WEAN SAFE

Statistical Analysis Plan

The aim is to collect a large "convenience sample" of patients weaning from invasive mechanical ventilation and the plan is to recruit >5,000 patients to the study. Patients still under invasive ventilation the day after their intubation will be included in the study. The data from LUNG SAFE showed that over a four week period, participating ICUs enrolled a median of 7 patients [IQR= 3-11] invasively ventilated on Day 2 following intubation. Based on these results and the aim to include a more diverse population than was the case for LUNG SAFE (only patients with acute hypoxemic respiratory failure were included), each participating ICU is anticipated to enroll ~10 patients invasively ventilated on Day 2 following intubation over a four week period. Therefore, the target is to register at least 500 ICUs to participate in WEAN SAFE.

The principal outcome measure is the rate of difficult and/or prolonged weaning. Based on the recent WIND study (Béduneau G, Pham T et al. *Am J Respir Crit Care Med* 2017), this rate can be estimated to be around 22% (calculation based on data from WIND database using the inclusion criteria for WEAN SAFE). A sample of 5000 patients would produce a two-sided 95% confidence interval with a width equal to 1.1%, which is considered adequate to obtain reliable estimates.

For each patient, the percentage of time spent weaning out of the total time on mechanical ventilation will be estimated. As there is no consensus on the moment weaning begins, different approaches will be used to define when the period of weaning begins (discontinuation of sedation, switching the ventilator to an assisted mode, patient starting to trigger the ventilator, first attempt to separate the patient from the ventilator, investigator stating that weaning has begun). These different approaches will be compared in order to determine which performs best in predicting difficult and/or prolonged weaning. To assess the possible impact of socioeconomic status on time to weaning, the gross national income per capita from the country where each patient was enrolled will be used as a proxy for socioeconomic status.

The rate of missing data will be reported. If this rate is between 10 and 30% for a variable that should be included in multivariable models, then a multiple imputation will be performed.

In regard to the demographic and clinical characteristics of patients at baseline, reporting proportions and means with standard deviations or medians with interquartile ranges will be provided according to the type of variable and its distribution. For each patient, the duration of invasive mechanical ventilation before (from the date of intubation to the moment weaning begins) and during the weaning period (from the moment weaning begins to final separation from the ventilator) will be calculated. The factors used to determine when patients enter the weaning phase and the approaches taken during the weaning period will be described as a prevalence of simple, difficult and/or prolonged weaning. The utility of different approaches to defining different weaning groups (simple, difficult and prolonged weaning) will also be tested. The baseline characteristics

between groups will be compared using a t-test, ANOVA, Wilcoxon signed-rank test, chi-square test and Fisher's exact test as appropriate for the distribution of data. Paired-tests will also be used to evaluate the changes in clinical characteristics between the first day of mechanical ventilation and the first day of the weaning period (using the different approaches mentioned previously).

Generalized linear regression models will be performed to determine the factors associated with: (a) the duration of weaning; and (b) the duration of invasive mechanical ventilation. The same approach will be used to assess the factors associated with difficult and/or prolonged weaning.

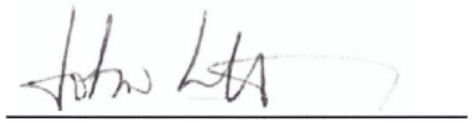
In-ICU and in-hospital mortality will be analyzed using univariate and multivariable logistic regression models adjusted for potential confounders to evaluate the impact of weaning strategies. Survival analysis (Kaplan-Meier estimator and Cox proportional-hazards model) will be carried out to investigate the time to death and time to weaning.

The study population will be stratified according to the duration of invasive mechanical ventilation before the start of weaning (early or delayed weaning). Analysis of subgroups will be performed by taking into account premorbid variables (chronic diseases, frailty, and obesity), initial illness severity, and patient status (total amount of sedation received and illness severity) at the commencement of weaning. Demographic, clinical, and center characteristics will be compared to evaluate any statistically significant differences between the patients. Depending on the distribution of the data, appropriate parametric or non-parametric tests will be selected.

The relationship between repeated variables and outcomes (weaning group, duration of weaning phase, duration of mechanical ventilation, ICU and hospital stay and mortality) will be investigated. Time-varying covariates will be taken into account to produce mixed effect models for repeated measures. The analyses will also be adjusted for possible confounding variables.

All statistical tests will be two-sided, with a p-value of <0.05 defining statistical significance and results will be presented according to the STrengthening the Reporting of OBservational studies in Epidemiology (STROBE) recommendations.

Sincerely,



Dr. John Laffey
WEAN SAFE Co-Principal Investigator

Dr. Giacomo Bellani
WEAN SAFE Co-Principal Investigator

Sept 05, 2017