Supplementary Online Content 4

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Statistical Analysis Plan

On-line Only Supplemental Material

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Statistical Analysis Plan (SAP)

Sepsis survivors monitoring and coordination in outpatient health care (SMOOTH)

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1. Background

1.1 Study design and objective

The study is a prospective, randomized, multicenter, two-armed intervention study to investigate whether health related quality of life of survivors of severe sepsis or septic shock can be improved by a specific disease management program compared to usual care. For details see references.

1.2 Data

Patients were randomized at ICU discharge. The targeted number of patients was 290.

At the following study visits, data was collected:

- **T-1:** Before sepsis (retrospective)
- **T0:** Baseline, at up to one month after ICU discharge
- **T1:** 1st follow-up at about 6 months after ICU discharge
- **T2:** 2nd follow-up at about 12 months after ICU discharge
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Primarily, data analysis follows the intention-to-treat (ITT) principle, i.e. all patients are analyzed in the group to which they are originally randomized, regardless whether the invention actually took place. Other patient populations will be considered later.

At the time of the primary analysis, which is described in this analysis plan, the biometricians are blinded concerning the two randomization groups.

2. Statistical analysis

2.1 Missing data and data quality

The number of missing values will be given for each variable and study visits analyzed. According to number and distribution of missing values, it will be discussed whether imputation is necessary. Values that are not available due to death or drop out of the patient are not considered as missing. The number of patients that dropped out or died at follow-up times are also presented.

Data quality will be inspected by plausibility checks. Implausible data will be double-checked in the original source data.

2.2 Baseline characteristics

Baseline characteristics will be given for all patients, treatment and control group. They include

- Sociodemographic characteristics: Age, sex, family status, education
- ICU stay: length of stay, renal replacement therapy and mechanical ventilation (if required), site of infection, Charlson comorbidity index, BMI
- Primary and secondary endpoints at baseline

For that, adequate statistics according to variable type will be used, such as arithmetic mean, median and IQR for continuous variables, number and percentage for discrete variables.

2.3 Primary endpoint

The primary outcome is the difference of the SF-36 (mental health) between T1 and baseline. It will be analyzed by a two-sided t-test with $\alpha=0.05$. If normal distribution cannot be assumed (after visual inspection) the Mann-Whitney U-test is applied.

2.4 Secondary endpoints

The following secondary endpoints will be analyzed:

- Difference of SF-36 (physical health) between T1-2 and baseline
- Difference of all SF-36 subscales (physical functioning, physical role function, bodily pain, general health perceptions, vitality, social role function, emotional role function, mental health) between T1-2and baseline
- Difference of MDI between T1-2and baseline
- Difference of PTSS-10 between T1-2and baseline
- XSMFA-F at T1
- XSMFA-B at T1
- Difference of GCPS-DS between T1-2and baseline
- Difference of GCPS-PI between T1-2and baseline
- Difference of NSS between T1-2and baseline
- MUST at T1-2
- Difference of BMI at T1-2and baseline
- Difference of TICS-M between T1-2and baseline
- RIS at T1-2
- KFM at T1-2
- Difference of PACIC between T1-2and baseline
- Difference of modified Morisky questionnaire between T1-2and baseline
- ADL at T1-2
- Mortality (censored time-to-event)
- Number of days in hospital from baseline up to T1-2
- Number of days with inability to work from baseline up to T1-2
- Number of days in rehabilitation clinic from baseline up to T1-2
- Number of remedies and therapeutic aids at T1-2
- Nursing level at T1-2
- Number of contacts to GPs/specialists from baseline up to T1-2

For details on primary and secondary endpoint see references.

For comparison of the intervention and control group, adequate two-sided tests will be employed. These include the t-test for continuous variables and alternatively the Mann-Whitney U-test, if normal distribution cannot be assumed (after visual inspection). Furthermore, we will apply the Chi-Squared or Fisher's exact test for binary and ordinal variables.

2.5 Figures

Continuous variables, that are measured repeatedly, will be depicted by boxplots for each measurement time point, separately for treatment and control group. Mortality will be presented in a Kaplan-Meier curve.

3. Further analyses

All data-driven analyses will be termed and published as 'unplanned analyses'.

3.1. Subgroup analyses

The following explorative subgroup analyses are planned:

	Subgroup	categorized by
1	Patients with pain	GCPS at T1 ≥ grade 2
2	Patients without posttraumatic symptoms	PTSS-10 at T1 < 23
3	Patients with mild posttraumatic symptoms	PTSS-10 at T0 ≥ 23 and < 35
4	Patients with severe posttraumatic symptoms	PTSS-10 at T0 ≥ 35
5	Educational status	“Fachhochschulabschluss” and higher
6	Educational status	“Mittlere Reife” and higher
7	Patients with physical conditions	XSMFA-F at T0 > 0
8	Patients with physical conditions	XSMFA-B at T0 > 0
9	Patients with physical conditions	SF-36 PHI at T0 < 45
10	Patients with physical conditions	SF-36 PHI at T0 < 24
11	Patients with mental conditions	mild/moderate/severe depression (MDI) at T0 and/or PTSS-10 at T0 ≥ 23
12	Multimorbidity	Charlson comorbidity index <3
13	Multimorbidity	Charlson comorbidity index ≥ 3 and < 6
14	Multimorbidity	Charlson comorbidity index ≥ 6
15	Old patients	Age > 70
16	Old patients	Age > 60
17	Age group	Age ≥ 18 and < 40
18	Age group	Age ≥ 40 and < 50
19	Age group	Age ≥ 50 and < 60
20	Age group	Age ≥ 60 and < 70
21	Age group	Age ≥ 70 and < 80
22	Age group	Age ≥ 80
23	Patients with long ICU stay	length of stay ≥ 30 days
24	Patients with long ICU stay	length of stay ≥ 14 days
25	Patients with long ventilation duration	Ventilation ≥ 7 days
26	Patients with renal replacement therapy	Renal replacement therapy
27	Patients with depressive symptoms	mild/moderate/severe depression (MDI) at T0
28	Female patients	Sex
29	Male patients	Sex
30	Patients with neuropathic symptoms	mild/moderate/severe symptoms (NSS) at T0
31	Patients with mental conditions and without physical conditions	mild/moderate/severe depression (MDI) at T0 and/or PTSS-10 at T0 ≥ 23, and SF-36 PHI at T0 ≥ 24
32	Per-protocol set: Patients with completed intervention (low intensity), if applicable	In intervention group: ≥ 1 GP training, patient training or monitoring in control group: all patients
33	Per-protocol set: Patients with completed intervention (high intensity), if applicable	In intervention group: GP training, patient training and ≥ 4 monitorings in control group: all patients

3.2 Multivariate analyses

To adjust for variables that show imbalances between the two groups in the baseline data and to examine the impact of further variables of interest, multivariate analyses will be conducted. According to the type of endpoint, linear, logistic and Cox regression models are applied.

3.3. Sensitivity analyses

Sensitivity analyses will be done to investigate whether patients that withdraw consent or did not complete the intervention are different from patients with complete intervention.

4. References

1. K. Schmidt, P. Thiel, F. Müller und J. Gensichen, „Studienprotokoll - Strukturierte Langzeitbegleichung für Patienten nach Sepsis (Sepsis survivors Monitoring and cOordination in OutpatienT Health care),“ Jena, Germany, 2011.
2. K. Schmidt, P. Thiel, F. Mueller, K. Schmuecker, S. Worrack, J. Mehlhorn, C. Engel, K. Brenk-Franz, S. Kausche, U. Jakobi, A. Bindara-Klippel, N. Schneider, A. Freytag, D. Davydow, M. Wensing, F. Brunkhorst and J. Gensichen, “Sepsis survivors monitoring and coordination in outpatient health care (SMOOTH): study protocol for a randomized controlled trial,” *Trials,* vol. 15, no. 1, p. 283, 11 Jul 2014.

5. Abbreviations

ADL	Activities of daily life
IQR	Interquartile range
GCPS	Graded Chronic Pain Scale
KFM	Short form for medication use
MDI	Major Depression Inventory
MUST	Malnutrition Universal Screening Tool
NSS	Neuropathic Symptom Score
PACIC	Patient Assessment of Care for Chronic Conditions
PTSS-10	Post-Traumatic Stress Syndrome
RIS	Regensburg Insomnia Scale
SF-36	Short Form 36 Health Survey
TICS-M	Telephone Interview of Cognitive Status
XSMFA-D	Short Musculoskeletal Function