# PRoFLUID statistical analysis plan

*The PRoFLUID investigators*

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## Methods

*Design*

PRoFLUID is an international prospective observational cohort study in critically ill invasively ventilated patients that receive ventilation for at least 24 hours. We expect a minimum of 200 ICUs from 30 countries to participate in this study. Patients in participating centers are screened on a daily basis. Eligible patients are included during a 28-day period, from Monday at 8:00 AM to the Monday 4 weeks later at 7:59 AM (in time zones of the participating centers).

Centers are expected to include 20 consecutive patients. After this, centers can either stop study inclusion or decide to enroll more patients. Centers that decide to continue enrollment will have to enroll the next 20 consecutive patients before they are given the option to stop study enrollment, until day 28.

Data regarding fluid administration, vasopressor use, diuretics use, oxygen exchange, and kidney function will be collected daily from the start of invasive ventilation. Collection will be retrospective, for the previous day. Clinical complications will be evaluated on day 90 after start of invasive ventilation, death or hospital discharge, whichever comes first.

*Patients*

Patients are eligible for participation in PRoFLUID if: (I) admitted to a participating ICU; (II) receiving invasive ventilation within three days of ICU admission; and (III) having received invasive ventilation for at least 24 hours. Patients younger than 16 years, and patients that are transferred under invasive ventilation form another ICU are excluded from participation in the study.

*Primary outcome*

The primary outcome is the provided fluid therapy in terms of volume per indication in the first 3 days after start of invasive mechanical ventilation, particularly the volumes of resuscitation fluid.

*Secondary outcome*

Secondary outcomes of this analysis consider the type of fluid used during the first 3 days after start of invasive mechanical; cumulative fluid balance over the first 7 days after start of invasive mechanical ventilation; the timing of start of diuretics or ultrafiltration . Additionally, secondary outcomes will include patient related outcomes such as mortality during ICU and hospital admission; ventilator free days at day 28; and duration of ventilation in survivors and non-survivors.

*Stratification*

Outcomes will be analyzed across the entire cohort. Stratification will be performed over tertiles of total sequential organ failure score (SOFA) on day of intubation, specifically:

- Moderate: First tertile
- Severe: Second tertile
- Very severe: Third tertile

If SOFA components are missing at baseline, the missing values will be imputed by the mean of the patient's available component scores to calculate the total SOFA score. Patients without any data on baseline SOFA are excluded from the analysis.

*Analysis plan*

Descriptive statistics will be used to describe study population and fluid management parameters. Data are presented as numbers and percentages for categorical variables and as means (+/- SD) or median and interquartile range [IQR] according to distribution. Where appropriate, statistical uncertainty will be expressed by 95% confidence intervals.

We will describe the volume per indication for intravenous fluid therapy over the following indication categories:

- Resuscitation fluid
    - Prescribed in response to hemodynamic impairment or shock
    - Usually, isotonic crystalloids or colloids
    - At a rate of at least 166ml/h (1L/6 hours)
    - Usually much faster or as a bolus
- Maintenance or replacement fluid:

    - Maintenance Fluids
        - Cover daily water and electrolyte needs
        - Up to 100 ml/h infusion rate.
    - Replacement fluids
        - To address fluid losses
        - For example given for burns, dehydration, losses through drains, keto-acidosis
        - Can have faster (e.g. > 100ml/h) infusion rates
        - Are not given as bolus
- Unknown indication
    - Prescribed intravenous fluid therapy for which it is impossible to distinguish between resuscitation, maintenance or replacement

The volumes of intravenous fluid therapy per indication will also be examined in the context of all other fluids that are provided:

- Fluid as a carrier for intravenous medication
- Fluid to ensure catheter patency
- Cellular blood product transfusion
- Oral feeding
- Oral fluids
- Parenteral feeding

These volumes will be described as absolute mean volumes in mL with 95% confidence interval, as mean volumes per kilogram of body weigh with 95% confidence interval, and relative to each other (as percentage of total).

Fluid volumes will be plotted using cumulative distribution plots that display fluid volumes over the first 3 days after intubation.

To adjust for case-mix differences across SOFA tertiles and investigate factors that influence fluid management, multivariate regression analysis will be performed, adjusting the administered fluid volumes for the following baseline variables: duration of first study day; sex; age; weight; and admission diagnosis. The differences in fluid administration between SOFA tertiles be evaluated.

Secondary endpoints may be described and differences in the distributions between SOFA tertiles regions may be tested using regression analysis or Kruskal-Wallis test. Associations between fluid balance and clinical outcomes will be assessed using Cox proportional hazards modelling with fluid balance as a time-dependent covariate. The model will be adjusted for duration of day 0, age, sex, weight, baseline SOFA, and admission diagnosis. Other covariates may also be considered for the model if deemed appropriate.

Sensitivity testing will be performed to assess the robustness of findings. All statistical analyses will be performed using R. We consider $p < 0.05$ to be statistically significant.

## Table 1 – Minimal list of proposed tables and figures

| | Description |
|---|---|
| **Main paper** | |
| Table 1 | Baseline Characteristics |
| Table 2 | Clinical outcomes |
| Figure 1 | Cumulative distribution of volumes per indication for fluid administration over the first 3 days after intubation:<br>*A four panels figure showing: A) Cumulative distribution of volume of resuscitation fluid per stratifying variable; B) Cumulative distribution of volume of maintenance or replacement fluid per stratifying variable C) Cumulative distribution of volume of IV medication per stratifying variable; and D) Cumulative distribution of volume of cellular blood product transfusion per stratifying variable* |
| Figure 2 | Fluid input, output and balance over first 7 days after intubation<br>*A three panels figure of line plots with 95% CI showing: A) total volume of fluid volume input per admission day by stratification variable; B) total volume of fluid volume output per admission day by stratification variable; C) Daily fluid balance by stratification variable.* |
| Figure 3 | Types of fluid prescribed<br>*A two panels figure of stacked bar plots showing proportional fluid composition. Panel A reports the proportional distribution of major fluid categories Panel B details the composition of the 'other' fluid category by SOFA class, Proportions are expressed relative to the total volume of fluid administered within each SOFA class.* |
| **Online Supplement** | |
| eTable 1 | Steering committee |
| eTable 2 | National coordinators |
| eTable 3 | Participating centers |
| eTable 1 | Proportion of missing data per variable |
| eTable 2 | Mean volumes per indication for fluid administration per study day and stratification variable. |
| eTable 3 | Mean volumes per type of fluid per study day and stratification variable. |
| eTable 4 | Factors associated with fluid management |
| eTable 5 | Results of multivariate regression for the association of fluid balance and mortality |
| eFigure 1 | Participant flow diagram |
| eFigure 2 | Cumulative distribution of volumes per indication for fluid administration for other indications |
| eFigure 3 | Proportional volume of fluid type per day and stratification variable. |
| eFigure 4 | Daily serum lactate, sodium and chloride. |
| eFigure 5 | Daily SOFA over the three days after intubation<br>*Line plot reporting A) total SOFA, B) cardiovascular SOFA, C) respiratory SOFA, and D) renal SOFA according to randomization group. Mean and 95% confidence intervals will be reported.* |