Statistical Analysis Plan

UMIMS

Understanding Magnetic Resonance Imaging in Multiple Sclerosis (UMIMS)

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Abbreviations

EFS	Evalued for Safety Set
IEC	Independent Ethics Committee
IRB	Institutional Review Board
ITT	Intention-to-treat
MRI	Magnetic Resonance Imaging
MS	multiple sclerosis
PP	Per Protocol
pwMS	people with multiple sclerosis
SAP	Statistical Analysis Plan

1 Introduction

This Statistical Analysis Plan (SAP) is based on the study protocol version 2.0 of August 30, 2020 and follows the guideline for statistical analysis plans (Gamble, et al., 2017)
Some points of the statistical methods and of the study design are already described in the study protocol. This Statistical Analysis Plan (SAP) aims to further specify the procedures and statistical methods applied during the final analysis of the study data.

1.1 Background and rationale

While Magnetic Resonance Imaging (MRI) plays a major role in the lives of people with multiple sclerosis (pwMS), studies have shown that MRI-specific knowledge in pwMS is limited. Moreover, poor knowledge was associated with negative feelings towards MRI (e.g. anxiety concerning MRI scan). Because information sources about MRI in MS for pwMS are not available, we designed and evaluated an evidence-based online educational platform about MRI in MS called “Understanding MRI in MS” (UMIMS). Based on a pilot study in n=104 subjects, an educational intervention was found to be feasible and effective. We hypothesize, that MRI-specific knowledge can be increased by using UMIMS and that, subsequently, negative feelings towards MRI will be reduced and shared decision-making competences increased.

1.2 Objectives

This study investigates whether the UMIMS programme increases MRI-specific risk knowledge compared to the control group.

2 Study Methods

2.1 Trial design

This randomized, controlled, double-blinded trial aimed to recruit n=120 pwMS. The intervention group received access to UMIMS. The control group received access to a specifically developed control website, which visually imitates UMIMS, and contains the standard information available by several MS self-help organisations. The change in MRI-specific knowledge assessed via the MRI-risk knowledge questionnaire (MRI-RIKNO) after the intervention was the primary outcome at 2 weeks.

2.2 Randomization

Permuted-block randomization was computer generated and performed by a statistician not involved in the conduct of the study. In a previous study, analysis of covariance did not reveal an influence of sociodemographic variables on MRI knowledge, therefore no stratification took place except for study site.

2.3 Sample size

It was calculated, that n=120 participants would have to be recruited to detect a difference of 16.3 vs 14.5 points in the MRI-RIKNO questionnaire with a power of 90% given an alpha of 5% and taking into account a 20% dropout rate.

For a detailed description of the sample size considerations please refer to the sample size section of the design paper (Schiffmann, et al., 2020).

2.4 Framework

UMIMS is planned to show superiority of the UMIMS intervention compared to the control group regarding the primary outcome change in the MRI-RIKNO questionnaire.

2.5 Statistical interim analyses and stopping guidance

No interim analyses were planned.

2.6 Timing of final analysis

The final analysis of the primary outcome will take place after the database has been reviewed for completeness and accuracy and database lock.

2.7 Timing of outcome assessments

The primary outcome was assessed two weeks after randomization. For the timing of other major outcomes of the UMIMS trial, see Table 1 in the design paper (Schiffmann, et al., 2020).

3 Statistical Principles

3.1 Confidence intervals and *P* values

All applicable statistical tests will be two-sided and will be performed using a 5% significance level. Analyses of secondary outcomes will be performed without adjustment for multiplicity. All confidence intervals presented will be 95% and two-sided.

3.2 Adherence and protocol deviations

At any point, patients in both groups were able to quit the study. Patients who withdrew from the study were asked whether they agreed to continue to fill in a limited set of questionnaires related to the primary study outcome. The data of non-adherent participants (e.g. who did not log use the website or those with missing questionnaires) will be included in the intention-to-treat analysis.

3.3 Analysis populations

3.3.1 Intention to treat Population (ITT)

The primary analysis population is the ITT (intention to treat) population. The ITT population consists of all patients randomized.

3.3.2 Per Protocol population (PP)

The Per Protocol population includes all patients randomized who have no major protocol violation.

Major protocol violations are any unapproved changes in the research study design and/or procedures that are within the investigator's control and not in accordance with the IEC/IRB -approved protocol that may affect the participant's rights, safety or well-being, or the completeness, accuracy and reliability of the study data.

Major protocol violation includes ineligible participants who were included in the trial by mistake, and those for whom the intervention or other procedure differed from that outlined in the protocol, or failure of consent process.

3.3.3 Evaluated for Safety Set (EFS)

All randomized patients will be included into the Evaluated for Safety (EFS) set.

4 Trial Population

4.1 Eligibility

The number of ineligible participants recruited, if any, will be reported, with reasons for ineligibility.

4.2 Recruitment

The CONSORT diagram in Figure 1 of the design paper will be updated with the actual recruitment figures.

4.3 Withdrawal/follow-up

Patients who withdrew from the study were asked whether they agree to continue to fill in a limited set of questionnaires related to the primary study outcome. We inquired causes for study withdrawal and will report those in case of disclosure to clarify whether there are any differences between the intervention and control groups.

4.4 Baseline patient characteristics

Available baseline data consists of demographic data, medical history, and clinical information including, among others, information on symptom onset, year of diagnosis, level of disability and experience with MRI.

Categorical data will be summarised by numbers and percentages. Continuous data will be summarised by mean, SD, median, IQR and range. Number of available observations and number of missing observations will be presented.

5 Analysis

5.1 Outcome definitions

The primary endpoint is MRI-risk knowledge measured by the MRI-risk knowledge questionnaire 2.0 (MRI-RIKNO) (11). It comprises n=14 items (maximum score of n=22) concerning basic neuroanatomy and lesion knowledge, the MRI procedure and the meaning of MRI for diagnosis, prognosis and treatment control. MRI-risk knowledge will be assessed twice during the trial: t0 (allocation) and t1 (after a 2-week-access to the intervention or control website). The primary endpoint is change of MRI-RIKNO score from baseline to t1.

5.2 Analysis methods

5.2.1 Primary outcome

The primary outcome will be analysed as change from baseline with the baseline value as covariate and random group as fixed factor in a linear mixed model with center as random intercept to map the stratified randomisation scheme. This is a model refinement from

the originally intended ANCOVA model in the design paper, taking into account the recommendations of Kahan et al (Kahan & Morris, 2013) (Kahan & Morris, 2012) for the analysis of stratified randomised trials.

5.2.2 Secondary outcomes

The secondary outcomes will be reported according to their respective scale.

The continuous outcomes

- Emotions and attitude towards MRI, assessed using the validated questionnaire "MRI emotions and attitude" (MRI-EMA) at t0, t1and t2
- Perceived involvement in decisional encounters concerning MRI results and their consequences, evaluated with the Multifocal Approach to Sharing in Shared Decision Making (MAPPIN'SDM) evaluation at t2
- Quality of life (QoL), assessed using the subscales of the HAmburg QUAlity of life questionnaire in MS (HAQUAMS) using subscales fatigue, cognition, communication and mood at t3

will be analysed using linear mixed models with time and random group and their interaction term as fixed effects and center as random effect. The binary and ordinal outcomes "decisions on future MRIs and treatment changes as well as acceptance of the intervention, assessed from patients using a standardised questionnaire immediately at t2 and t3", and "Autonomy preference, assessed using the Control Preference Scale (CPS) at t0, t1 and t2" will be analysed using generalised logistic linear mixed models with the same covariate structure as above.

5.3 Missing data

Altman (Altman, 2009) addressed that there is no ideal method to address missing data. Therefore, different common imputation techniques will be applied and reported with as well as without imputation techniques as suggested by Altman (Altman, 2009). Multiple imputation techniques will be conducted in the sensitivity analysis.

5.4 Additional analyses

It is planned to externally evaluate the SDM process in a subgroup of at least n = 5 patients from both groups using audiotaped encounter.

5.5 Harms

The intervention website contains complex medical information, which has the potential to overwhelm participants. Additionally, it provides information on the prognostic value of MRI and participants may learn, that they fulfill negative prognostic criteria. However, our previous work has shown, that pwMS understand complex medical information and are able to cope with negative information. We do not foresee any other harm of the intervention. As relevant adverse events are unlikely, a data monitoring committee does not exist, no interim analyses are planned and no stopping rules will be applied. Nevertheless, safety measures are applied as tertiary endpoints to control for anxiety and depression.

5.6 Statistical software

- STATA 14 or newer
- R 4.1.1 or newer
- SPSS 25.0 or newer

6 References

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