Studie teilnehmen, wenn:

1. Bei Ihnen im letzten Jahr eine MS Verdachtsdiagnose oder definitive Diagnose einer schubförmigen MS gestellt wurde.
2. Sie seit mindestens 6 Monaten keine Immuntherapie erhalten und in den nächsten 3 Monaten keine Immuntherapie geplant ist.
3. In den letzten 4 Wochen keine Cortisontherapie erfolgte und sie nicht schwanger sind.
4. Im Kernspin des Kopfes und Rückens mindestens 2 Entzündungsherde zu sehen sind.
5. Sie einen Internetzugang und ein internetfähiges Gerät (z.B. Laptop oder Tablet) haben.
6. Sie zwischen 18 und 65 Jahre alt sind.

Gibt es Risiken?

Risiken, jenseits der oben genannten zur Datensicherheit, liegen nicht vor.

Was passiert, wenn ich einen Schub habe oder neue Herde im MRT erscheinen?

Im Falle eines Schubes müssen Sie Ihren behandelnden Arzt aufsuchen. Dieser wird mit Ihnen zum einen über eine Schubtherapie und zum anderen über eine MS Immuntherapie entscheiden. Genauso liegt, bei Nachweis neuer Herde im MRT, eine Immuntherapieentscheidung an. Dabei kann die Entscheidung auch vertagt werden oder auch eine Entscheidung gegen eine Therapie gefällt werden. Direkt nach diesem Entscheidungsgespräch erfolgt, arzt- und patientenseitig, eine Bewertung. Zusätzlich möchten wir in diesem Fall aus der Studienzentrale eine kurze telefonische Befragung, innerhalb von 4 Wochen, mit Ihnen durchführen.

Was passiert mit meinen Daten?

Ihre Kontaktdaten werden an die Studienzentrale in Hamburg übermittelt. Ihre E-Mail-Adresse und Mobilfunknummer werden im Programm POWER@MS1 hinterlegt. Das Programm erinnert Sie regelmäßig, wenn neue Materialien für Sie bereit liegen. Dieser Kontakt erfolgt primär per E-Mail oder SMS. Ferner kann es sein, dass Sie kurze Verhaltenstipps per E-Mail oder SMS erhalten. Aus Datenschutzgründen sind E-Mail-Absender über das Programm so allgemein gehalten, dass nicht auf die MS rückgeschlossen werden kann. Hier müssen Sie darauf achten, dass die Nachrichten nicht im Spam-Ordner verschwinden. Zusätzlich kann es sein, dass Sie über die Studien-E-Mail (powerms1@uke.de) von Mitarbeitern/innen der Studien-

zentrale in Hamburg kontaktiert werden, mit der Bitte, bestimmte Studienfragen zu beantworten. Alle Patientendaten werden bis zum Studienende pseudonymisiert in einer Datenbank des deutschen MS-Registers gesammelt. Parallel dazu werden die Kernspindaten in Hamburg pseudonymisiert ausgewertet. Beide Datenbanken werden am Studienende verbunden und zusammen ausgewertet.

Zusätzlich werden die Zugriffszeiten auf der Studienwebsite erfasst, sodass wir abschätzen können, wie intensiv Sie sich mit den Materialien befasst haben. Diese Daten werden, wie alle anderen Daten, pseudonymisiert ausgewertet.

Nach Abschluss der Auswertung werden die Daten (inklusive Audiodaten) in Hamburg am INIMS auf einem geschützten Computer, über einen Zeitraum von 10 Jahren, sicher gelagert und anschließend vernichtet. Mit Ihrer Einwilligung werden darüber hinaus Ihre MS-bezogenen Daten in der Forschungsplattform des MS-Registers gespeichert (siehe Extraeinwilligung MS-Register). Ihre Einwilligung und die Teilnahme Ihres Zentrums am MS-Register vorausgesetzt, werden Ihre Daten gemeinsam mit dem Gesamtdatenbestand des MS-Registers, entsprechend Ihrer Einwilligung, ausgewertet. Die Daten können darüber hinaus der wissenschaftlichen Öffentlichkeit zugänglich gemacht werden, damit unsere Ergebnisse überprüft und gegebenenfalls auch mit anderen Ergebnissen verglichen werden können. Dazu werden die Daten anonymisiert, sodass keine Identifizierung mehr möglich ist. Stimmen Sie im Falle des Widerrufs Ihrer Einwilligungserklärung einer Weiterverwendung Ihrer sicher anonymisierten Daten nicht zu, ist eine Teilnahme an der Studie nicht möglich.

Teilnahme, Haftung, Versicherung, Aufwandsentschädigung

Die Teilnahme an der Studie ist freiwillig. Sie können Ihre Einwilligung jederzeit und ohne Angabe von Gründen widerrufen, ohne dass dadurch Nachteile für Sie entstehen.

Da es sich nicht um eine Studie zur Prüfung eines neuen Arzneimittels oder Medizinproduktes oder eines neuen Anwendungsgebietes handelt, ist keine besondere Studienversicherung (Probandenversicherung) zur Gefährdungshaftung vorgesehen. Es gelten die allgemeinen Haftungsgrundsätze.

Die wissenschaftliche Leitung hat Prof. Dr. med. Christoph Heesen (Telefon: 040-7410-53776). Die Studienkoordinatorin ist Nicole Krause (Telefon: 040-7410-54077). Sollten Sie noch weitere Fragen haben, stehen Ihnen der Versuchsleiter und die Studienkoordinatorin zur Beantwortung gerne zur Verfügung.

Für die Teilnahme an dieser Studie können keinerlei finanzielle Aufwandsentschädigungen gewährt werden.

Wir würden uns sehr freuen, wenn Sie dieses Projekt durch Ihre Teilnahme unterstützen.

Mit freundlichen Grüßen

Prof. Dr. med. Christoph Heesen Nicole Krause

Datenschutzerklärung

Die erhobenen Daten unterliegen der Schweigepflicht und den datenschutzgesetzlichen Bestimmungen. Die Daten werden ausschließlich für wissenschaftliche Zwecke verwendet. Zugriff auf diese Daten haben die Projektleiter/Innen. Die Datenauswertung erfolgt durch Prof. Dr. Heesen und seine explizit autorisierten Mitarbeiter ohne Bezug zu den persönlichen Daten der Studienteilnehmer. Die in den Studien erhobenen Daten werden in pseudonymisierter[1] Form ausgewertet und für die Dauer von 10 Jahren gespeichert. Bei der Pseudonymisierung wird dem richtigen Namen ein Pseudonym (also ein Nummern- und Buchstabencode, z.B. A01, B01) zugeordnet. In den Dokumenten wird nur auf das Pseudonym und nicht auf den Namen verwiesen, sodass personenbezogene Daten nicht oder nur durch einen unverhältnismäßig großen Aufwand einer bestimmten Person zugeordnet werden können. Die personenbezogenen Daten sind gegen unbefugten Zugriff gesichert. Nach Beendigung der Studie werden die Tonaufnahmen der Interviews vernichtet. Ein individueller Widerruf der Erlaubnis zur Verwendung Ihrer Daten ist jederzeit möglich.

Eine Weitergabe der erhobenen Daten im Rahmen der Studie erfolgt nur in anonymisierter[2] Form. Die beteiligten Personen sind zur Verschwiegenheit verpflichtet. Gleiches gilt für die Veröffentlichung der Studienergebnisse.

Die Studienteilnehmer/innen haben das Recht, über die von Ihnen erhobenen personenbezogenen Daten Auskunft zu verlangen und über möglicherweise anfallende personenbezogene Ergebnisse der Studie ggf. informiert zu werden.
Diese Studie ist auch durch die zuständige Ethik-Kommission der Ärztekammer Hamburg beraten worden. Der zuständigen Landesbehörde kann ggf. Einsichtnahme in die Studienunterlagen gewährt werden. Im Falle des Widerrufs Ihrer Einwilligungserklärung werden die bereits erhobenen anonymisiert[2] und in dieser Form weiter genutzt.

[1] *Pseudonymisieren ist das Ersetzen des Namens und anderer Identifikationsmerkmale durch ein Kennzeichen zu dem Zweck, die Identifizierung des Betroffenen auszuschließen oder wesentlich zu erschweren (§ 3 Abs. 6a Bundesdatenschutzgesetz).*

[2] *Anonymisieren ist das Verändern personenbezogener Daten derart, dass die Einzelangaben über persönliche oder sachliche Verhältnisse nicht mehr oder nur mit einem unverhältnismäßig großen Aufwand an Zeit, Kosten und Arbeitskraft einer bestimmten oder bestimmbaren natürlichen Person zugeordnet werden können (§ 3 Abs. 6 Bundesdatenschutzgesetz).*

Ergänzende Information für Studienteilnehmer gemäß Europäischer Datenschutz-Grundverordnung[3]:

Hiermit informieren wir Sie über die in der DSGVO festgelegten Rechte (Artikel 12 ff. DSGVO)**:**

Rechtsgrundlage: Die Rechtsgrundlage zur Verarbeitung der Sie betreffenden personenbezogenen Daten bildet bei klinischen Studien Ihre freiwillige schriftliche Einwilligung gemäß DSGVO sowie der Deklaration von Helsinki (Erklärung des Weltärztebundes zu den ethischen Grundsätzen für die medizinische Forschung am Menschen) und der Leitlinie für Gute Klinische Praxis. Zeitgleich mit der DSGVO tritt in Deutschland das überarbeitete Bundesdatenschutzgesetz (BDSG-neu) in Kraft.

Für die Datenverarbeitung verantwortliche Person: Der Studienleiter des Universitätsklinikums Hamburg-Eppendorf: **Prof. Dr. Christoph Heesen**

Recht auf Auskunft: Sie haben das Recht auf Auskunft über die Sie betreffenden personenbezogenen Daten, die im Rahmen der klinischen Studie erhoben, verarbeitet oder ggf. an Dritte übermittelt werden (Aushändigen einer kostenfreien Kopie) (Artikel 15 DSGVO, §34 BDSG-neu).

Recht auf Berichtigung: Sie haben das Recht, Sie betreffende unrichtige personenbezogene Daten berichtigen zu lassen (Artikel 16 und 19 DSGVO).

Recht auf Löschung: Sie haben das Recht auf Löschung Sie betreffender personenbezogener Daten, z. B. wenn diese Daten für den Zweck, für den sie erhoben wurden, nicht mehr notwendig sind (Artikel 17 und 19 DSGVO, §35 BDSG-neu).

Recht auf Einschränkung der Verarbeitung: Unter bestimmten Voraussetzungen haben Sie das Recht, eine Einschränkung der Verarbeitung zu verlangen, d.h. die Daten dürfen nur gespeichert, aber nicht verarbeitet werden. Dies müssen Sie beantragen. Wenden Sie sich hierzu bitte an Ihren Studienleiter oder an den Datenschutzbeauftragten des Prüfzentrums (Artikel 18 und 19 DSGVO).

Recht auf Datenübertragbarkeit: Sie haben das Recht, die Sie betreffenden personenbezogenen Daten, die Sie dem Verantwortlichen für die klinische Studie bereitgestellt haben, zu erhalten. Damit können Sie beantragen, dass diese Daten entweder Ihnen oder, soweit technisch möglich, einer anderen von Ihnen benannten Stelle übermittelt werden (Artikel 20 DSGVO).

Widerspruchsrecht: Sie haben das Recht, jederzeit gegen konkrete Entscheidungen oder Maßnahmen zur Verarbeitung der Sie betreffenden personenbezogenen Daten Widerspruch einzulegen (Art 21 DSGVO, § 36BDSG-neu). Eine solche Verarbeitung findet anschließend grundsätzlich nicht mehr statt.

Einwilligung zur Verarbeitung personenbezogener Daten und Recht auf Widerruf dieser Einwilligung: Die Verarbeitung Ihrer personenbezogenen Daten ist nur mit Ihrer Einwilligung rechtmäßig (Artikel 6 DSGVO). Sie haben das Recht, Ihre Einwilligung zur Verarbeitung personenbezogener Daten jederzeit zu widerrufen. Im Falle des Widerrufs müssen Ihre personenbezogenen Daten grundsätzlich gelöscht werden (Artikel 7, Absatz 3 DSGVO). Es gibt allerdings Ausnahmen, nach denen die bis zum Zeitpunkt des Widerrufs erhobenen Daten

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[3] Verordnung (EU) 2016/679 des Europäischen Parlaments und des Rates vom 27. April 2016 zum Schutz natürlicher Personen bei der Verarbeitung personenbezogener Daten, zum freien Datenverkehr und zur Aufhebung der Richtlinie 95/46/EG (Datenschutz-Grundverordnung)

weiter verarbeitet werden dürfen, z.B. wenn die weitere Datenverarbeitung zur Erfüllung einer rechtlichen Verpflichtung erforderlich ist (Art. 17 Abs. 3 b DSGVO).

Möchten Sie eines dieser Rechte in Anspruch nehmen, wenden Sie sich bitte an den Studienleiter Ihres Prüfzentrums.

Außerdem haben Sie das **Recht, Beschwerde bei einer Aufsichtsbehörde/n einzulegen,** wenn Sie der Ansicht sind, dass die Verarbeitung der Sie betreffenden personenbezogenen Daten gegen die DSGVO verstößt. Wenn Sie Bedenken hinsichtlich des Umgangs mit Ihren personenbezogenen Datenhaben, können Sie sich an die für Sie zuständige Datenschutzbehörde wenden:

Die für das UKE beauftragte Behörde	**Datenschutz-Aufsichtsbehörde**
Datenschutzbeauftragter des Universitätsklinikums Hamburg-Eppendorf	Hamburgische Beauftragte für Datenschutz und Informationsfreiheit
Matthias Jaster	
Martinistraße 52 20246 Hamburg 040 / 7410 - 56890	Ludwig-Erhard-Str. 22 20459 Hamburg 040 / 42854 - 4040
m.jaster@uke.de	mailbox@datenschutz.hamburg.de

Einwilligungserklärung zur Teilnahme an der Studie POWER@MS1

Teilnehmer, Teilnehmerin (Name in Druckbuchstaben):

……..

Bitte ankreuzen und unterschreiben

O Hiermit willige ich zur freiwilligen Teilnahme an der Studie ein.

Ich wurde mündlich ausführlich und verständlich über das Anliegen, die Bedeutung und die Tragweite der Studie aufgeklärt. Das Informationsschreiben zur Studie und zum Umgang mit den erfassten Daten habe ich gelesen und verstanden. Meine Fragen zur Studie wurden erläutert und beantwortet.

Zur Einwilligung hatte ich ausreichend Zeit. Meine Teilnahme ist freiwillig und kann jederzeit ohne Angaben von Gründen widerrufen werden, ohne dass für mich Nachteile entstehen. Ich habe keinerlei Kosten oder finanziellen Nutzen durch die Teilnahme an dieser Studie. Es gelten die Richtlinien des Datenschutzes.

Eine Kopie der Einwilligungserklärung habe ich erhalten und erkläre hiermit meine freiwillige Teilnahme an dieser Studie.

Ort, Datum	Unterschrift des Teilnehmers / der Teilnehmerin
……	……
Ort, Datum	Unterschrift des Arztes
……	……

SPIRIT

STANDARD PROTOCOL ITEMS: RECOMMENDATIONS FOR INTERVENTIONAL TRIALS

SPIRIT 2013 Checklist: Recommended items to address in a clinical trial protocol and related documents*

Section/item	Item No	Description	Addressed on page number
Administrative information			
Title	1	Descriptive title identifying the study design, population, interventions, and, if applicable, trial acronym	1
Trial registration	2a	Trial identifier and registry name. If not yet registered, name of intended registry	2
	2b	All items from the World Health Organization Trial Registration Data Set	N/A
Protocol version	3	Date and version identifier	1
Funding	4	Sources and types of financial, material, and other support	12
Roles and responsibilities	5a	Names, affiliations, and roles of protocol contributors	1
	5b	Name and contact information for the trial sponsor	12
	5c	Role of study sponsor and funders, if any, in study design; collection, management, analysis, and interpretation of data; writing of the report; and the decision to submit the report for publication, including whether they will have ultimate authority over any of these activities	12
	5d	Composition, roles, and responsibilities of the coordinating centre, steering committee, endpoint adjudication committee, data management team, and other individuals or groups overseeing the trial, if applicable (see Item 21a for data monitoring committee)	11

Introduction			
Background and rationale	6a	Description of research question and justification for undertaking the trial, including summary of relevant studies (published and unpublished) examining benefits and harms for each intervention	2-3
	6b	Explanation for choice of comparators	6
Objectives	7	Specific objectives or hypotheses	3
Trial design	8	Description of trial design including type of trial (eg, parallel group, crossover, factorial, single group), allocation ratio, and framework (eg, superiority, equivalence, noninferiority, exploratory)	3-4
Methods: Participants, interventions, and outcomes			
Study setting	9	Description of study settings (eg, community clinic, academic hospital) and list of countries where data will be collected. Reference to where list of study sites can be obtained	4
Eligibility criteria	10	Inclusion and exclusion criteria for participants. If applicable, eligibility criteria for study centres and individuals who will perform the interventions (eg, surgeons, psychotherapists)	4
Interventions	11a	Interventions for each group with sufficient detail to allow replication, including how and when they will be administered	4-6
	11b	Criteria for discontinuing or modifying allocated interventions for a given trial participant (eg, drug dose change in response to harms, participant request, or improving/worsening disease)	6
	11c	Strategies to improve adherence to intervention protocols, and any procedures for monitoring adherence (eg, drug tablet return, laboratory tests)	5
	11d	Relevant concomitant care and interventions that are permitted or prohibited during the trial	6
Outcomes	12	Primary, secondary, and other outcomes, including the specific measurement variable (eg, systolic blood pressure), analysis metric (eg, change from baseline, final value, time to event), method of aggregation (eg, median, proportion), and time point for each outcome. Explanation of the clinical relevance of chosen efficacy and harm outcomes is strongly recommended	6-9
Participant timeline	13	Time schedule of enrolment, interventions (including any run-ins and washouts), assessments, and visits for participants. A schematic diagram is highly recommended (see Figure)	9

Sample size	14	Estimated number of participants needed to achieve study objectives and how it was determined, including clinical and statistical assumptions supporting any sample size calculations	9
Recruitment	15	Strategies for achieving adequate participant enrolment to reach target sample size	9

Methods: Assignment of interventions (for controlled trials)

Allocation:			
Sequence generation	16a	Method of generating the allocation sequence (eg, computer-generated random numbers), and list of any factors for stratification. To reduce predictability of a random sequence, details of any planned restriction (eg, blocking) should be provided in a separate document that is unavailable to those who enrol participants or assign interventions	9
Allocation concealment mechanism	16b	Mechanism of implementing the allocation sequence (eg, central telephone; sequentially numbered, opaque, sealed envelopes), describing any steps to conceal the sequence until interventions are assigned	9
Implementation	16c	Who will generate the allocation sequence, who will enrol participants, and who will assign participants to interventions	9
Blinding (masking)	17a	Who will be blinded after assignment to interventions (eg, trial participants, care providers, outcome assessors, data analysts), and how	9
	17b	If blinded, circumstances under which unblinding is permissible, and procedure for revealing a participant's allocated intervention during the trial	N/A

Methods: Data collection, management, and analysis

Data collection methods	18a	Plans for assessment and collection of outcome, baseline, and other trial data, including any related processes to promote data quality (eg, duplicate measurements, training of assessors) and a description of study instruments (eg, questionnaires, laboratory tests) along with their reliability and validity, if known. Reference to where data collection forms can be found, if not in the protocol	10
	18b	Plans to promote participant retention and complete follow-up, including list of any outcome data to be collected for participants who discontinue or deviate from intervention protocols	10

Data management	19	Plans for data entry, coding, security, and storage, including any related processes to promote data quality (eg, double data entry; range checks for data values). Reference to where details of data management procedures can be found, if not in the protocol	10
Statistical methods	20a	Statistical methods for analysing primary and secondary outcomes. Reference to where other details of the statistical analysis plan can be found, if not in the protocol	10-11
	20b	Methods for any additional analyses (eg, subgroup and adjusted analyses)	10
	20c	Definition of analysis population relating to protocol non-adherence (eg, as randomised analysis), and any statistical methods to handle missing data (eg, multiple imputation)	10-11
Methods: Monitoring			
Data monitoring	21a	Composition of data monitoring committee (DMC); summary of its role and reporting structure; statement of whether it is independent from the sponsor and competing interests; and reference to where further details about its charter can be found, if not in the protocol. Alternatively, an explanation of why a DMC is not needed	11
	21b	Description of any interim analyses and stopping guidelines, including who will have access to these interim results and make the final decision to terminate the trial	11
Harms	22	Plans for collecting, assessing, reporting, and managing solicited and spontaneously reported adverse events and other unintended effects of trial interventions or trial conduct	11
Auditing	23	Frequency and procedures for auditing trial conduct, if any, and whether the process will be independent from investigators and the sponsor	11
Ethics and dissemination			
Research ethics approval	24	Plans for seeking research ethics committee/institutional review board (REC/IRB) approval	2, 11, 12
Protocol amendments	25	Plans for communicating important protocol modifications (eg, changes to eligibility criteria, outcomes, analyses) to relevant parties (eg, investigators, REC/IRBs, trial participants, trial registries, journals, regulators)	12

Consent or assent	26a	Who will obtain informed consent or assent from potential trial participants or authorised surrogates, and how (see Item 32)	11
	26b	Additional consent provisions for collection and use of participant data and biological specimens in ancillary studies, if applicable	N/A
Confidentiality	27	How personal information about potential and enrolled participants will be collected, shared, and maintained in order to protect confidentiality before, during, and after the trial	10, 11
Declaration of interests	28	Financial and other competing interests for principal investigators for the overall trial and each study site	12
Access to data	29	Statement of who will have access to the final trial dataset, and disclosure of contractual agreements that limit such access for investigators	11
Ancillary and post-trial care	30	Provisions, if any, for ancillary and post-trial care, and for compensation to those who suffer harm from trial participation	N/A
Dissemination policy	31a	Plans for investigators and sponsor to communicate trial results to participants, healthcare professionals, the public, and other relevant groups (eg, via publication, reporting in results databases, or other data sharing arrangements), including any publication restrictions	2, 11
	31b	Authorship eligibility guidelines and any intended use of professional writers	11
	31c	Plans, if any, for granting public access to the full protocol, participant-level dataset, and statistical code	11
Appendices			
Informed consent materials	32	Model consent form and other related documentation given to participants and authorised surrogates	Appendix II°
Biological specimens	33	Plans for collection, laboratory evaluation, and storage of biological specimens for genetic or molecular analysis in the current trial and for future use in ancillary studies, if applicable	N/A

*It is strongly recommended that this checklist be read in conjunction with the SPIRIT 2013 Explanation & Elaboration for important clarification on the items. Amendments to the protocol should be tracked and dated. The SPIRIT checklist is copyrighted by the SPIRIT Group under the Creative Commons "Attribution-NonCommercial-NoDerivs 3.0 Unported" license.

°Available in German.