
**Statistical Analysis Plan**
On-line Only Supplemental Material

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

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 α=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 T1-2 and baseline
- Difference of MDI between T1-2 and baseline
- Difference of PTSS-10 between T1-2 and baseline
- XSMFA-F at T1
- XSMFA-B at T1
- Difference of GCPS-DS between T1-2 and baseline
- Difference of GCPS-PI between T1-2 and baseline
- Difference of NSS between T1-2 and baseline
- MUST at T1-2
- Difference of BMI at T1-2 and baseline
- Difference of TICS-M between T1-2 and baseline
- RIS at T1-2
- KFM at T1-2
- Difference of PACIC between T1-2 and baseline
- Difference of modified Morisky questionnaire between T1-2 and 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:

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


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