4.1 Title:

Comparing Oxygenation Targets: A Large, Cluster-crossover Trial (COROLLA)

4.2 Objectives:

Primary Objective: To compare the effect of a low (≤92%), intermediate (92-96%), and high (≥96%) SpO2 target as the routine, unit-level oxygenation strategy for mechanically ventilated adults in the ED and ICU on 90-day in-hospital mortality.

Secondary Objective: To compare the effect of a low (≤92%), intermediate (92-96%), and high (≥96%) SpO2 target as the routine, unit-level oxygenation strategy for mechanically ventilated adults in the ED and ICU on 6-month cognitive function.

4.3 Design:

COROLLA is a cluster-randomized, multiple-crossover, multicenter, un-blinded, pragmatic, comparative effectiveness trial comparing the use of a low, intermediate, and high SpO2 target (3 arms) as the routine unit-level oxygenation strategy among critically-ill mechanically-ventilated adults in the ED and ICU. Duration of the trial will be 12 months. Participating EDs and ICUs within a hospital will serve as a unit (cluster), with all patients in a unit allocated to the same SpO2 target. Treatment allocation (low, intermediate, or high SpO2 target) will crossover in each unit at the conclusion of each pre-defined period. The sequence of SpO2 targets will be selected randomly. During the first 6 months of the trial, period length will be 2 months. The trial will include one interim analysis using data from patients enrolled during the first 4 months (2 periods), with the potential to drop one intervention arm and change period length to 3 months for the final 6 months of the trial. Trial data will be collected via queries of the electronic health record (EHR) at participating hospitals.

4.4 Population:

The trial will be executed in EDs and ICUs of 24 hospitals in the NHLBI PETAL Clinical Trials Network. Prior to the trial, PETAL investigators, in collaboration with other hospital leaders, will select which EDs and ICUs at their sites will participate in the trial. EDs and ICUs will be eligible to participate in the trial if they fulfill both of the following criteria:

1) Usual care oxygenation practices of mechanically ventilated adults in the unit before the trial routinely included SpO2 levels specified in all 3 intervention arms; that is, usual care oxygenation in the unit spanned the range from ≤92% to ≥96%.
2) Unit leadership approved the trial protocol for use in their unit, including implementation of different SpO2 targets at the low, middle, and high end of the SpO2 range that had been delivered in usual care before the trial.

The primary population for analysis will be adults (age ≥18 years) who receive invasive mechanical ventilation in a participating ICU. SpO2 targets in the ED will be coordinated with the

participating ICUs, such that the pre-ICU SpO2 target in the ED will match the SpO2 target in the ICU. A secondary population (the COROLLA-ED population) will include adults who receive invasive mechanical ventilation in a participating ED but were not admitted to a participating ICU. Long-term cognitive outcomes will be assessed at 6-months in a randomly-selected subset of 1000 patients included in the primary population.

4.5 Intervention Groups:

The trial includes 3 intervention groups—a low, intermediate, and high SpO2 target as defined in the table below:

Group	SpO2 Target	Acceptable SpO2 Range	PaO2 Target[a]	Acceptable PaO2 Range[a]
Low	≤92%	≤92%[b]	≤65 mm Hg	≤65 mm Hg
Intermediate	94%	92% - 96%	70 mm Hg	65 – 80 mm Hg
High	≥96%	≥96%[c]	≥80 mm Hg	≥80 mm Hg

[a] Only use PaO2 when SpO2 is not available.

[b] The lower bound for the acceptable SpO2 range for the low target is selected locally according to usual care; a lower bound below 88% is not recommended.

[c] The upper bound for the acceptable SpO2 range for the high target group is selected locally according to usual care.

4.6 Delivery of the Intervention:

The trial will be embedded into ongoing clinical care, with the intervention largely executed by non-study treating clinicians. Trial-specified SpO2 targets will be disseminated to clinicians via signs posted on ventilators, electronic order sets, and continuous feedback and education. Clinicians will titrate FiO2 according to trial-specified protocols to maintain SpO2 within target ranges. Trial-specified SpO2 targets will be the default oxygen strategy for the entire duration of mechanical ventilation in participating units. Clinicians will maintain autonomy to use off-protocol SpO2 targets for any individual patient they believe would be more safely treated with an off-protocol oxygenation strategy.

4.7 Outcomes:

The primary outcome is death from any cause prior to hospital discharge or 90 days, whichever occurs first (“90-day in-hospital mortality”). The secondary outcome is cognitive function at 6 months after enrollment (“6-month cognition”), which will be measured with the Montreal Cognitive Assessment-Blind (MoCA-Blind) instrument and collected by phone from a randomly-selected 1,000-patient subset of trial participant survivors.

4.8 Statistical Plan:

As a pragmatic, cluster-crossover trial, sample size will be dependent on the number of patients who receive mechanical ventilation in participating units at the 24 participating hospitals during the 12-month trial.

[Additional statistical details to be added.]