Early Continuous Positive Airway Pressure (CPAP) in COVID-19 Confirmed or Suspected Patients

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General Design Issues

This is a prospective, single-center, parallel group, open-label, randomized clinical trial. The primary objective is to evaluate the efficacy and safety of the use of CPAP versus control in COVID-19 suspected or confirmed patients with pneumonia or respiratory illness. The primary efficacy endpoint is a **non-weighted composite endpoint comprised of the following components:**

- **All-cause mortality within 14 days of randomization**
- **Hospital Admission (including ED visit) within 14 days of randomization**
- **Oxygen saturation less than 90 during the 72-hour observation period from randomization**
- **Absolute reduction in oxygen saturation of more than 4% during the 72-hour observation period from randomization**

Sample Size and Power

Sample size was restricted by the availability of CPAP and the need for rapid answers during the exceptional health care challenges and fluid epidemiological conditions. The table below summarizes the effect sizes (% reduction in the proportion of patients with a negative outcome) that can be detected with sufficient power (>80%) under several scenarios assuming a total sample size of 200 patients (100 per arm) using a two-sided Fisher's exact test at the 0.05 significance level. Preliminary data from the Mount Sinai Health System indicated that about 25% of the COVID-19 positive patients with respiratory distress were sent home and subsequently hospitalized. We assumed that the proportion of patients with a negative outcome in the control group will range between 25% to 50%. Depending on these values, the planned sample size will allow us to detect a relative treatment reduction between 64% to 42% in this range (see table below).

Furthermore, given the short follow-up time for the assessment of the primary outcome and the nature of the primary outcome, we anticipate that we will be able to assess the primary outcome on all patients. We also believe that patients will be supportive of this intervention and compliant with treatment, so sample size was not adjusted for drop-out rates. However, if due to unforeseen circumstances we will conservatively set any missing primary outcome assessment to "negative" or "failure". Power calculations were performed in SAS 9.4 using the PROC POWER function.

Proportion of patients with Negative outcome	**Control**	0.25	0.30	0.35	0.4	0.45	0.5
	CPAP	0.09	0.12	0.16	0.20	0.25	0.29
	Relative reduction in CPAP arm (%)	64	60	54	50	44	42

Randomization Design and Procedure

Patients will be randomized using a 1:1 allocation to CPAP versus control group. The randomization will be stratified by BMI (>=30 and <30), gender and age (<60, >=60). A random permuted block design will be employed, with random blocks of size 2 and 4.

Data Monitoring and Analysis

Primary Efficacy Analysis
The primary efficacy endpoint is the proportion of patients with a negative composite endpoint within 14 days of randomization and will be compared between CPAP and control groups. The null hypothesis is that the proportion of patients with a negative outcome will be the same between patients randomized to CPAP versus control arm. This hypothesis will be tested using a two-sided Fisher's exact test at 0.05 alpha level. The primary analysis will be conducted according to the intention-to-treat principle.

Early stopping rule: If three deaths are observed in the CPAP group, enrollment will be halted pending DSMB review and recommendations. As of April 03, the death rate for COVID-19 positive patients in NYC was 2.99% [95% Clopper Pearson CI= 2.986, 2.997]. The rate is expected to be lower for our patient population. As such, 3 deaths among 100 patients will indicate a proportion of 3% [95% CI: 2.57%, 3.78%].

Analyses of Secondary Endpoints

Safety
Safety analyses will be conducted according to randomization assignment and treatment actually received. Adverse event rates will be calculated as the ratio of the total number of events over 14 days divided by total patient-days at risk for the specific event from randomization. A Poisson model with robust variance estimation will be used to compare SAEs between CPAP and control patients.

Time-to-events outcomes
Time from randomization to event outcomes (Hospitalization or ED visit, ICU admission, intubation and mechanical ventilation) within 14 days of randomization will be compared between randomization groups using a log-rank test or Gray's test in the presence of competing risk of death. In addition, survival at days 14 and 28 post-randomization will be described by Kaplan-Meier curves and a log-rank test will be used to compare survival between the two groups.

Respiratory Function
- Improvement in oxygen saturation will be compared between randomization groups using linear mixed-effect models with patient as a random effect**.**
- Improvement in respiratory symptoms, as measured by the Clinical COPD Questionnaire, will be compared between randomization groups using linear mixed-effect models with patient as a random effect**.**

Conversion rate of family members
The conversion rates (yes/no) of family members in the two randomization groups will be compared using a Fisher's exact test. If there is sufficient variability, a zero-inflated count model may be considered as well.

Continuation of CPAP for greater than 72 hours
The proportion of patients in the CPAP group who elected to continue CPAP use after 72 hours will be estimated along with 95% Coppler-Pearson confidence intervals.

Exploratory Analyses
Exploratory analyses will be conducted similarly as the primary analysis except that it will be only in the control arm comparing OSA versus non-OSA patents and obese vs non-obese patients.