**Sample Size Calculation:**

We used standard sample size calculations for a randomized control trial where the randomization is carried out at the individual patient level. Sample size estimates are based on the primary outcome of reduction in length of mechanical ventilation (LoMV).

A clinically relevant effect size is assumed to be a 25% reduction in the LoMV. Equal allocations to the control and intervention are assumed. One-sided testing for a reduction in LoMV is assumed as only a beneficial effect is expected. A minimum power of 80% and d-sided significance level of 5% is assumed below. The distribution of LoMV in the usual population is heavily skewed to the right. Hence, a Mann-Whitney-Wilcoxon rank sum test for the positive difference in between the control and intervention medians is used below. But these are consistent with a two sample t-test (on the logarithmic scale due to multiplicative reduction) and Kolmogorov-Smirnov test.

A Monte Carlo simulation study based on historical patients’ records is used to determine the minimum sample size required to identify the specified effect size, at the chosen power and significance level. Data for all mechanical ventilated patients in the Christchurch Hospital Intensive care unit (ICU) for 2011 - 2014 were analyzed. The patients’ APACHE 3 diagnostic code and their length of mechanical ventilation were used.

1. A total of 5176 patients were available
2. Exclusion criteria were imposed to obtain an estimated total sample size for the simulation. The exclusion criteria were:
   1. patients who are likely to be discontinued from MV within 24 hours;
   2. patients who have moderate or severe traumatic brain injury;
   3. patients who have a high or spinal cord injury with loss of motor function;
   4. patients who have significant weakness from any neurological disease;
   5. patients who have acute severe pancreatitis and are expected to be ventilated for more than 10 days; and
   6. patients who have asthma as the primary presenting condition.
3. After these exclusions 974 patients remained. (mean(LoMV)=5.90, sd(LoMV)=7.62, median(LoMV)=2.91)

It is important that all patients who are likely to discontinued from MV in less than 24 hours can be identified in the allocations and excluded from the trial. Inclusion of these individuals leads to approximately a tripling of the required sample size, to achieve the same power and significance level for the prescribed effect size.

Further, patients who are expected to require long term MV (who are not excluded by the other criteria listed above) must also be retained. A-priori identification and exclusion of such long term MV patients (e.g. those likely to require more than 15 days of MV) substantially reduces the power of the test, leading to needing a sample size orders of magnitude higher to achieve the same power and significance level for the prescribed effect size.

A minimum sample size of 160 patients per arm is required identify a 25% reduction in the median LoMV, with a power of 80% and double sided significance level of 5%.

However, in the case of a 5% mortality rate difference between the two cohorts, use of the Ventilator-Free-Days outcome metric would allow for a smaller sample size of 130 patients per arm.