Statistical Analysis Plan (SAP)

The Safe Fast track study (The SafeFT-study)

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Statistical Analysis Plan (SAP)

1. Introduction

This Statistical Analysis Plan (SAP) outlines the methodology for analyzing data from a multicenter randomized controlled trial investigating the use of D-dimer results to inform emergency department (ED) management decisions. Globally, EDs are under increasing strain due to rising patient volumes, many of whom require hospital services, though some could be more effectively managed through alternative care pathways. D-dimer, a biomarker with unique properties, is non-specific and elevated in numerous acute conditions. Studies have demonstrated that a normal D-dimer on arrival to the ED is strongly associated with a very low risk of 30-day all-cause mortality.

This trial explores whether providing physicians with D-dimer-based risk information can influence disposition decisions and improve resource utilization within EDs. The SAP describes the planned statistical approach to evaluate these potential effects on patient flow, resource use, and clinical outcomes.

2. Objectives

Primary Objective

- To evaluate whether providing physicians with information about patients' 30-day all-cause mortality risk, based on D-dimer levels, reduces ED length of stay.

Secondary Objectives

- To assess the impact of D-dimer-based risk information on 7- and 30-day all-cause mortality.
- To evaluate the effect on the proportion of patients re-contacting any ED within 30 days.
- To determine whether D-dimer information influences the number of contacts (virtual or physical consultations) with general practitioners within 30 days.
- To analyze the number of hospital-free days within 30 days of emergency department arrival.
- To examine the proportion of patients discharged directly from the emergency department.
- To measure the effect of D-dimer information on the number of blood and radiological tests ordered within 24 hours of emergency department arrival.
- To evaluate the impact on the proportion of patients diagnosed with venous thromboembolism within three months.
- To assess the effect of D-dimer-based risk information on the proportion of patients diagnosed with cancer within three months.

3. Study Design

This is a multicenter, prospective, randomized controlled trial conducted in four emergency departments in Denmark. Eligible participants include ambulatory adults (18+ years) presenting with normal vital signs and no immediate need for resuscitation. Please see the study protocol for more details about inclusion and exclusion criteria. Patients are randomized into two groups:

1. **Intervention group**: Physicians are informed of patients' D-dimer levels and the associated risk of 30-day all-cause mortality.
2. **Control group**: Standard care without disclosure of D-dimer results.

The randomization process uses block randomization with a 1:1 allocation ratio through REDCap. Outcomes will be analyzed on both an intention-to-treat and per-protocol basis.

3.1 Sample Size Calculation

The study targets a reduction in emergency department length of stay from 4 to 2.5 hours (SD = 10 hours) with a significance level of 0.05 and 80% power. The required sample size is 1,398 participants, increasing to 1,538 with a 10% dropout rate.

4. Outcomes

4.1 Primary Outcome

- ED length of stay.

4.2 Secondary Outcomes

1. 7- and 30-day all-cause mortality.
2. Emergency department recontacts within 30 days
3. The number of contacts (virtual or physical consultations) with the general practitioner within 30 days
4. Hospital-free days within 30 days.
5. Proportion of direct discharges from the emergency department.
6. Number of blood and radiological tests ordered within 24 hours.
7. Number of Venous thromboembolism within 3 months.
8. Number of cancer diagnoses within 3 months.

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5. Populations and Subgroups to Be Analyzed

5.1 Populations

- **Intention-to-Treat (ITT)**: All randomized participants.
- **Per-Protocol (PP)**: Participants with no protocol violations, excluding physicians who did not utilize the D-dimer blood sample.

5.2 Subgroups

- By centre (four sites)
- Physician experience

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6. Analyses

All outcomes will be presented using descriptive statistics: normally distributed data will be summarized with the mean and standard deviation (SD), while skewed distributions will be presented with the median and interquartile range (IQR). Binary and categorical variables will be reported as counts and percentages. Statistical analysis will be conducted using Stata 18.

6.1 Primary Outcome

- **Length of ED stay:** Differences in the primary outcome will be tested using non-parametric bootstrapping of differences, resampling the data (rep 1000) to assess group differences without relying on parametric assumptions.

6.2 Secondary Outcomes

- **Mortality rates**: Absolute and relative differences in rates will be estimated using log-binomial regression. Additionally, absolute differences will be estimated using G-computation.
- **Emergency department recontacts**: Analyzed as a binary outcome using time-to-event regression
- **General practitioner consultations**: Differences will be tested using non-parametric bootstrapping of differences
- **Number of hospital free days within 30 days of arrival:** Differences will be tested using non-parametric bootstrapping of differences
- **Number of individual blood tests:** Differences will be tested using non-parametric bootstrapping of differences
- **Proportion of patients discharged directly from the emergency department:** Absolute and relative differences in rates will be estimated using log-binomial regression. Additionally, absolute differences will be estimated using G-computation.
- **Proportion of patients with venous thromboembolism:** Absolute and relative differences in rates will be estimated using log-binomial regression. Additionally, absolute differences will be estimated using G-computation.
- **Proportion of new cancer diagnoses**: Absolute and relative differences in rates will be estimated using log-binomial regression. Additionally, absolute differences will be estimated using G-computation.

7. Missing Data

We anticipate minimal missing data, as most endpoints will be extracted from hospital electronic systems, and the primary endpoint will be collected in real-time by dedicated research staff. The extent of missing data will be reported, and if missingness is substantial, sensitivity analyses using model-based multiple imputations will be applied to both primary and secondary outcomes.