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Statistical Analysis Plan

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Interactive Web Platform for EmPOWERment in Early Multiple Sclerosis

POWER@MS1

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Sponsor	University Medical Centre Hamburg Eppendorf Martinistraße 52 20246 Hamburg, Germany
Coordinating Investigator	Prof. Dr. Christoph Heesen Institute of Neuroimmunology and Multiple Sclerosis University Medical Centre Hamburg Eppendorf Martinistraße 52 20246 Hamburg

Approval of the Statistical Analysis Plan

Interactive Web Platform for EmPOWERment in Early Multiple Sclerosis (POWER@MS1)

Protocol Version No: 1.0/22.06.2023

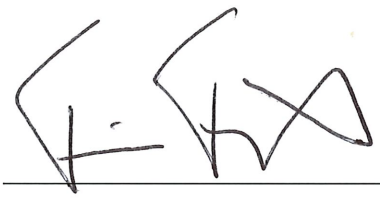
Coordinating Investigator Prof. Dr. Christoph Heesen	14.07.2023 Date	 Signature
Biostatistician Prof. Dr. Tim Friede	13.07.2023 Date	 Signature

Table of Contents

List of Figures

No table of figures entries found.

List of Tables

List of Abbreviations

BSA-F	*Physical Activity, Exercise and Sport Questionnaire (Bewegungs- und Sportaktivität Fragebogen)*
CG	Control group
CI	Confidence interval
CPS	*Control Preference Scale*
EBPI	Evidence-based patient information
EDSS	*Expanded Disability Status Scale*
EQ-5D-5L	*EuroQol 5-Dimension 5-Level*
GLTEQ	*Godin Leisure-Time Exercise Questionnaire*
HAQUAMS	*Hamburg Quality of Life in Multiple Sclerosis Scale*
HADS	*Hospital Anxiety and Depression Scale*
HR	Hazard ratio
IG	Intervention group
MS	Multiple sclerosis
PAM	*Patient Activation Measure*
PwMS	Persons with MS
RCT	Randomised controlled trial
RIKNO	*Risk Knowledge in Relapsing Multiple Sclerosis*
RMS	Relapsing multiple sclerosis

1 Introduction

This document has been written based on the study protocol version 1.3 from 16.02.2021. A design paper was published (Krause N, Riemann-Lorenz K, Steffen T, *et al*., 2021).

1.1 Background and Rationale

Multiple Sclerosis (MS) is an inflammatory and degenerative disease of the central nervous system that affects more than 200,000 people in Germany and mostly young adults. In about 85% of the persons with MS (PwMS), MS first progresses in relapses, later chronically progressive. In addition, considerable neuropsychiatric symptoms such as depression, fatigue and cognitive problems may occur in the course of the disease. Uncertainty and the resulting psychological stress in turn may have a negative effect on MS disease activity.

POWER@MS1 aims to encourage patients with MS to find the best way of dealing with the disease based on evidence-based patient information (EBPI) and a complex behaviour change programme (EBBC programme). The web-based EBBC programme is based on the Artificial Intelligence-based software platform broca® and will serve as a disease accompanying empowerment programme with 16 modules for persons at an early stage of MS.

1.2 Objectives and Endpoints

This study investigates the hypothesis that behavioural and web-based information on immunotherapy decision making, disease management, and lifestyle can reduce the inflammatory disease activity in MS and change patient behaviour.

Clinical endpoints are evaluated by the trial statistician, while endpoints related to health economic aspects of the trial are evaluated by the health economics team and therefore not specified in this SAP. Primary and secondary endpoints are listed in Table 1.

Table 1 Objectives and related endpoints

	Objective	**Endpoint**
Primary	To determine whether the EBBC programme reduces inflammatory disease activity in MS and changes patient behaviour.	Time to a new T2-lesion or new relapse.
Secondary	To determine the impact of the EBBC programme on patient autonomy and empowerment.	Change in the PAM from baseline to 12 months.
	To determine whether the EBBC programme promotes informed decisions on immunotherapy.	Comparison of the CPS after 12 months as well as after reaching the primary endpoint.
	To determine the impact of the EBBC programme on quality of life.	Change in the HAQUAMS from baseline to 12 months. Change in the EQ-5D-5L.

	Objective	Endpoint
	To determine whether the EBBC programme reduces anxiety and depression.	Change in the HADS from baseline to 12 months.
	To determine whether the EBBC programme leads to an increase in physical activity and a healthy dietary behaviour.	Change in the Readiness to change from baseline to 12 months. Change in GLTEQ from baseline to 12 months. Change in the BSA from baseline to 12 months. Change in food group (Questionnaire of healthy diet) from baseline to month 3 and to 12 month. Change in nutrient intake (myfood24) from baseline to 12 month.

1.3 Primary objective and endpoint

To determine the impact of the intervention programme on disease activity, the time to a new relapse or a new lesion on T2-weighted MRI images as surrogate for inflammatory disease activity is used. An experienced, blinded rater will evaluate MRI scans. Participating neurologists will clinically evaluate relapses. The characteristic of the relapse, e.g. duration of complaints, symptoms and degree of impairment, is assessed. In case of relapse or new T2 lesions, the primary endpoint is formally reached. However, study participants were asked to remain in the study.

1.4 Secondary objective and endpoint

Key secondary endpoint is quality of life measured by the HAQUAMS. Secondary endpoints are given in Table 1. For further details on the definition of the endpoints, see Section 5.1.

2 Study methods

2.1 Trial design

Power@MS1 is a national, multicentre, investigator-blinded, interventional, randomised controlled, parallel group trial with multiple measurement time points. The intervention group (IG) received access to the EBBC programme, while the control group (CG) received access to an information platform based on information material from the German Multiple Sclerosis Society with optimised standard care.

2.2 Randomization

PwMS are randomized in a 1:1 ratio to either intervention or control group by block randomisation through a computer-generated system in secuTrial®. After the amendment, the therapy status was

used for stratification. All patients, that were included and randomized before the amendment, were therapy naive.

2.3 Sample Size

One event (relapse or at least one new T2 lesion) is expected in every second PwMS within 12 month in the CG. The 100 events result in a statistical power of 85% for a two-sided significance level of 5%. The assumed HR of 0.55 represents a reduction of 45% by IG compared with the CG. With a mean observation time of 12 month, the 100 events can be expected to be observed in 262 PwMS. Due to the assumption of 20% drop-outs over 1 year, it was plant to randomise 328 PwMS (164 per group).

The blinded sample size recalculation report dated on 15th September 2021 is based on a blinded data export of August 16th 2021 comprising events of 135 included patients at that time (Kloid and Friede, 2021). In the first definition of the primary endpoint events, only definite relapses were counted. In the second definition, possible relapses were counted, additionally. The first definition resulted in 46 primary endpoint events, while the second resulted in 51 primary endpoint events. The calculation of event rates according to the first definition and an assumed dropout rate of 20% resulted in 250 PwMS (125 per group) that have to be randomized. The calculation of event rates according to the second definition and an assumed dropout rate of 20% resulted in 216 PwMS (108 per group) that have to be randomized. The blinded sample size recalculation report resumed, that a sample size of at least 240 PwMS should be targeted.

2.4 Framework

All endpoints are tested for superiority of the intervention programme over control.

2.5 Statistical Interim Analyses and Stopping Guidance

As no significant harms are to be expected, no stopping guidelines are planned.

2.6 Timing of the Final Analysis

The final analysis will take place when all outcomes have been collected and the database is locked.

2.7 Timing of Outcome Assessments

Data is collected over a period of 12 months, with a flexible follow-up of up to 24 months in early recruited PwMS. Several measurement time points for outcome assessment are intended. They are calculated based on the randomization date: t_1 and t_0 take place before randomization; V_1 is scheduled in month 1 (30 days after randomization), V_2 in Month 3 (+90 days), V_3 in Month 6 (+180 days), V_4 in Month 12 (+365 days). For early recruited PwMS, V_5 takes place in Month 18 and V_6 in Month 24. After reaching the primary endpoint, t_x takes place. Deviations from the ideal time point are allowed to the degree of ± 28 days. Table 2 displays the assessment of variables within these time points.

Table 2 Assessments and measurement time points

Instrument	Measurement time points								
	t_{-1}	t_0	V_1	V_2	V_3	V_4	V_5^*	V_6^*	t_x
Demographic Data	X								
MRI		X		X	X	X	X	X	
Clinical visit		X	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			
RIKNO				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-F		X				X			
Questionnaire of healthy diet		X		X		X			
myfood24		X				X			
Process evaluation	X	X	X	X	X	X	X	X	
Health economic parameters		X			X	X	X	X	

*Only in in early recruited PwMS.

3 Statistical Principles

3.1 Confidence intervals and p-values

All tests will be performed two-sided with 5% significance level. Confidence intervals (CI) will be reported with 95% confidence level.

3.2 Adherence and protocol deviations

In order to ensure patient adherence, the usage of the IG and CG programme is monitored biweekly and reacted on after 4 weeks of non-usage.

3.3 Analysis populations

The primary analysis will follow the intention-to-treat (ITT) principle. The ITT population contains all randomised patients.

The modified ITT contains all randomised patients with at least one registration in the programme. The per protocol population contains all randomised patients that used the programme regularly and reached the endpoints.

4 Trial population

4.1 Screening data

Screening data will be reported and described within a CONSORT flowchart.

4.2 Eligibility

Persons aged between 18 and 65 years with clinically isolated syndrome, suspected or confirmed MS for less than 12 months and signed informed consent, will be included. Study participants must have at least two MS-typical lesions on T2-weighted images on MRI scans and MS typical cerebrospinal fluid finding with detection of oligoclonal bands. Furthermore, access to the internet and ability to use websites is mandatory.

PwMS who are not able to provide informed consent or have a substantial psychiatric disorder or a severe cognitive deficit will be excluded. Corticosteroid therapy within 4 weeks prior to study inclusion, pregnancy and claustrophobia lead to exclusion.

4.3 Recruitment

Recruitment numbers will be summarized within a CONSORT flow diagram.

4.4 Withdrawal/follow-up

Reasons for study withdrawal will be documented using a CONSORT flowchart.

4.5 Baseline patient characteristics

All baseline patient characteristics will be summarized using descriptive statistics (e.g. mean, standard deviation, median, IQR for continuous variables and frequencies (percentages) for categorical variables) and appropriate graphical methods (e.g. boxplots, histograms, barplots) depending on the data type.

5 Analysis

5.1 Outcome definitions

A full list of outcomes and their timing is described in Section 2.7.

MRI lesion: The lesions are counted on T2-weighted MRI images. An experienced, blinded rater will evaluate MRI scans. At *baseline*, in the case that the number of lesions cannot be accurately determined, the number of lesions is set on 11 if there are more than 10 and less than 20 lesions (analog for every increment of ten). The during follow-up observed lesions are exactly counted.

Hamburg Quality of Life in MS Scale Version 10.0 (HAQUAMS) is a questionnaire for measuring quality of life in PwMS (Gold *et al.*, 2001). It consists of 44 items with mostly 5-point-likert scale. Twenty-eight of the items are subdivided into the six subscales:

- Fatigue: Items 6, 7, 8, 9
- Cognition: Items 10, 11, 12, 13
- Lower extremity: Items 17,18,19, 20
- Upper extremity: Items 21, 22, 23, 24, 25
- Communication: Items 29, 30, 31, 32, 33, 34
- Mood: Items 36, 37, 38, 39, 40.

Mean subscale scores are calculated, the total score is built by calculating the mean of the subscale score means: *HAQUAMS total score = mean(mean(upper extremity), mean(lower extremity), mean(fatigue), mean(cognition), mean(communication), mean(mood))*. A high total score indicates low quality of life. In case of missing data, mean substitutions are allowed for missing items.

EuroQol 5-Dimension 5-Level (EQ-5D-5L) is used to measure quality of life additionally and to calculate quality-adjusted life years (QALYs). It generates a descriptive health profile by a 5-digit code with 3125 possible health states assessing the domains mobility, self-care, usual activities, pain/discomfort, and anxiety/depression with 5-point-likert scaled responses from no problems (1) to extreme problems (5) (Herdman, 2011). This health state is transformed into index values using the German validation set. Additionally, the health on the examination day is raised on a scale ranging from 0 (worst health) to 100 (best health) (EuroQol Research Foundation, 2019).

An abbreviated 10-item version of the **Risk Knowledge in Relapsing Multiple Sclerosis V.2.0 (RIKNO)** is used to assess the risk knowledge (Heesen, 2017). Each item of the RIKNO is scored on a scale from 0 to 2. The total RIKNO score is calculated by summing the scores of all 10 items, ranging from 0 to 20, with higher scores indicating greater knowledge.

Control Preference Scale (CPS) is used to assess decision quality, preferred and realised role preference in decision discussion concerning immunotherapy (Degner, 1997). It consists of five response options ranging from completely passive to fully active.

Immunotherapy status is raised. If immunotherapy is started during the trial period, type, use and adherence rates will be collected during the clinical visits.

Patient Activation Measure (PAM) is used to measure the extent of patient activation (Hibbard, 2004). It consists of 13 questions and assesses the confidence and knowledge to take action in managing health and healthcare. The item scales range from 1 (Disagree at all) to 4 (Fully agree). The raw score is the sum of the items divided by the number of answered questions (excepting non-applicable items) and multiplied with 13. Afterwards the scale is transformed to a range from 0 to 100 (Moljord, 2015).

PAM13 calculation expressed as formula: $100 \times \frac{\left(\left(\frac{sum\ score}{Number\ of\ answered\ questions} \times 13\right) - 13\right)}{(52-13)}$

Items 1, 3 and 4 presented in Bann *et* al., are used to measure changes in empowerment and range from 1 (disagree at all) to 4 (agree fully).

Items 10 and 24 of the **Coping Self-efficacy Scale (CSE)** are used to assess the coping capability in order to measure extent of patient activation (Chesney, 2006). The items range from 1 (Disagree at all) to 4 (agree fully).

Readiness to change is used to determine the interventions impact on willingness to change fruit and vegetable consumption resp. physical activity (Lippke, 2009). The stages are non-intenders (pre-contemplation/contemplation), intenders (preparation) and actors (action/maintenance).

Hospital Anxiety and Depression Scale (HADS) is a self-reported questionnaire and is used as a measure for depression and anxiety (Zigmond, 1983). It consists of two 7-item subscales, one for anxiety and one for depression, with a maximum score of 21 for each subscale (each item is scoring from 0 to 3), with higher scores representing higher levels of anxiety or depression. A maximum of one missing item per subscale can be estimated by the rounded mean of the six remaining items of the same subscale.

Expanded Disability Status Scale (EDSS) measures the disability in MS and is determined by the treating neurologist (Kurtzke, 1983). It ranges from 0 to 10 in half-point increments, with higher scores indicating greater disability.

Godin Leisure-Time Exercise Questionnaire (GLTEQ) is a self-reported questionnaire used to assess an individual's leisure-time physical activity levels over the previous seven days (Shephard, 1997). The *Weekly Leisure-Time Activity Score* and the *Health Contribution Score* are the sum of the product of weekly frequency and intensity of physical activity (strenuous, moderate, mild) with more than 15 minutes duration:
Weekly Leisure-Time Activity Score = $(9 \times Strenuous) + (5 \times Moderate) + (3 \times Mild)$,
Health Contribution Score = $(9 \times Strenuous) + (5 \times Moderate)$.
The Health Contribution Score can be classified into insufficiently active (<14), moderately active (14-23) and active (≥24).

Physical Activity, Exercise and Sport Questionnaire (BSA-F) is used to measure engagement in regular exercise activity within the past 4 weeks (Fuchs, 2015). BSA is a self-report questionnaire designed to assess physical activity levels in adults that includes 17 items asking about the frequency, duration, intensity and type of physical activities at work and during leisure as well as sports activity. The *total score for physical activity at work* is the sum of the received points for seated work (none = 3, rather little = 2, rather more = 1, much = 0), moderate and intense movement (none = 0, rather little = 1, rather more = 2, much = 3). The *physical activity in leisure score* is the total of the products of frequency and duration for the first seven items divided by four (unit: minutes/week). The *sports activity score* is the total of the products of frequency and duration divided by four (unit: minutes/week). The *physical activity during leisure* and *sports activity score* give the *total activity during leisure score* (only calculated both scores are available). This score can be classified into little (< 30 minutes/week), medium ($30 - 120$ minutes/week) and much (≥ 120 minutes/week).

Questionnaire of Healthy Diet is used to measure the frequency of intake of characteristic food groups within the last 7 days (Jannasch, 2022). The number of portion/day or week is compared with current recommendations leading to the *diet score*. This score ranges from 0 to 10, with higher scores indicating better adherence to a healthy diet.

myfood24, a 24-hour dietary recall, is used to provide nutrient intake data (Wark, 2018). In each case, it is used three times within a period of 1-3 weeks (2 weekdays, 1 weekend day).

5.2 Analysis methods

In the analysis of primary and secondary endpoints, centres with fewer than 10 patients are pooled into one centre.

The primary endpoint is analysed using a Cox proportional hazard model that includes treatment and study centre as factors. The hazard ratio (HR) will be reported with 95% CIs and p-values testing the null hypothesis of no group differences ($H_0: HR = 1$). Kaplan-Meier curves for both groups will be used to illustrate the treatment effect. The proportional hazards assumption will be checked visually by graphical diagnostics including scaled Schoenfeld residuals.

```
library(survival)

SurvObj <- Surv(FU, prim.end, data = primEndpoint)
cox.regr <- coxph(SurvObj ~ intervention + site, data = primEndpoint)
summary(cox.regr)
# check ph assumption
test.ph <- cox.zph(cox.regr)
ggcoxzph(test.ph)
# plot KM curve
plot(survfit(cox.regr))
km.by.treat <- survfit(SurvObj ~ intervention, data = primEndpoint,
                       conf.type = "log-log")
```

Secondary endpoints will be analysed using group mean comparisons between the intervention groups (δ) adjusted for baseline assessments and centre in analysis of covariance (ANCOVA) models. Least square group differences will be reported with 95% CIs and p-values testing the null hypothesis of no intervention effect ($H_0: \delta = 0$).

```
library(emmeans)


mod.sec <- lm(var ~ intervention + var_baseline + site,
                        data = secEndpoints)
# report least square group differences
tmt.means <- emmeans(mod.sec, ~ intervention)
tmt.means
pairs(tmt.means)
```

Additionally, longitudinal assessed endpoints will be analysed using Gaussian linear models for repeated measures with intervention group, time, intervention-by-time interaction and study centre as factors and baseline score as a covariate (mixed model for repeated measurements, MMRM). The error terms are assumed to follow a multivariate normal distribution with unstructured covariance matrix. Least square group differences will be reported with 95% CIs and p-values testing the null hypothesis of no intervention effect ($H_0: \delta = 0$).

```
library(lme4)
library(car)
library(emmeans)

mod.sec <- lmer(var ~ baseline_var + intervention + time + intervention * time +
                  site + (1|Patient.Id), data = secEndpoints)
summary(mod.sec)
res <- Anova(mod.sec, type = "III", test.statistic = "F")
res
tmt.means <- emmeans(mod.sec, ~ intervention * time)
pairs(tmt.means)
```

For the Readiness to Change and the Control Preference Scale, ordinal regression with logit link (proportional odds model) will be used with intervention, study centre as covariates and for readiness to change the baseline value. The model assumption will be checked.

```
library(ordinal)
library(emmeans)

# Ordinal regression for the Readiness to Change
mod.sec <- clm(var_rtc ~ baseline_rtc + intervention + site, link = 'logit',
                   data = secEndpoints)
summary(mod.sec)
# Predicted marginal response probabilities stratified for baseline
emmeans(mod.sec, ~ var_rtc | intervention / baseline_rtc, mode = 'prob')

# Ordinal regression for the Control Preference Scale
mod.sec <- clm(cps ~ intervention + site, link = 'logit',
                  data = secEndpoints)
summary(mod.sec)

emmeans(mod.sec, ~ cps | intervention, mode = 'prob')

# Check model assumptions
nominal_test(mod.sec) # test partial proportional odds assumption
scale_test(mod.sec) # test for signs of scale effects
```

Data obtained through myfood24 will be used to analyse intake of selected nutrients of interest comparing mean changes in intake from baseline with post intervention between IG and CG, adjusting for baseline intake.

```
library(lme4)
library(emmeans)

mod.sec.food <- lmer(var_food ~ food_baseline + intervention + (1|Patient.Id),
                     data = secEndpoints)
# report least square group differences
tmt.means <- emmeans(mod.sec.food, ~ intervention)
pairs(tmt.means)
```

MRI lesion counts will be analysed using a negative binomial regression model adjusted for baseline MRI and centre and time to last observed lesion as offset. If observations are censored, the model would be adapted accordingly.

```
library(MASS)

mod.les <- glm.nb(lesions_fu ~ lesions_baseline + intervention + site +
                     offset(log(time_lastObs)), data = secEndpoints)
summary(mod.les)
tmt.means <- emmeans(mod.les, ~ intervention)
pairs(tmt.means)
```

5.3 Missing data

In case of missing data, all PwMS will be analysed following the intention-to-treat principle.

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 resp. follow-up assessments, multiple imputation will be applied. Predictive mean matching is used for imputing numeric, logistic regression for binary and polytomous logistic regression for nominal variables. The number of imputations will be set on five and the number of iterations for each imputation will be set on its default value of five.

5.4 Additional analyses

Subgroup and moderator variable analysis on lifestyle behaviour (smoker vs non-smoker, obese vs non-obese, physically active vs non-active) and on clinical characteristics (number of lesions, relapse rate, EDSS, early therapy vs no therapy, gender), are planned to be performed. The plausibility of the diet score is validated using the myfood24 data.

5.5 Harms

No safety data was recorded as no significant harms are to be expected.

5.6 Statistical software

All analyses will be performed in the current version of R or alternatively in SAS (version 9.4 or higher). All R packages are used in their current version and will be reported within the statistical report. For data visualization, *ggplot2* is used. For multiple imputation, *mice* is used.

5.7 References

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