CRITICAL CARE AND RESUSCITATION

## Online Appendix

**This appendix was part of the submitted manuscript and has been peer reviewed.**
**It is posted as supplied by the authors.**

Appendix to: Maia IS, Kawano-Dourado L, Zampieri FG, et al; RENOVATE Investigators and the BRICNet. High flow nasal catheter therapy versus non-invasive positive pressure ventilation in acute respiratory failure (RENOVATE trial): protocol and statistical analysis plan. *Crit Care Resusc* 2022; doi: 10.51893/2022.1.OA8.

## Appendix: Electronic Supplementary Material

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**S1. Subgroups stopping rules:**

### 1.1.1. Early Futility

If the posterior probability of non-inferiority ($F_{i)}$ is too low at an interim, the group will stop enrollment for early futility. Specifically,

$$Pr(\theta_g < 0.442) < F_i.$$

The values of $F_i$ by interim are given in the following table:

| Interim # | 1 | 2 | 3 | 4 | 5 | 6 |
|---|---|---|---|---|---|---|
| $F_i$ | 0.3 | 0.55 | 0.67 | 0.77 | 0.85 | 0.93 |

### 1.1.2. Early Success for Superiority

If the posterior probability of superiority ($S_i$) is sufficiently high at an interim, then the group will stop enrollment for early success on superiority. Specifically,

$$Pr(\theta_g < 0) > S_i.$$

The values of $S_i$ by interim are given in the following table:

| Interim # | 1 | 2 | 3 | 4 | 5 | 6 |
|---|---|---|---|---|---|---|
| $S_i$ | 0.9985 | 0.997 | 0.995 | 0.993 | 0.991 | 0.988 |

### 1.1.3. Early Success for Non-Inferiority

If the posterior probability of non-inferiority ($N_i$) is sufficiently high at an interim, while simultaneously, the posterior probability of superiority is not high, then the group will stop enrollment for early success on non-inferiority. Specifically, both of the following conditions must hold:

$$Pr(\theta_g < 0.442) > N_i$$
$$Pr(\theta_g < 0) < C_i$$

The values of $N_i$ and $C_i$ by interim are given in the following table:

| Interim # | 1 | 2 | 3 | 4 | 5 | 6 |
|---|---|---|---|---|---|---|
| $N_i$ | 0.999 | 0.998 | 0.996 | 0.9935 | 0.991 | 0.988 |
| $C_i$ | 0.30 | 0.55 | 0.67 | 0.77 | 0.85 | 0.93 |

### 1.1 .4 Final Analysis

The final analysis will occur when full data is obtained for the trial. Full data means the trial will recruit 2,000 patients or, before that, if all subgroups meet stopping thresholds. The trial will report posterior probabilities individually in each subgroup based on a model (dynamic borrowing) that allows information to be shared between subgroups. The amount of sharing is dependant on how similiar/dissimilar the subgroups are

The final analysis will declare the treatment is superior within the subgroup if:

$$Pr(\theta_g < 0) > 0.98.$$

If superiority success is not obtained for the subgroup, then the final analysis will declare the treatment is non-inferior within the subgroup if:

$$Pr(\theta_g < 0.442) > 0.98.$$

If neither of these conditions are met, then the final analysis for the subgroup is futility.

## S2. Power Simulations:

### 1.1.4. Simulation Assumptions

#### *1.1.4.1. Patient Accrual*

The simulations assumed that patients will be recruited into the study with prevalence proportions:

| Group | Proportion |
|---|---|
| **Hypoxemic ARF** | 0.70 |
| **COPD** | 0.15 |
| **Immunocompromised ARF** | 0.10 |
| **ACPE** | 0.05 |

Dropouts were assumed to occur at a 10% rate regardless of group or treatment assignment. Dropouts were simply considered as missing and ignored for analysis but used for enrollment limits and interim timing.

Due to a required delay between the *enrollment* of the subject that triggers an interim and the time that the full data is available to *perform* the interim analysis and implement the decisions, some overrun of enrollment is expected. The overrun was simulated as a Poisson distribution with mean 25 if the Hypoxemic ARF subgroup was enrolling at the time of the interim, or 5 if the Hypoxemic ARF group had been previously stopped.

#### *1.1.4.2. Control Rates*

The assumed intubation rates for the four groups under the standard of care NIPPV are based on published rates:

| Group | Rate | Reference |
|---|---|---|
| **Hypoxemic ARF** | 0.305 | Xu et al CCM 2017 |
| **COPD** | 0.123 | Osadnik et al Cochrane Reviews 2017 |
| **Immunocompromised ARF** | 0.320 | Huang et al Crit Care 2017 |
| **ACPE** | 0.054 | Weng et al Ann Int Med 2010 |

#### *1.1.4.3. HFNC Treatment Effect Scenarios*

Six scenarios were evaluated in detail, to assess a variety of potential outcomes for the true treatment effect across subgroups.

1. 'Null Sup' scenario: treatment is equivalent to control in all subgroups.

2. 'Null Non-inf' scenario: the treatment effect is at the non-inferiority margin of 0.442 [in log-odds] in all subgroups.

3. 'All moderate' scenario: the treatment is superior in all subgroups, with the same effect level [in log-odds].

4. 'Mixed 1' scenario: the Hypoxemic ARF and COPD subgroups are equivalent to control, while the Immunocompromised ARF and ACPE subgroups are at the non-inferiority margin.

5. 'Mixed 2' scenario: the Hypoxemic ARF subgroup has a small positive (slightly inferior) effect, the COPD subgroup has a moderate negative (superior) effect, while the Immunocompromised ARF and ACPE subgroups are at the non-inferiority margin.

6. ‘Bad Nugget’ scenario: the Hypoxemic ARF, COPD, and Immunocompromised ARF subgroups are equivalent to control, while the ACPE subgroup has a doubled intubation rate in the treatment arm.

The hierarchical model is expected to perform well in scenarios 1, 2, and 3, since the effects are equivalent across subgroups, where borrowing is the right analysis. Scenarios 4 and 5 have mixed effects, where the borrowing may be beneficial for some subgroups and not for others. The mixture aspect of the hierarchical model is designed to help in scenario 6, where the treatment effect is substantially different in the ACPE subgroup.

The assumed treatment rates for each scenario are shown in the table below and plotted in Figure S2.1. The intubation rates for the six scenarios are given in the table below:

**Table 1** Control and treatment rates used for the scenarios under study. The control rates are the same across scenarios, so they are listed only once.

| | Control | Null Sup | Null Non-inf | All moderate | Mixed 1 | Mixed 2 | Bad Nugget |
|---|---|---|---|---|---|---|---|
| Hypoxemic ARF | 0.305 | 0.305 | 0.406 | 0.244 | 0.305 | 0.315 | 0.305 |
| COPD | 0.123 | 0.123 | 0.179 | 0.094 | 0.123 | 0.085 | 0.123 |
| Immunocompromised ARF | 0.320 | 0.320 | 0.423 | 0.257 | 0.423 | 0.423 | 0.320 |
| ACPE | 0.054 | 0.054 | 0.082 | 0.040 | 0.082 | 0.082 | 0.108 |

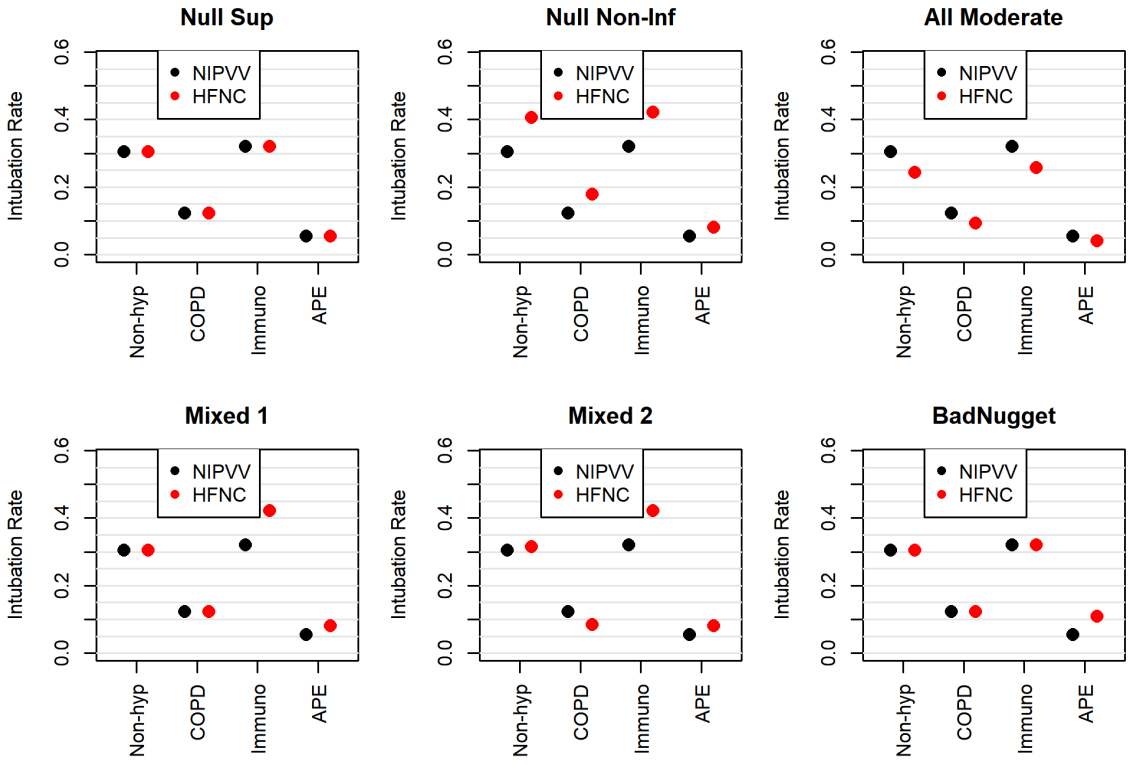


**Figure S2.1** Graphical depiction of the control and treatment rates for the scenarios under study.

#### *1.1.4.4. Simulation Details*

For each assumed scenario, 5000 trials were simulated. For each analysis (i.e. each interim within each trial), posterior distributions were estimated via Markov chain Monte Carlo (MCMC) methods using 11,000 iterations, discarding the first 1000 iterations as burn-in. The simulations were performed using custom software coded in C++.

#### *1.1.4.5. Simulation Output*

For each scenario, the following operating characteristics are reported:

- Proportion of trials that declare each subgroup superior at the final analysis

- Proportion of trials that declare each subgroup non-inferior at the final analysis
- Proportion of trials that declare each subgroup futile at the final analysis
- Average sample size by subgroup and overall
- Average interim number at which enrollment stopping is triggered for each subgroup
- Proportion of trials that declare at least one subgroup superior at the final analysis (labeled as "Overall superiority" in the tables below)
- Proportion of trials that declare at least one subgroup non-inferior with none superior at the final analysis (labeled as "Overall non-inferiority" below)
- Proportion of trials that were futile for all subgroups
- Average interim number at which the trial stopped. Note that this is typically higher than all of the averages for individual subgroups, as it is the average of the maximum.

In-depth information is also provided for one simulated example trial. This illustrates the flow and outcome of possible trials based on the pre-specified statistical decision rules.

### 1.1.5. Results

The operating characteristics for the scenarios are given in the following success along with brief discussion. The final outcome proportions are color coded to highlight the desired result, given the underlying truth, with green indicating a result consistent with the underlying truth for the scenario.

#### *1.1.5.1. Null Superiority Scenario*

For this scenario, the desired result in each subgroup is non-inferiority. Type I error control at the 0.025 level is demonstrated for declaration of superiority.

| | Hypoxemic | COPD | Immunocompromised | ACPE | Overall |
|---|---|---|---|---|---|
| Futile | 0.027 | 0.220 | 0.210 | 0.730 | 0.025 |
| Non-Inferiority | 0.950 | 0.775 | 0.784 | 0.265 | 0.951 |
| Superiority | 0.024 | 0.005 | 0.006 | 0.005 | 0.024 |
| Avg. N | 774.3 | 208.0 | 124.8 | 83.1 | 1190.1 |
| Avg. Stop Interim | 4.3 | 5.6 | 5.5 | 5.4 | 6.4 |

The borrowing is generally helping in this scenario. For the average sample size observed with each group, if no borrowing were performed, and a standard frequentist test were performed, the power would be lower for each subgroup – approximately 0.86, 0.30, 0.32, and 0.14, respectively.

#### *1.1.5.2. Null Non-Inferiority Scenario*

For this scenario, the desired result in each subgroup is futility. Type I error control at the 0.025 level is demonstrated for declaration of non-inferiority.

| | Hypoxemic | COPD | Immunocompromised | ACPE | Overall |
|---|---|---|---|---|---|
| Futile | 0.979 | 0.997 | 0.995 | 0.999 | 0.978 |
| Non-Inferiority | 0.021 | 0.003 | 0.005 | 0.001 | 0.022 |
| Superiority | 0.000 | 0.000 | 0.000 | 0.000 | 0.000 |
| Avg. N | 568.6 | 126.8 | 76.6 | 53.1 | 825.1 |
| Avg. Stop Interim | 2.8 | 2.8 | 2.8 | 2.9 | 3.5 |

Of note for this scenario is the rate of early stopping. On average, each subgroup is stopped earlier than the third interim, and the trial as a whole by the fourth interim.

#### *1.1.5.3. All Moderate Scenario*

For this scenario, the desired result in each subgroup is superiority, as each group has a moderate negative effect.

| | Hypoxemic | COPD | Immunocompromised | ACPE | Overall |
|---|---|---|---|---|---|
| Futile | 0.000 | 0.005 | 0.004 | 0.520 | 0.000 |
| Non-Inferiority | 0.228 | 0.596 | 0.561 | 0.233 | 0.224 |
| Superiority | 0.772 | 0.399 | 0.435 | 0.247 | 0.776 |
| Avg. N | 791.1 | 215.4 | 128.2 | 80.5 | 1215.3 |
| Avg. Stop Interim | 4.4 | 5.9 | 5.7 | 5.5 | 6.5 |

The borrowing is generally helping in this scenario, particularly for the smaller subgroups, as superiority is difficult to achieve with small samples and a modest effect size.

#### *1.1.5.4. Mixed 1 Scenario*

For this scenario, the desired result in each subgroup is non-inferiority for the Hypoxemic ARF and COPD groups and futility for the others.

| | Hypoxemic | COPD | Immunocompromised | ACPE | Overall |
|---|---|---|---|---|---|
| Futile | 0.050 | 0.467 | 0.644 | 0.906 | 0.050 |
| Non-Inferiority | 0.941 | 0.532 | 0.356 | 0.094 | 0.941 |
| Superiority | 0.008 | 0.001 | 0.000 | 0.000 | 0.008 |
| Avg. N | 784.8 | 214.9 | 133.8 | 66.1 | 1199.6 |
| Avg. Stop Interim | 4.3 | 5.9 | 5.9 | 4.7 | 6.6 |

Because the subgroups have different true effect sizes, the borrowing affects the subgroup outcomes differently. The two effective subgroups have greater power than they would had they been treated independently, but the two inferior groups are being labeled as non-inferior more often than they would be in an independent analysis. The outcome is still preferable to a fully pooled analysis for those two subgroups, since a pooled analysis would declare non-inferiority at a high rate and would be applied to all subgroups.

#### *1.1.5.5. Mixed 2 Scenario*

For this scenario, the desired result is non-inferiority for the Hypoxemic ARF subgroup (though the effect is slightly inferior), superiority in the COPD subgroup, and futility in the others.

| | Hypoxemic | COPD | Immunocompromised | ACPE | Overall |
|---|---|---|---|---|---|
| Futile | 0.061 | 0.280 | 0.598 | 0.909 | 0.059 |
| Non-Inferiority | 0.933 | 0.719 | 0.402 | 0.091 | 0.935 |
| Superiority | 0.006 | 0.001 | 0.000 | 0.001 | 0.006 |
| Avg. N | 783.7 | 208.6 | 139.6 | 68.6 | 1200.4 |
| Avg. Stop Interim | 4.3 | 5.6 | 5.9 | 4.7 | 6.5 |

This scenario has the greatest variation in true effect amongst the scenarios explored here, where the borrowing model is imperfect. The true effects (in log-odds) for the non-ACPE groups are 0.0, -0.412, and 0.442. The estimates of the effects for those groups get shrunk toward each other, resulting in estimated effects generally closer to 0.0, and leading to a greater

proportion of non-inferiority results for all three groups than would be obtained by an independent analysis.

#### *1.1.5.6. Bad Nugget Scenario*

For this scenario, the desired result is futility for the ACPE subgroup, and non-inferiority for the others. It is desirable for the trial to stop the ACPE group fairly early and often, since it is actually slightly worse than non-inferior and is the subgroup most likely to be inferior, since it has the least prior clinical evidence to support it.

| | Hypoxemic | COPD | Immunocompromised | ACPE | Overall |
|---|---|---|---|---|---|
| Futile | 0.026 | 0.234 | 0.216 | 0.965 | 0.025 |
| Non-Inferiority | 0.954 | 0.763 | 0.779 | 0.034 | 0.955 |
| Superiority | 0.020 | 0.003 | 0.005 | 0.001 | 0.020 |
| Avg. N | 773.1 | 208.8 | 126.0 | 62.1 | 1169.9 |
| Avg. Stop Interim | 4.3 | 5.6 | 5.5 | 4.1 | 6.1 |

This scenario is identical to the Null Superiority scenario except for the ACPE subgroup, and the mixture component of the model is generally able to help separate out the ACPE, with fewer than 4% of trials reaching a non-inferiority result.

#### *1.1.5.7. Equal Group Effect Scenarios*

To provide a more general view of power across a range of effects, the following graphs are provided for scenarios where the effect size is equal across the subgroups. The effect size is then varied to provide a graph of power versus effect. The first graph plots the effect as the log-odds effect size – i.e., the space in which the effect is equal (Figure S2.2). The second graph provides the same numbers but plots versus the probability of intubation (Figure S2.3)

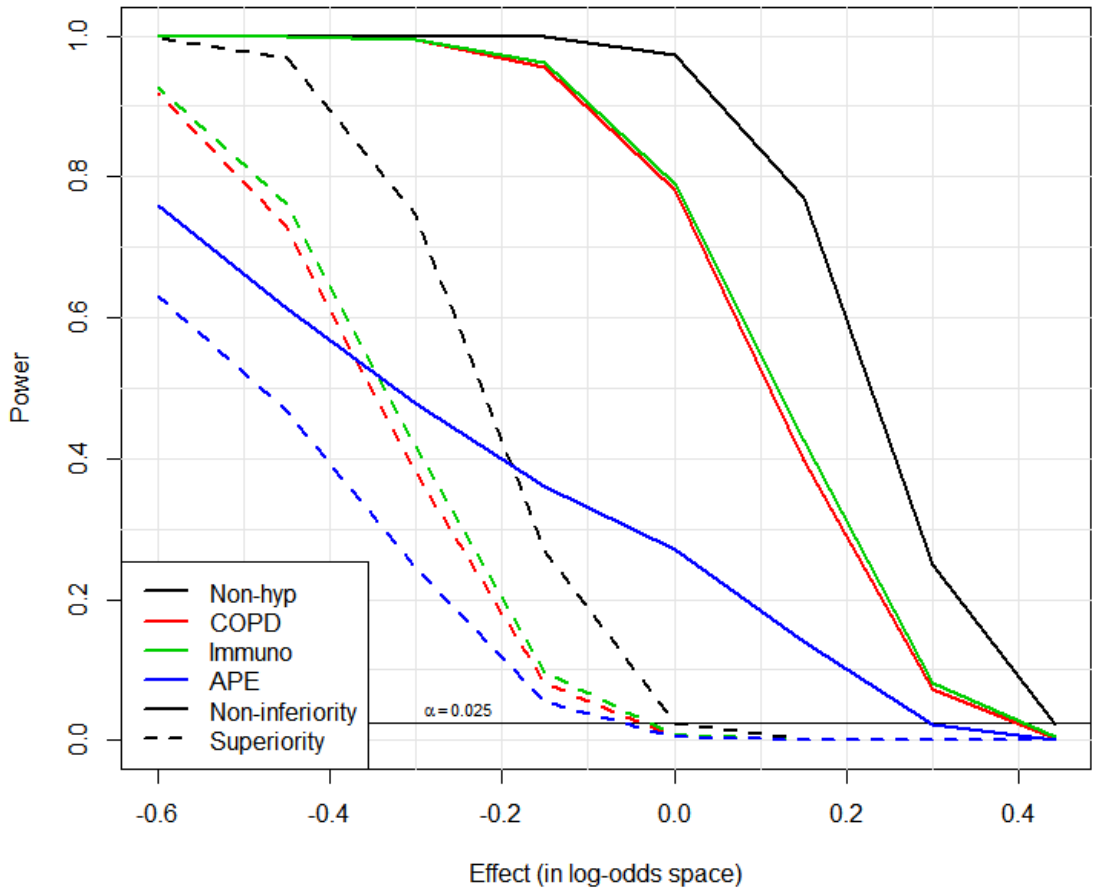


**Figure S2.2** Plot of power versus effect size for scenarios where the treatment effect is the same across groups.

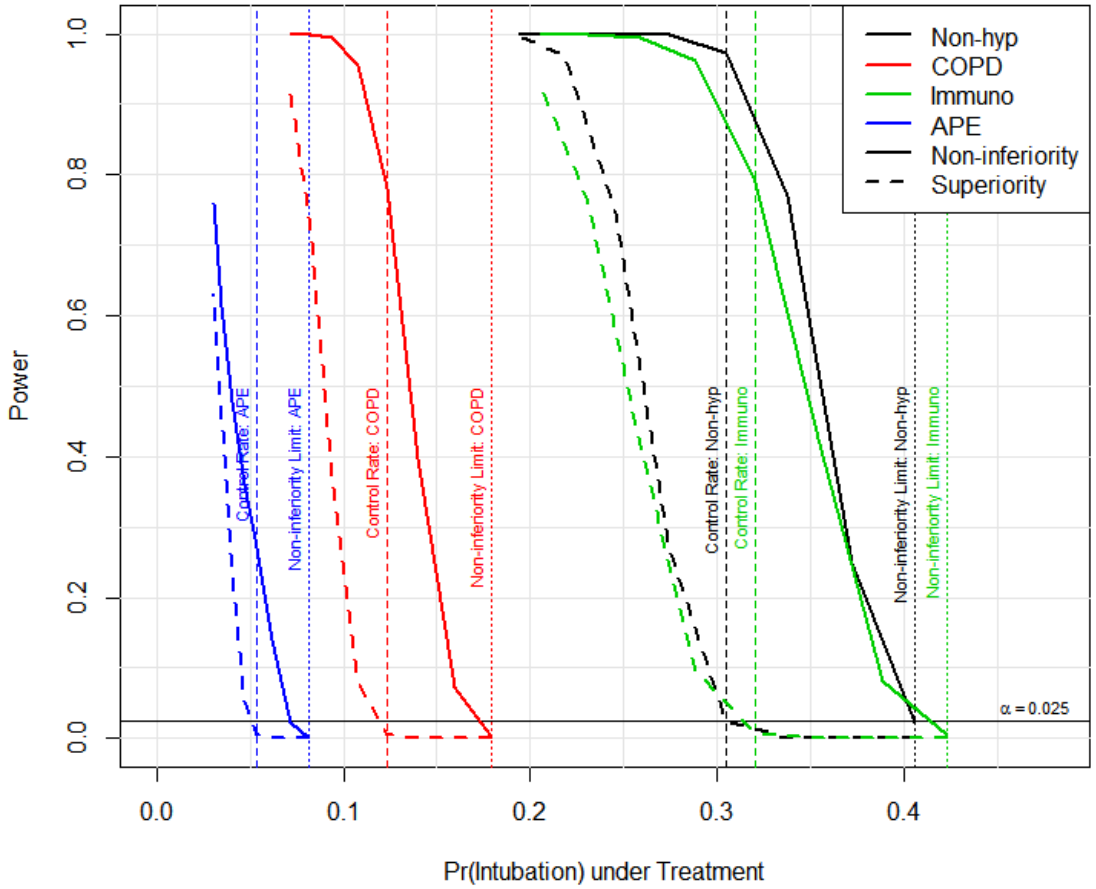


**Figure S2.3** Plot of power versus probability of intubation under the treatment arm, for scenarios where the treatment effect is the same across groups.

**S3: Secondary outcomes description**

**Secondary Analysis: 28-day Mortality**

This secondary analysis is intended as descriptive and not integrated into the design of the trial, in the sense that interim decisions will not be based on this analysis, though the analysis could be provided to the data safety monitoring committee as part of safety review.

Modeling of the secondary endpoint will use the same structure as the model for the primary endpoint, with modification to prior distributions to reflect the differing rates for 28-day mortality, and with no consideration of a non-inferiority margin.

Historical information for 28-day mortality of NIPPV is given below:

| Group | Rate | Reference |
|---|---|---|
| **Non-hypercapnic** | 0.267 | Rochewerg Metanalysis ERJ 2017 |
| **COPD** | 0.088 | Rochewerg Metanalysis ERJ 2017 |
| **Immunocompromised** | 0.241 | Lemiale JAMA 2015 |
| **ACPE** | 0.152 | Gray 3CPO NEJM 2003 |

The priors for control rates for the secondary analysis will thus be specified as:

(1) Non-hypercapnic: $\text{logit}(\pi_{\text{Non-hyp,nippv}}) \sim \text{N}(-1.010, 0.5^2)$

(2) COPD: $\text{logit}(\pi_{\text{COPD,nippv}}) \sim \text{N}(-2.338, 0.5^2)$

(3) Immunocompromised: $\text{logit}(\pi_{\text{Immuno,nippv}}) \sim \text{N}(-0.1.147, 0.5^2)$

(4) Cluster pattern 1 – ACPE: $\text{logit}(\pi_{\text{ACPE,nippv}}) \sim \text{N}(-1.719, 0.5^2)$

Cluster pattern 2 – ACPE: : $\text{logit}(\pi_{\text{ACPE,nippv}}) \sim \text{N}(-1.719, 0.2^2)$

The mean of these four prior distributions corresponds to the log-odds for rates of 26.7%, 8.8%, 24.1%, and 15.2%, respectively. The value of the standard deviation for these priors (0.5 and 0.2 for ACPE in cluster pattern 2) was chosen to match the primary analysis, since variation in log-odds should be similar.

The hierarchical model for the treatment effect models the $\theta_g$ effect parameters as coming from the same distribution:

$$\theta_g \sim N(\mu, \tau^2).$$

$$\mu \sim N(0, 1^2)$$

The parameter $\tau$, which controls the amount of borrowing will be specified as:

$$\tau^2 \sim \text{Inverse-Gamma}(5.0, 0.34)$$

For the cluster pattern 2 model,

$$\theta_{\text{ACPE}} \sim N(0, 0.5^2)$$

**Other secondary and other pre-specified outcome definitions:**

**Mortality**: vital status at day 28 and day 90.

**Ventilator, vasopressors and ICU free days**: number of days alive and out of ICU within 28 days. Patients who die within 28 days are assigned 0 free days. For patients surviving beyond day 28, the free days were defined as the number of days (1-to-28) that the patient was not in invasive mechanical ventilation or using vasopressors or out of the ICU for at least 48 hs. Return to ICU were included in the calculation of total duration of MV, vasopressors or ICU stay to study day 28

Hospital and ICU length of stay at 90 days: continuous outcome variable. This variable will be truncated at 90-days

Proportion of patients with DNI order after randomization up 7 days: dichotomous endpoint at 7 days

Patient comfort score-continuous outcome measured in millimeters of the 100 mm Visual Analog Scale

**S4. Results of new simulations performed after the first interim analysis. In these simulations, an updated proportion of the different ARF subgroups based on actual recruited patients was used.**

Note: The updated simulation results for the RENOVATE trial aimed at providing operating characteristics under observed recruitment rates for the four pre-specified subgroups:

1. Hypoxemic De Novo ARF (Hypoxemic ARF)
2. Chronic obstructive pulmonary disease (COPD)
3. Hypoxemic De Novo ARF in the Immunocompromised (Immunocompromised ARF)
4. Acute cardiogenic pulmonary edema (ACPE)

The statistical design is unchanged for the simulations presented. The only distinction is the assumed accrual rates in the trial, which were set to the empirical rates observed as of late November 2020.

| Group | Proportion |
|---|---|
| Hypoxemic ARF | 0.718 |
| COPD | 0.038 |
| Immunocompromised ARF | 0.212 |
| ACPE | 0.032 |

**Simulations**

**S4. 1 HFNC Treatment Effect Scenarios**

Five scenarios were evaluated, to assess a variety of potential outcomes for the true treatment effect across groups.

7. 'Null Sup' scenario: treatment is equivalent to control in all groups.
8. 'Null Non-inf' scenario: the treatment effect is at the non-inferiority margin of 0.442 [in log-odds] in all groups.
9. 'All moderate' scenario: the treatment is superior in all groups, with the same effect level [in log-odds] .
10. 'Bad COPD' scenario: the treatment is equivalent to control in all groups except the COPD group, which is set at the non-inferiority margin.
11. 'Good COPD' scenario: the treatment effect is at the non-inferiority margin for all groups except COPD, which is moderately superior.

The first three scenarios match scenarios detailed in the original design report. Scenarios 4 and 5 are scenarios where the COPD group differs from the others, where the updated smaller accrual rate in this group may be detrimental to detection of the difference within the COPD group.
The assumed treatment rates for each scenario are shown in the table below and plotted in Figure S4.1. The intubation rates for the six scenarios are given in the table below:

**Table 1** Control and treatment rates used for the scenarios under study. The control rates are the same across scenarios, so they are listed only once.

| | Control | Null Sup | Null Non-inf | All moderate | Bad COPD | Good COPD |
|---|---|---|---|---|---|---|
| Hypoxemic ARF | 0.305 | 0.305 | 0.406 | 0.244 | 0.305 | 0.406 |
| COPD | 0.123 | 0.123 | 0.179 | 0.094 | 0.179 | 0.094 |
| Immunocomp ARF | 0.320 | 0.320 | 0.423 | 0.257 | 0.320 | 0.423 |
| APE | 0.054 | 0.054 | 0.082 | 0.040 | 0.054 | 0.082 |

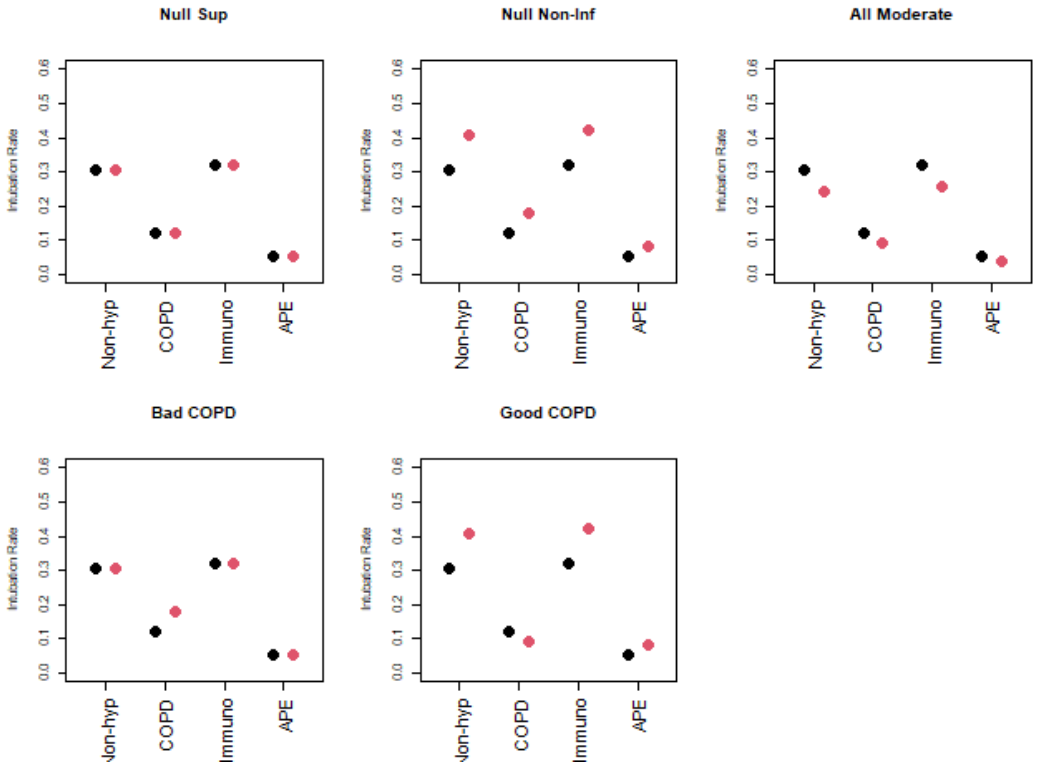


**Figure S4.1** Graphical depiction of the control and treatment rates for the scenarios under study.

### S4.2 Simulation Details

For each assumed scenario, 5000 trials were simulated. For each analysis (i.e. each interim within each trial), posterior distributions were estimated via Markov chain Monte Carlo (MCMC) methods using 11,000 iterations, discarding the first 1000 iterations as burn-in. The simulations were performed using custom software coded in C++.

### S4.3 Simulation Output

For each scenario, the following operating characteristics are reported:

- Proportion of trials that declare each group superior at the final analysis
- Proportion of trials that declare each group non-inferior at the final analysis
- Proportion of trials that declare each group futile at the final analysis
- Average sample size by group and overall
- Proportion of trials that are non-inferior due to the minimum number required not being achieved. Note: this row was added to examine whether the low COPD group accrual is affected by the group minimum requirement.
- Average interim number at which enrollment stopping is triggered for each group
- Proportion of trials that declare at least one group superior at the final analysis (labeled as "Overall superiority" in the tables below)
- Proportion of trials that declare at least one group non-inferior with none superior at the final analysis (labeled as "Overall non-inferiority" below)
- Proportion of trials that were futile for all groups
- Average interim number at which the trial stopped. Note that this is typically higher than all of the averages for individual groups, as it is the average of the maximum.

In-depth information is also provided for one simulated example trial. This illustrates the flow and outcome of possible trials based on the pre-specified statistical decision rules.

## S4.4 Results

The operating characteristics for the scenarios are given in the following success along with brief discussion. The final outcome proportions are color coded to highlight the desired result, given the underlying truth, with green indicating a result consistent with the underlying truth for the scenario.

### S4.4.1 Null Superiority Scenario

For this scenario, the desired result in each group is non-inferiority. Type I error control at the 0.025 level is demonstrated for declaration of superiority.

| | Non-Hyp | COPD | Immuno | ACPE | Overall |
|---|---|---|---|---|---|
| Futile | 0.016 | 0.295 | 0.143 | 0.684 | 0.014 |
| Non-Inferiority | 0.963 | 0.703 | 0.849 | 0.310 | 0.964 |
| Superiority | 0.021 | 0.003 | 0.008 | 0.006 | 0.022 |
| Avg. N | 784.8 | 75.2 | 245.4 | 57.0 | 1162.4 |
| Min N Unreached | 0.000 | 0.003 | 0.000 | 0.000 | |
| Avg. Stop Interim | 4.2 | 6.0 | 5.1 | 5.2 | 6.4 |

Power is increased except for the COPD group in this scenario compared to the original assumptions. Overall sample size is decreased on average. The COPD group occasionally fails

to reach the required minimum sample size of 50, though the occurrence rate is low. The average number of interims required to reach conclusion is similar to the original assumptions.

### S4.4.2 Null Non-Inferiority Scenario

For this scenario, the desired result in each group is futility.

| | Non-Hyp | COPD | Immuno | ACPE | Overall |
|---|---|---|---|---|---|
| Futile | 0.949 | 0.991 | 0.974 | 0.990 | 0.944 |
| Non-Inferiority | 0.051 | 0.009 | 0.026 | 0.010 | 0.056 |
| Superiority | 0.000 | 0.000 | 0.000 | 0.000 | 0.000 |
| Avg. N | 571.5 | 64.1 | 159.2 | 38.1 | 833.0 |
| Min N Unreached | 0.000 | 0.000 | 0.000 | 0.000 | |
| Avg. Stop Interim | 2.7 | 4.1 | 2.8 | 3.2 | 4.3 |

This scenario is relatively unaffected by the updated assumptions, though the trial tends to run longer, and the type I error rate sample size has increased to approximately slightly more than 5% for this scenario.

### S4.4.3 All Moderate Scenario

For this scenario, the desired result in each group is superiority, as each group has a moderate negative effect.

| | Non-Hyp | COPD | Immuno | ACPE | Overall |
|---|---|---|---|---|---|
| Futile | 0.000 | 0.013 | 0.002 | 0.540 | 0.000 |
| Non-Inferiority | 0.250 | 0.723 | 0.521 | 0.141 | 0.240 |
| Superiority | 0.750 | 0.264 | 0.477 | 0.319 | 0.760 |
| Avg. N | 804.8 | 78.0 | 256.1 | 53.1 | 1192.0 |
| Min N Unreached | 0.000 | 0.007 | 0.000 | 0.000 | |
| Avg. Stop Interim | 4.4 | 6.2 | 5.4 | 5.3 | 6.6 |

The power differences from the original assumptions are similar to the changes seen in the Null Superiority scenario. There is a small chance that the COPD group does not reach the required minimum sample size of 50, and a modest chance that it becomes the only group accruing in the trial for the final interim, which could lead to a long delay to conclusion and finalization of the trial.

### S4.4.4 Bad COPD Scenario

For this scenario, the desired result in each group is non-inferiority except COPD, which should be futile.

| | Non-Hyp | COPD | Immuno | ACPE | Overall |
|---|---|---|---|---|---|

| | | | | | |
|---|---|---|---|---|---|
| Futile | 0.024 | 0.560 | 0.188 | 0.681 | 0.022 |
| Non-Inferiority | 0.959 | 0.439 | 0.806 | 0.316 | 0.961 |
| Superiority | 0.016 | 0.000 | 0.006 | 0.002 | 0.017 |
| Avg. N | 782.5 | 85.4 | 248.1 | 53.5 | 1169.4 |
| Min N Unreached | 0.000 | 0.007 | 0.000 | 0.000 | |
| Avg. Stop Interim | 4.2 | 6.3 | 5.2 | 5.2 | 6.6 |

The results are similar to the Null Superiority scenario, except that the COPD group is declared non-inferior about 44% of the time, since strong borrowing across the groups pulls the COPD group toward non-inferiority if the small number of COPD patients have worse than non-inferior outcomes.

### S4.4.5 Good COPD Scenario

For this scenario, the desired result in each group is futility except COPD, which should be superior.

| | Non-Hyp | COPD | Immuno | ACPE | Overall |
|---|---|---|---|---|---|
| Futile | 0.973 | 0.994 | 0.990 | 0.997 | 0.971 |
| Non-Inferiority | 0.027 | 0.006 | 0.010 | 0.003 | 0.029 |
| Superiority | 0.000 | 0.000 | 0.000 | 0.000 | 0.000 |
| Avg. N | 612.3 | 64.3 | 170.0 | 39.0 | 885.6 |
| Min N Unreached | 0.000 | 0.000 | 0.000 | 0.000 | |
| Avg. Stop Interim | 3.0 | 4.3 | 3.0 | 3.4 | 4.5 |

The appropriate decision is generally made in the non-COPD groups, though power in the COPD group is extremely poor. Its sample size is generally insufficient to either distinguish itself from the other groups, nor to influence the other groups' conclusions.

## S4.5 Conclusions

The low accrual in the COPD group has a moderately detrimental effect on the power in the COPD group, though the strong borrowing salvages some power in the group when the effects are similar across the groups. The ability to distinguish a differential effect in the COPD group is generally poor due to the low sample size and strong borrowing. The type I error in the Null Non-Inferiority scenario is somewhat elevated.

The minimum sample size requirement for the COPD group can generally be met without adjusting the requirement. However, there is greater potential that the COPD and/or ACPE groups could be the only groups accruing in the trial at later interims, and the low accrual rate could lead to lengthy time intervals between interim analyses and final conclusions.

*S5. SPIRIT 2013 CHECKLIST*

| Section/item | Item | Description | Page |
|---|---|---|---|
| **Administrative information** | | | |
| Title | 1 | Descriptive title identifying the study design, population, interventions, and, if applicable, trial acronym | 1 |
| Trial registration | 1 | Trial identifier and registry name. If not yet registered, name of intended registry | 3,5 |
| | 2 | All items from the World Health Organization Trial Registration Data Set | 3 |
| Protocol version | 2 | Date and version identifier | 5 |
| Funding | 2 | Sources and types of financial, material, and other support | 1 |
| Roles and responsibilities | 1,21 | Names, affiliations, and roles of protocol contributors | 1,34 |
| | 2 | Name and contact information for the trial sponsor | 1 |
| | 2 | Role of study sponsor and funders, if any, in study design; collection, management, analysis, and interpretation of data; writing of the report; and the decision to submit the report for publication, including whether they will have ultimate authority over any of these activities | 1 |

| | | | |
|---|---|---|---|
| | 16 | Composition, roles, and responsibilities of the coordinating centre, steering committee, endpoint adjudication committee, data management team, and other individuals or groups overseeing the trial, if applicable (see Item 21a for data monitoring committee) | 15,16 |
| **Introduction** | | | |
| Background and rationale | 4 | Description of research question and justification for undertaking the trial, including summary of relevant studies (published and unpublished) examining benefits and harms for each intervention | 4,5 |
| | 4 | Explanation for choice of comparators | 6 |
| Objectives | 5 | Specific objectives or hypotheses | 7,8 |
| Trial design | 6 | Description of trial design including type of trial (eg, parallel group, crossover, factorial, single group), allocation ratio, and framework (eg, superiority, equivalence, noninferiority, exploratory) | 7,10 |
| **Methods: Participants, interventions, and outcomes** | | | |
| Study setting | 7 | Description of study settings (eg, community clinic, academic hospital) and list of countries where data will be collected. Reference to where list of study sites can be obtained | 7 |
| Eligibility criteria | 7,8 | Inclusion and exclusion criteria for participants. If applicable, eligibility criteria for study centres and individuals who will perform the interventions (eg, surgeons, psychotherapists) | 8,9,10 |

| | | | |
|---|---|---|---|
| Interventions | 9 | Interventions for each group with sufficient detail to allow replication, including how and when they will be administered | 11 |
| | 9 | Criteria for discontinuing or modifying allocated interventions for a given trial participant (eg, drug dose change in response to harms, participant request, or improving/worsening disease) | 12,13 |
| | 9,10 | Strategies to improve adherence to intervention protocols, and any procedures for monitoring adherence (eg, drug tablet return, laboratory tests) | 13,14,18 |
| | 9,10 | Relevant concomitant care and interventions that are permitted or prohibited during the trial | 10,11 |
| Outcomes | 5,13-15 | Primary, secondary, and other outcomes, including the specific measurement variable (eg, systolic blood pressure), analysis metric (eg, change from baseline, final value, time to event), method of aggregation (eg, median, proportion), and time point for each outcome. Explanation of the clinical relevance of chosen efficacy and harm outcomes is strongly recommended | 7,8,17 |
| Participant timeline | Figure 1 | Time schedule of enrolment, interventions (including any run-ins and washouts), assessments, and visits for participants. A schematic diagram is highly recommended (see Figure) | Figure 1 |
| Sample size | 12,13 | Estimated number of participants needed to achieve study objectives and how it was determined, including clinical and statistical assumptions supporting any sample size calculations | 14,15 |

| | | | |
|---|---|---|---|
| Recruitment | 7,8 | Strategies for achieving adequate participant enrolment to reach target sample size | 8,9,18 |
| **Methods: Assignment of interventions (for controlled trials)** | | | |
| Allocation: | | | |
| Sequence generation | 6 | Method of generating the allocation sequence (eg, computer-generated random numbers), and list of any factors for stratification. To reduce predictability of a random sequence, details of any planned restriction (eg, blocking) should be provided in a separate document that is unavailable to those who enrol participants or assign interventions | 10 |
| Allocation concealment mechanism | 6 | Mechanism of implementing the allocation sequence (eg, central telephone; sequentially numbered, opaque, sealed envelopes), describing any steps to conceal the sequence until interventions are assigned | 10 |
| Implementation | 6 | Who will generate the allocation sequence, who will enrol participants, and who will assign participants to interventions | 8,9,10 |
| Blinding (masking) | 7 | Who will be blinded after assignment to interventions (eg, trial participants, care providers, outcome assessors, data analysts), and how | 10 |
| | N/A | If blinded, circumstances under which unblinding is permissible, and procedure for revealing a participant's allocated intervention during the trial | N/A |
| **Methods: Data collection, management, and analysis** | | | |

| | | | |
|---|---|---|---|
| Data collection methods | 14,15,16 | Plans for assessment and collection of outcome, baseline, and other trial data, including any related processes to promote data quality (eg, duplicate measurements, training of assessors) and a description of study instruments (eg, questionnaires, laboratory tests) along with their reliability and validity, if known. Reference to where data collection forms can be found, if not in the protocol | 13,14,18 |
| | 14,15,16 | Plans to promote participant retention and complete follow-up, including list of any outcome data to be collected for participants who discontinue or deviate from intervention protocols | 12,13,18 |
| Data management | 14,16 | Plans for data entry, coding, security, and storage, including any related processes to promote data quality (eg, double data entry; range checks for data values). Reference to where details of data management procedures can be found, if not in the protocol | 13,13,18 |
| Statistical methods | 13,14 | Statistical methods for analysing primary and secondary outcomes. Reference to where other details of the statistical analysis plan can be found, if not in the protocol | 15,16 |
| | 15 | Methods for any additional analyses (eg, group and adjusted analyses) | 17 |
| | 13, 15 | Definition of analysis population relating to protocol non-adherence (eg, as randomised analysis), and any statistical methods to handle missing data (eg, multiple imputation) | 12, 15 |

**Methods: Monitoring**

| | | | |
|---|---|---|---|
| Data monitoring | 18,19 | Composition of data monitoring committee (DMC); summary of its role and reporting structure; statement of whether it is independent from the sponsor and competing interests; and reference to where further details about its charter can be found, if not in the protocol. Alternatively, an explanation of why a DMC is not needed | 18,19 |
| | 15 | Description of any interim analyses and stopping guidelines, including who will have access to these interim results and make the final decision to terminate the trial | 15 |
| Harms | 15 | Plans for collecting, assessing, reporting, and managing solicited and spontaneously reported adverse events and other unintended effects of trial interventions or trial conduct | 12 |
| Auditing | NA | Frequency and procedures for auditing trial conduct, if any, and whether the process will be independent from investigators and the sponsor | NA |
| **Ethics and dissemination** | | | |
| Research ethics approval | 17 | Plans for seeking research ethics committee/institutional review board (REC/IRB) approval | 19 |
| Protocol amendments | 17 | Plans for communicating important protocol modifications (eg, changes to eligibility criteria, outcomes, analyses) to relevant parties (eg, investigators, REC/IRBs, trial participants, trial registries, journals, regulators) | 19 |

| | | | |
|---|---|---|---|
| Consent or assent | 17 | Who will obtain informed consent or assent from potential trial participants or authorised surrogates, and how (see Item 32) | 19 |
| | NA | Additional consent provisions for collection and use of participant data and biological specimens in ancillary studies, if applicable | NA |
| Confidentiality | 14,15 | How personal information about potential and enrolled participants will be collected, shared, and maintained in order to protect confidentiality before, during, and after the trial | 13,14 |
| Declaration of interests | 21 | Financial and other competing interests for principal investigators for the overall trial and each study site | 21 |
| Access to data | 13,14 | Statement of who will have access to the final trial dataset, and disclosure of contractual agreements that limit such access for investigators | 13,14 |
| Ancillary and post-trial care | NA | Provisions, if any, for ancillary and post-trial care, and for compensation to those who suffer harm from trial participation | NA |
| Dissemination policy | 17 | Plans for investigators and sponsor to communicate trial results to participants, healthcare professionals, the public, and other relevant groups (eg, via publication, reporting in results databases, or other data sharing arrangements), including any publication restrictions | 19,20 |
| | 17 | Authorship eligibility guidelines and any intended use of professional writers | 19,20 |
| | 14,19,20 | Plans, if any, for granting public access to the full protocol, participant-level dataset, and statistical code | 14,19,20 |

**Appendices**

| | | | |
|---|---|---|---|
| Informed consent materials | NA, per Brazilian law | Model consent form and other related documentation given to participants and authorised surrogates | NA, per Brazilian law |
| Biological specimens | NA | Plans for collection, laboratory evaluation, and storage of biological specimens for genetic or molecular analysis in the current trial and for future use in ancillary studies, if applicable | NA |

*S6: DSMB CHARTER*

**Data Safety Monitoring Board Charter**

***RENOVATE Study***

***Randomized Clinical Trial Comparing High Flow Nasal Catheter versus Noninvasive Positive Pressure Ventilation in Acute Respiratory Failure***

**Version 1.0**

Date Accepted: *26 november 2020*

**Table of Contents**

## 2. 1.0 Introduction

This charter is the Data Safety Monitoring Board (DSMB) charter for the RENOVATE Study: a Randomized clinical trial comparing high flow nasal catheter (HFNC) versus non-invasive positive pressure ventilation (NIPPV) in acute respiratory failure (ARF).

The primary objective of the study is to demonstrate the non-inferiority of HFNC in reducing the endotracheal intubation rate or death in the first week of intervention (D7). The demonstration of superiority is also considered if accrued data shows promise in the interim analysis.

This Charter is a living document that may be revised by the DSMB as required to facilitate their role in providing trial guidance, oversight, and protecting human subjects from avoidable risk. Such revisions will be subject to approval of the trial Sponsor, PROADI-SUS/Hospital do Coração (HCor)

## 3. 2.0 Responsibilities of the Data Safety Monitoring Board

### 3.1. 2.1 General Role and Responsibilities

The role of the DSMB is to act as an independent advisor to the sponsor, providing guidance to help ensure:

- The protection of human subjects participating in the study;
- The proper conduct of the trial and interpretation of interim and final data;
- The ongoing scientific validity, integrity, and clinical and scientific relevance of the study.

The DSMB will provide recommendations about continuing, modifying, and/or stopping the study based on considerations of treatment efficacy, participant safety, and trial futility as appropriate. In addition, the DSMB may make observations or recommendations to the sponsor about, but not limited to, the following:

- Participant safety;
- Identification of and responses to adverse events and patterns in adverse events;
- Benefit/risk ratio of procedures and participant burden;
- Selection, recruitment, and retention of participants;
- Adherence to protocol requirements;
- Efficacy of the study intervention;
- Completeness, quality, and analysis of measurements;
- Amendments to the study protocol and consent forms; and
- Performance of individual centers and core labs.

Please see Section 9.0 for information regarding the communication of recommendations from the DSMB.

### 3.2. 2.2 Role of DSMB in Reviewing and Monitoring Adverse Events

Adverse event data, including information regarding adverse events (AEs) and serious adverse events (SAEs), will be reported by investigators, as detailed in the protocol. Information regarding adverse events that meet the definition of unanticipated adverse device effects (UADE) will be forwarded to the DSMB chair within 10 days of receipt by the sponsor. The DSMB will review the reports and relay any comments, concerns, or recommendations to the Sponsor within 30 days of receipt.

At each DSMB meeting, tabulations of UADEs and SAEs will be reviewed.

### 3.3. 2.3 Role of DSMB in Interim Analyses

As part of the DSMB reviews, specific reviews will occur at the timing of the interim analyses. Interim analyses are pre-specified in the protocol and adaptive design report and a first interim analysis will be conducted after complete data is available for the first 500 patients. For this purpose, *complete* data means that the patient has either dropped out of the study or has been followed for seven days and the occurrence/non-occurrence of an intubation has been recorded.

After the first interim, up to six subsequent interims will be performed. Trial will be continued provided that at least one group has not been stopped by the group early stopping rules. Each subsequent interim is triggered when an additional $X_i$ patients with complete data have been enrolled, where the value of $X_i$ depends on whether or not the hypoxemic ARF group has been stopped. Since approximately 70% of patients are expected to be in the hypoxemic ARF group, $X_i$=250 if this group has not been stopped, and $X_i$=50 if it has been stopped.

The final analysis will occur after all groups have been stopped and any remaining enrolled subjects have complete data.

At each interim analysis, the primary endpoint, *intubation rate or death in 7 days*, will be analyzed and that may lead or not to possible pre-specified adaptations to the trial. The adaptations possible are: *dropping arms according to futility, early success for superiority or for non-inferiority, changing overall hypothesis from non inferiority to superiority, and replanning sample size*. Complete details of the pre-specified interim analyses and eligible adaptations at each interim analysis are included in the statistical methods section of the protocol.

The interim analyses will be performed by a Statistical Analysis Committee (SAC) of independent statisticians who will provide a summary of results for the DSMB members in an interim analysis report. The interim analysis report from the SAC will include a brief summary of enrollment and subject status, and the adaptive algorithm results. The interim analysis report will not be a full summary of trial results and will not include safety summaries.

The DSMB deliberations will be guided by the trial design as defined in the study protocol, although the DSMB may make recommendations that deviate from the trial design if

necessary to protect patient safety, or based on considerations of treatment efficacy, harm, or trial futility. DSMB recommendations will be communicated to the sponsor senior management representative, as detailed in Section 9.0. At the time of the interim analysis, the sponsor may request that the DSMB discusses results with representatives from regulatory authorities such as the ANVISA (Brazilian National Drug Agency).

## 4. 3.0 Responsibilities of the Sponsor

The sponsor is responsible for the following:

- Provide resources necessary for the DSMB to perform its functions and to carry out its responsibilities in a timely manner.
- Designate a sponsor's senior management representative to act as a sponsor point of contact for the DSMB that is separate from day to day trial activities.
- Designate independent statisticians with expertise in adaptive designs to form an SAC that will conduct the interim analyses in accordance with the adaptive design report protocol attachment.
- Designate a separate independent statistical group to receive data from the data management center to support the DSMB and SAC, and to generate full DSMB reports.
- Implementation of any actions resulting from pre-specified interim analyses, e.g. stopping trial for futility.
- Communication of all pertinent regulatory information to regulatory agencies.

## 5. 4.0 Responsibilities of the Data Management Center

The data management center is responsible for:

- Ensuring the completeness and accuracy of data collected to the extent required by the DSMB and Sponsor.
- Providing database extracts from *Redcap software*, as specified by the Independent Statistical Group. The database extracts will be used to generate full DSMB reports as well as to create the analysis datasets the SAC will use to perform the interim analyses.
    - Database extracts for DSMB reports will be, at most, 5 days before the report is distributed to the DSMB, i.e. 10days before the DSMB meeting.
    - If DSMB reports coincide with interim analyses, the database extracts for both reports will be made on the same day.

## 6. 5.0 Responsibilities of the Independent Statistical Group Preparing the DSMB reports

The first of the two independent statistical teams will be responsible for preparing the reports for the DSMB. This group will be responsible for the following:

- Receive database extracts from the data management center.
- Prepare full DSMB reports for both the open and closed sessions. The open session reports will contain only aggregate/blinded summaries. The closed session reports will contain summaries by treatment assignment and only be available to unblinded parties. Reports will be sent to the DSMB in five business days before the scheduled meetings.
- Respond to requests for additional analyses from the DSMB.
- Participate in DSMB meetings to answer questions regarding the report contents or questions regarding the data.

## 7. 6.0 Responsibilities of the Statistical Analysis Committee Performing the Interim Analyses

The second independent statistical team is the Statistical Analysis Committee (SAC) i.e. the independent statisticians performing the pre-specified interim analyses as described in the adaptive design report attached to the protocol. The SAC will have the following responsibilities:

- Participate in the DSMB kick-off meeting, present the design, and answer DSMB questions regarding the design.
- Receive unblinded analysis datasets from the Independent Statistical Group. The analysis datasets will be a subset of the complete data and limited to the information required for performing and evaluating the interim analyses.
- Perform the interim analyses as pre-specified by the adaptive design report and review whether the adaptive algorithms are running appropriately and have the appropriate information.
- Prepare a summary report of the results of each interim analysis and send to the DSMB. Interim analyses and reports will be created within approximately 5 business days of receiving the data transfer.
- Participate in the DSMB meetings to present the interim analysis results and provide interpretation of results if requested.
- Respond to any questions from the DSMB regarding the interim analyses and perform additional analyses directly related to the interim analysis analyses if requested by the DSMB.

## 8. 7.0 Membership

The DSMB will consist of a minimum of *four* voting members with expertise in clinical research methodology, bioethics and *statistics*. The membership includes at least one statistician. The initial membership is given in Appendix 1. In the event that a DSMB member is unable to complete their duties, a suitable replacement will be identified by the DSMB Chair in cooperation with the sponsor.

A quorum will require *four* DSMB members including the chair. In an extraordinary circumstance in which the chair is unable to participate in DSMB deliberations, and an urgent DSMB meeting is required to ensure research subject safety, an acting DSMB chair may be selected by the DSMB members.

## 9. 8.0 DSMB Meetings

### 9.1. 8.1 Calling of Meetings

A meeting of the DSMB may be called at any time by the chair of the DSMB or the Sponsor. If the DSMB chair and the Sponsor are in disagreement regarding the need for a DSMB meeting, the opinion of the DSMB chair will prevail.

The DSMB will conduct meetings at least once every 6 months. Scheduled DSMB meetings may coincide with the pre-specified interim analyses or may be in addition to meetings evaluating the interim analyses. DSMB meetings may be called at any time in response to adverse events or other subject experience. Additional meetings may be called as prespecified above.

### 9.2. 8.2 Meeting Format

DSMB meetings may be held in person, by telephone conference, or a combination of the two. DSMB sessions may be either *open* or *closed* and, in general, each DSMB meeting will include both an open and a closed session. During an open session, the sponsor clinical trial team and/or other interested parties may be present. During open sessions, only non-confidential information that does not threaten the integrity or feasibility of the study will be discussed, such as general information regarding patient enrollment, amendments and modifications to the protocol, and external information which may impact the conduct of the study.

Closed DSMB sessions may only include full voting members of the DSMB, the unblinded study statistician supporting the DSMB, the SAC performing the interim analyses, and personnel whose presence is explicitly determined to be required by a majority vote of the DSMB. All matters and information, impacting the safety, ethics, and scientific validity and integrity of the study may be discussed during closed sessions. All formal recommendations considered by the DSMB will be discussed during closed sessions.

At the conclusion of the closed session, participants in the open session may be re-convened so that the DSMB Chair may provide a summary of the DSMB's recommendations, if applicable, providing an opportunity for the Sponsor clinical trial team to obtain clarification regarding the recommendations.

### 9.3. 8.3 Meeting Minutes

Meeting minutes are prepared by the DSMB chair or his designee. The minutes of open sessions including recommendations, if applicable, may be distributed freely (e.g., to other investigators, sponsor representatives), as deemed appropriate by the sponsor and DSMB chair. The minutes of closed sessions may only be distributed to personnel present at those sessions, until after the formal termination of the study. Once the study is formally terminated and all statistical analyses have been completed, the minutes of closed sessions will be released by the DSMB chair. Minutes for the closed session should include the DSMB rationale and considerations for any recommendation.

### 9.4. 8.4 Voting

The DSMB members, and only the DSMB members, vote on all recommendations to be submitted to the sponsor. To vote, a committee member must be present in person or participating via conference call.

## 10. 9.0 Procedures for Communication Letter to the Sponsor Representative

Within 10 business days of each DSMB meeting, the DSMB Chair will communicate the results of the meeting to the designated Sponsor Representative. DSMB communication(s) and/or recommendation(s) will be transmitted in written format to the Sponsor Representative who will review the information and, as appropriate, forward it to other personnel. The rationale for a DSMB recommendation may or may not be given, consistent with maintaining the scientific integrity of the study. The letter will be transmitted in a secure manner. The sponsor representative will acknowledge receipt of the letter from the DSMB within 1 business day.

If, in the opinion of the DSMB, rapid communication of information or recommendations from the DSMB to trial investigators is required to ensure the safety of study participants or the integrity of the trial, then the DSMB chair will communicate this to the Sponsor Representative during or immediately after the final open session of a DSMB meeting. Preferably then, but at the latest within 3 working days, the DSMB chair will prepare a recommendation for communication to trial investigators, which, after mutual agreement with the clinical trial team lead will be forwarded to all participating investigators by the Sponsor Representative. It is expected that trial investigators will not communicate with DSMB members about the study directly, except when making presentations or responding to questions at DSMB meetings or during conference calls.

If the DSMB does not identify any safety or other protocol-related concerns during a meeting then, within 10 days after receiving the written summary of the DSMB meeting, the clinical trial team lead will prepare a statement or Summary Report for distribution to the clinical centers that will state that:

- A review of outcome data, adverse events, and information relating to study performance (e.g., data timeliness, completeness, and quality) across all centers took place on a given date; and
- The DSMB recommended that the study continue without modification of the protocol or informed consent.

If concerns are identified, the Summary Report will include the DSMB's recommendation, instructions from the Sponsor clinical trial team lead and/or other interested parties, if any, and the remaining Summary Report content will be modified appropriately.

The DSMB will NOT provide communication letters directly to the study team.

If the DSMB decides to deviate from the pre-specified trial design (e.g., not make recommendations to the sponsor in a manner that is in accordance with the pre-specified adaptations or other decision rules defined by the trial design), then the following must occur:

- The DSMB must immediately contact the SAC personnel who created the report on which their recommendation is based and explain their rationale for not following the pre-specified decision criteria, and one of the following approaches must be taken to solve the issue:
    - If the DSMB and SAC agree that a <u>temporary</u> deviation from the pre-specified decision criteria (e.g., while additional data are collected or verified, or additional sensitivity analyses are performed), then:
        - The DSMB and SAC must agree on the steps necessary to address outstanding issues so that the question of following the pre-specified trial design can be reconsidered;
        - The sponsor does not need to be notified of the deviation while the outstanding issues are being addressed, as doing so might unnecessarily unblind the sponsor to interim results; and
        - The DSMB and SAC must agree on the maximum duration of time that can elapse before the Sponsor is informed, with or without resolution of the outstanding issues and, if that time elapses without resolution of the issue then the Sponsor must be notified of the deviation.
    - If the DSMB and SAC agree that there should be a <u>permanent</u> deviation from the pre-specified decision criteria (e.g., if it is found that a decision rule is no longer appropriate because of unanticipated patterns in the data or new information, such as safety data) then:
        - This joint decision and the rationale will be recorded in the closed minutes of the DSMB and by the chair of the SAC; and

- The sponsor does not need to be notified of the deviation until the termination of the trial or a time at which the deviation must be revealed to allow the Sponsor to continue to conduct the trial.

- If the DSMB and SAC disagree on the need to deviate from the pre-specified trial design, then:
  - The DSMB must inform the sponsor representative of the decision or action defined by the pre-specified trial design, their recommendation, and their rationale for deviating from the pre-specified design.

## 11. 10.0 Data Access and Reports

To ensure trial integrity, study investigators and other interested parties will not be allowed access to data sets containing explicit or implicit treatment arm identifiers which, if present, could allow comparisons of outcomes across treatment arms.

To fulfil its duties, the DSMB will require access to both blinded and unblinded trial data. Required reports may include, by not necessarily be limited to information on study enrollment, subject status, subject demographics and comorbidities, therapies administered, AEs, SAEs, UADEs, and outcomes.

Requests for additional content or reports will be communicated by the DSMB chair directly to the unblinded independent statistical group preparing the reports or the SAC performing the interim analyses. The nature of such requests will not be communicated to the Sponsor, other investigators, or other study personnel, to avoid biasing or impacting study content.

For each meeting, the unblinded statistical group will prepare summary reports and tables to facilitate the oversight role of the DSMB. The reports will be provided to the DSMB 5 business days before each scheduled meeting. The database extract for the data transfer will be no more than 5 days before the report is sent to the DSMB members, i.e. at most 10 days before each DSMB meeting.

## 12. 11.0 Confidentiality

All members will treat as confidential the data, reports, meeting discussions, and minutes.

The DSMB members agree to keep completely confidential and not make accessible to third parties any confidential information, business secrets and other proprietary information furnished by the other party pursuant to the establishment of the DSMB. This provision shall be in force during and after the termination of the participation in the DSMB. The terms and conditions are more particularly set out in a Confidentiality Agreement already signed by each DSMB member. The Confidentiality Agreement is a binding part of this Agreement.

Confidential Information means all information relating to studies with the Sponsor disclosed by or on behalf of the Sponsor, whether disclosed in writing, verbally or by any other means and regardless of the date it was disclosed.

## 13. 12.0 Conflict of Interest Guidelines

Members of the DSMB must not have a conflict of interest with the sponsor or the trial, including both financial and intellectual conflicts of interest. Intellectual conflicts of interest could include established medical opinions regarding the value of the investigational treatment, or competing treatment strategies, or involvement in trials of similar or competing treatment strategies.

Members of the DSMB will not buy, sell, or hold stock options in the sponsor for the following periods from the first meeting of the DSMB until the study results are made public. Any potential conflicts of interest by an DSMB member will be brought to the attention of the DSMB Chair. The guidelines will also apply to the members' spouses and dependents.

Whether a potential conflict of interest is disqualifying will be determine by the DSMB Chair in collaboration with the *insert sponsor name*.

## 14. 13.0 Signatures of DSMB Members

By signing this present document, I declare to have no conflict of interest, as outlined in Section 12.0, and to adhere to the procedures of this Charter.

Name

(Chair) _____

Date Signature

Name _____

Date Signature

Name _____

Date Signature

Name

Date Signature

## 15. DSMB Membership and Contact Information

DSMB Members

| | |
|---|---|
| 1. Anna McGothlin | anna@berryconsultants.net |
| 2. Otavio Tavares Ranzani | otavio.ranzani@isglobal.org |
| 3. Kathryn M. Rowen | kathy.rowan@icnarc.org |
| 4. Christopher W. Seymour | seymourc@pitt.edu |

Sponsor's Representative

| | |
|---|---|
| *Fernando G. Zampieri* | *fzampieri@hcor.com.br* |
| *Israel Maia* | *ismaia@hcor.com.br* |
| *Letícia Kawano Dourado* | *ldourado@hcor.com.br* |

Independent Statistical Group preparing DSMB reports

Statistical Analysis Committee preparing interim analysis reports

| | |
|---|---|
| *Mark Fitzgerald* | *mark@berryconsultants.com* |

*S7. CONSERVE-SPIRIT EXTENSION CHECKLIST 06/25/2021*

| Section/item | Item | No Change | Impact | Mitigating Strategy | Page |
|---|---|---|---|---|---|
| **Administrative information** | | | | | |
| Title | 1 | X | | | 1 |
| Trial registration | 2a | X | | | 3,5 |
| | 2b | X | | | 3 |
| Protocol version | 3 | X | | | 5 |
| Funding | 4 | X | | | 1 |
| Roles and responsibilities | 5a | X | | | 1,34 |
| | 5b | X | | | 1 |
| | 5c | X | | | 1 |
| | 5d | X | | | 15,16 |
| **Introduction** | | | | | |
| Background and rationale | 6a | X | | | 4,5 |
| | 6b | X | | | 6 |
| Objectives | 7 | X | | | 7,8 |
| Trial design | 8 | X | | | 7,10 |
| **Methods: Participants, interventions, and outcomes** | | | | | |

| | | | | | |
|---|---|---|---|---|---|
| Study setting | 9 | X | | | 7 |
| Eligibility criteria | 10 | X | | | 8,9,10 |
| Interventions | 11a | X | | | 11 |
| | 11b | X | | | 12,13 |
| | 11c | | 1.Sites misgiving about increase transmission with NIPPV<br>2.Increase beliefs of better performance of HFNC over NIPPV in Covid 19 patients | 1.Increase information about the topic<br>2. Use of NIPPV in isolated negative pressure chambers<br>3.Clarification about the equipoise maintained to centers with newsletter, email, conference call, investigator meetings | 13,14,18 |
| | 11d | X | | | 10,11 |
| Outcomes | 12 | X | | | 7,8,17 |

| | | | | | |
|---|---|---|---|---|---|
| Participant timeline | 13 | | 1a. Delayed device arrival and mounting at sites<br>1b.Delayed training sites for protocol, eCRF and device handling | 1a. Local outsourcing<br>1b. Remote training | |
| Sample size | 14 | X | | | 14,15 |
| Recruitment | 15 | Yes | 1.Delayed some sites initiation<br>2.Important decrease in recruitment rate in some centers and completely stop in others | 1. Increase contact with centers: newsletter, email, investigators meetings,<br>2. Remote training<br>3. Increase number of sites | |
| **Methods: Assignment of interventions (for controlled trials)** | | | | | |
| Allocation: | | x | | | |
| Sequence generation | 16a | X | | | 10 |
| Allocation concealment mechanism | 16b | X | | | 10 |
| Implementation | 16c | X | | | 8,9,10 |

| | | | | | | |
|---|---|---|---|---|---|---|
| Blinding (masking) | 17a | | X | | | 10 |
| | 17b | | X | N/A | | |
| **Methods: Data collection, management, and analysis** | | | | | | |
| Data collection methods | 18a | Yes | | 1. Delayed data entry by centers | 1.eCRF revision to turn it more simple<br>2.Increased queries | |
| | 18b | | X | | | 12,13,18 |
| Data management | 19 | | X | | | 13,13,18 |
| Statistical methods | 20a | | | Change in previous groups of ARF prevalence assumptions: increase in hypoxemic population immuno and non immunocompromised, decrease COPD exacerbations | Verificaton of the analysis plan with Monte Carlo Markov simulations to make sure power was maintained (suppl 2) | |
| | 20b | | | Increase Covid 19 population | Inclusion of Covid 19 group analysis | |
| | 20c | | X | | | 12, 15 |

| | | | | | |
|---|---|---|---|---|---|
| **Methods: Monitoring** | | | | | |
| Data monitoring | 21a | | Interim data evaluations | 5a.Increase DSMB awareness about possible signal of harms in different groups because of Covid 19 patients<br>5b.Strict pre defined futility rules | |
| | 21b | | Mobility restrictions | Remote monitoring | 15 |
| Harms | 22 | X | | | |
| Auditing | 23 | X | NA | | |
| **Ethics and dissemination** | | | | | |
| Research ethics approval | 24 | X | | | 19 |

| | | | | | |
|---|---|---|---|---|---|
| Protocol amendments | 25 | | Increase centers clinical workload<br>Limited families hospital visits | Protocol ammendments to revise data collection complexity limiting it to those of highest priorities and informed consent at distance (telephone) | |
| Consent or assent | 26a | | Limited numbers of next of kin present at hospital admission and families visit | Introduction of oral informed consent with posterior or remote signing (telephone) | |
| | 26b | X | NA | | |
| Confidentiality | 27 | X | | | 13,14 |
| Declaration of interests | 28 | X | | | 21 |
| Access to data | 29 | X | | | 13,14 |

| | | | | | |
|---|---|---|---|---|---|
| Ancillary and post-trial care | 30 | X | NA | | |
| Dissemination policy | 31a | X | | | 19,20 |
| | 31b | X | 19,20 | | |
| | 31c | X | 14,19,20 | | |
| **Appendices** | | | | | |
| Informed consent materials | 32 | | Less families contact with trial team | Change of informed consent text to include oral informed consent by telephone and remote signing | |
| Biological specimens | 33 | X | NA | | |