High Flow Nasal Catheter compared to Noninvasive Positive Pressure Ventilation in Acute Respiratory Failure (RENOVATE trial)

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Berry Consultants
Statistical Innovation

Simulation Updates for Accommodating COVID-19 in the RandomizEd Adaptive Trial of High-Flow Nasal Oxygen Cannula Compared to Non-Invasive Ventilation for AcuTE Respiratory Failure (RENOVATE) Trial

By Berry Consultants, LLC
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1 Introduction

This document contains an update to the RENOVATE design along with simulation results, a correction to the report issued in February 2023. These updates are aimed at accommodating the presence of COVID-19 patients in the trial. This design cannot be considered pre-specified but is a good faith effort to match the original spirit of the design, while allowing inference about the COVID-19 group as a separate group.

The primary changes to the design are:

1. Introduction of COVID-19 patients as a separate group, in addition to the four pre-specified groups: Hypoxemic De Novo ARF (Hypoxemic ARF), Chronic obstructive pulmonary disease (COPD), Hypoxemic De Novo ARF in the Immunocompromised (Immunocomp ARF), Cardiogenic acute pulmonary edema (APE).
2. Introduction of a time-varying effect for the COVID-19 group, to account for a potential change in standard of care for COVID patients.

Except where noted in this report, all design assumptions for the original design are used.

2 Statistical Model

2.1 Mixture Model

The original design used a mixture model with two different cluster patterns to allow for potentially differential effect in the APE group. The updated design uses a mixture model but with four different cluster patterns, to allow for the possibility of a differential effect in the COVID group. The four cluster patters are:

	Cluster 1	Cluster 2	Cluster 3
Cluster Pattern 1	Hypoxemic ARF, COPD, Immunocomp ARF, APE, COVID-19		

Cluster Pattern 2	Hypoxemic ARF, COPD, Immunocomp ARF, COVID-19	APE	
Cluster Pattern 3	Hypoxemic ARF, COPD, Immunocomp ARF, APE	COVID-19	
Cluster Pattern 4	Hypoxemic ARF, COPD, Immunocomp ARF	APE	COVID-19

The full model for the parameters has the form:

$$f(\pi_{nippv}, \theta) = p_1 \cdot f_1(\pi_{nippv}, \theta) + p_2 \cdot f_2(\pi_{nippv}, \theta) + p_3 \cdot f_3(\pi_{nippv}, \theta) + p_4 \cdot f_4(\pi_{nippv}, \theta)$$

where p_1, p_2, p_3, and p_4 are probabilities (that sum to 1) for the four cluster models, with f_1, f_2, f_3, and f_4 representing the probability densities for the individual cluster models. An agnostic prior is used for the probability of the 4 models. That is, a priori:

$$p_1 = p_2 = p_3 = p_4 = 0.25.$$

Note that the decision quantities can be written in a similar fashion:

$$P(\theta_g < t) = p_1^* \cdot P\left(\theta_g < t \middle| \text{cluster model 1}\right) + p_2^* \cdot P\left(\theta_g < t \middle| \text{cluster model 2}\right) + p_3^* \cdot P\left(\theta_g < t \middle| \text{cluster model 3}\right) + p_4^* \cdot P\left(\theta_g < t \middle| \text{cluster model 4}\right)$$

where p_c^* is the *posterior* probability of cluster model c. The marginal probability that the effect for a group is less than some threshold t is model-averaged across the alternative clustering models. All inference is performed on these marginal probabilities.

All prior distributions for the effects in the Hypoxemic ARF, COPD, Immunocomp ARF, and APE groups are the same as specified in the original design, as well as the prior for the variance components of the model. The prior distribution for the COVID-19 group is specified as:

$$\text{logit}(\pi_{COVID-19,nippv}) \sim N(-0.69315, 1.5^2),$$

for all cluster patterns.

2.2 Time-Machine Model

Since treatment of COVID-19 began after the start of the RENOVATE trial, and there was no established standard of care for COVID-19 patients, it is plausible that the intubation rate under standard care was not constant over the course of the trial. The statistical model needs to accommodate this potential variation. This is implemented here in the style of the "time machine" [see Saville BR, Berry DA, Berry NS, Viele K, Berry SM. The Bayesian Time Machine: Accounting for temporal drift in multi-arm platform trials. *Clinical Trials*. 2022;19(5):490-501. doi:10.1177/17407745221112013], though it is utilized *only* for the COVID-19 group.

The model for the COVID-19 group uses the following construction:

$$Y_{i,COVID-19} \sim \text{Bernoulli}\left(\pi_{i,COVID-19}\right)$$

$$\text{logit}\left(\pi_{i,COVID-19}\right) = \text{logit}\left(\pi_{COVID-19,nippv}\right) + \theta_{COVID-19} I(trt = HFNC_i) + \alpha_i$$

Here the α_i's represent the time component. The time components are modeled as:

$$\alpha_0 \equiv 0$$

$$\alpha_1 \sim N(0, \tau^2)$$

$$\alpha_i \sim N(2 \cdot \alpha_{i-1} - \alpha_{i-2}, \tau^2), \text{ for } i = 2, 3, \ldots$$

Time epoch 0 represents the most recent 90 days in the trial, so that estimates for the control group (NIPPV) correspond to the current time. Time epochs 1, 2, … represent 90-day time periods moving backward in time from the most recent randomization date. The prior distribution for the time variation parameter is:

$$\tau^2 \sim \text{Inverse Gamma}(1, 0.1)$$

2.3 Updated Stopping Rules

In order to keep the type I error rate for the "Null Superiority" and "Null Non-Inferiority" scenarios similar to the original design, the stopping rules for declaring success and non-inferiority were made more stringent. The rule adjusted the threshold according to the formula:

$$T^* = 1 - M \cdot (1 - T)$$

Where T^* is the new threshold, and T is the original threshold. Different values of M were explored until the desired type I error rate was achieved.

The thresholds for stopping for early success were thus set to:

Interim	1	2	3	4	5	6
S_i	0.9994	0.9988	0.9980	0.9972	0.9964	0.9952

The final assessment of success was set as:

$$Pr(\theta_g < 0) > 0.992.$$

The thresholds for stopping for early non-inferiority were set to:

Interim	1	2	3	4	5	6
N_i	0.9996	0.9992	0.9984	0.9974	0.9964	0.9952

The final assessment of non-inferiority was set as:

$$Pr(\theta_g < 0.442) > 0.992.$$

3 Simulations

Simulations were performed to assess operating characteristics of the updated design. The simulations did not attempt to account for past decision made in the trial, but rather simulated as if the trial were operating in this manner from the beginning of the trial.

A new assumption was required for the simulations to accommodate the time machine model. An average patient accrual rate of 180 patients per 90-day time epoch was used, and actual arrival times followed an exponential distribution.

The proportions in the patient groups were updated to reflect the observed rates:

Group	Proportion
Hypoxemic ARF	0.19
COPD	0.02
Immunocomp ARF	0.08
APE	0.08
COVID-19	0.63

3.1.1 Simulation Scenarios

Six different treatment effect scenarios were evaluated with constant intubation rate for the COVID-19 patient group.

1. 'Null Sup' scenario: treatment is equivalent to control in all groups.
2. 'Null Non-inf' scenario: the treatment effect is at the non-inferiority margin of 0.442 [in log-odds] in all groups.
3. 'All moderate' scenario: the treatment is superior in all groups, with the same effect level [in log-odds] .

4. 'Bad COVID-19' scenario: the treatment is equivalent to control in all groups except the COVID-19 group, which is set at the non-inferiority margin.
5. 'Good COVID-19' scenario: the treatment effect is at the non-inferiority margin for all groups except COPD, which is moderately superior.
6. 'Bad APE' scenario: the treatment effect is equivalent to control in all groups except the APE group, which has a worse than non-inferior rate.

The first three scenarios match scenarios detailed in the original design report. Scenarios 4 and 5 are scenarios where the COVID-19 group differs from the others, to assess potential differences in treatment effect for that group. Scenario 6 is another scenario from the original design, used to evaluate whether a difference in the APE group might be detected.

The assumed treatment rates for each scenario are shown in the table below and plotted in Figures 1-6. 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 COVID-19	Good COVID-19	Bad APE
Hypoxemic ARF	0.305	0.305	0.406	0.244	0.305	0.406	0.305
COPD	0.123	0.123	0.179	0.094	0.123	0.179	0.123
Immunocomp ARF	0.320	0.320	0.423	0.257	0.320	0.423	0.320
APE	0.054	0.054	0.082	0.040	0.054	0.082	0.108
COVID-19	0.333	0.333	0.438	0.270	0.438	0.270	0.333

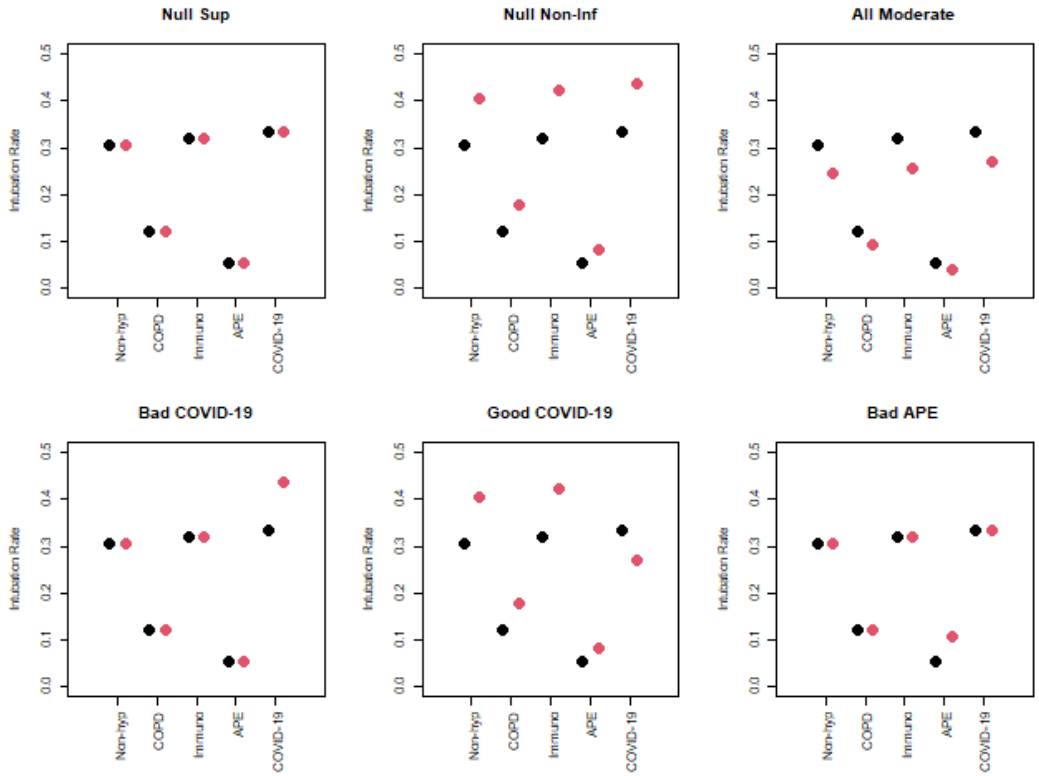

Figure 1 Graphical depiction of the control and treatment rates for the scenarios under study.

Two scenarios with time variation were explored as well. These correspond to the Null Superiority scenario is every way except for the added time component in the COVID-19 group.

A. "Down-Flat" scenario: the intubation rate drops from the beginning of the trial but then remains flat thereafter.
B. "Down-Up" scenario: the intubation rate drops from the beginning of the trial but then slow increases.

These scenarios are depicted in the graphs below. The drift is piecewise-linear in log-odds.

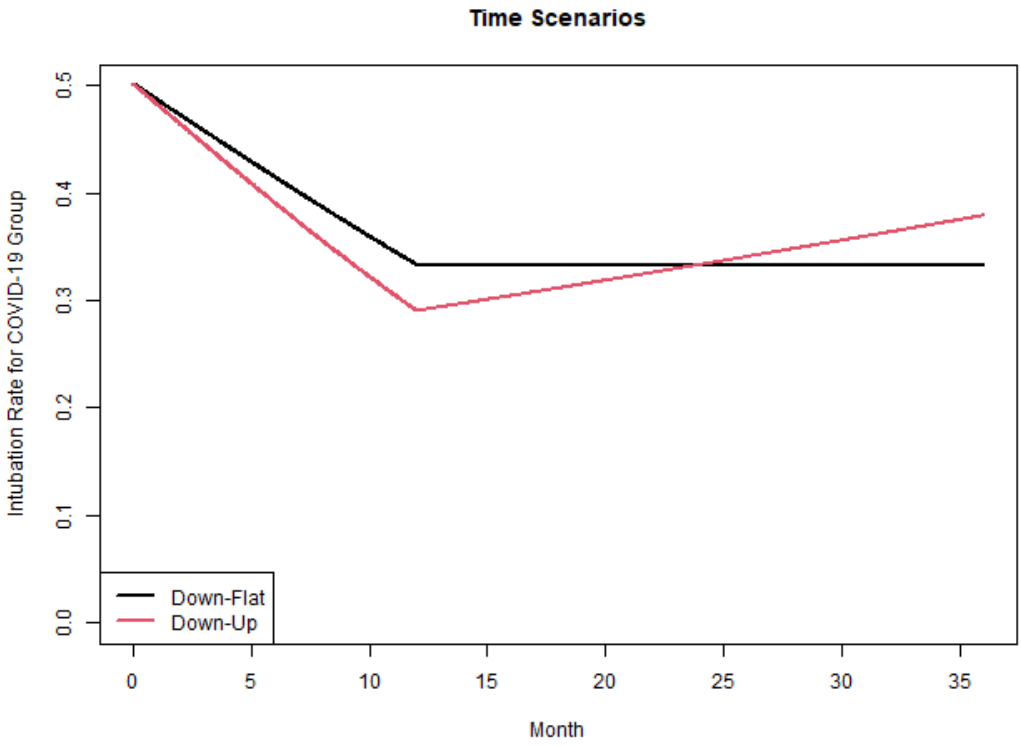

Figure 2 Intubation rate change over the course of the first 3 years of the trial, for the two scenarios simulated in this report.

3.1.2 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++.

3.1.3 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

3.2 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.

3.2.1 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	APE	COVID-19
Futile	0.140	0.314	0.236	0.945	0.055
Non-Inferiority	0.849	0.685	0.761	0.055	0.925
Superiority	0.011	0.001	0.003	0.000	0.021

In this scenario, power is slightly decreased for groups compared to the original design, with a notable drop in power for the APE group. The Type I error rate is comparable to the original design, though it is noticeably lower in the non-COVID-19 groups.

3.2.2 Null Non-Inferiority Scenario

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

	Non-Hyp	COPD	Immuno	APE	COVID-19
Futile	0.990	0.999	0.996	0.999	0.980
Non-Inferiority	0.010	0.001	0.004	0.001	0.020
Superiority	0.000	0.000	0.000	0.000	0.000

In this scenario, the Type I error rate is comparable to the original design, though it is noticeably lower in the non-COVID-19 groups.

3.2.3 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	APE	COVID-19
Futile	0.008	0.024	0.016	0.834	0.000
Non-Inferiority	0.512	0.697	0.610	0.166	0.369
Superiority	0.480	0.279	0.374	0.001	0.632

The change in power from the original design is about as may be expected for the first three groups, due to a reduction in sample size for those groups and the

elevated success threshold. The power for the APE group is quite poor, due to a combination of the increased success threshold and the modified mixture model.

3.2.4 Bad COVID-19 Scenario

For this scenario, the desired result in each group is non-inferiority except COVID-19, which should be futile.

	Non-Hyp	COPD	Immuno	APE	COVID-19
Futile	0.200	0.626	0.414	0.947	0.965
Non-Inferiority	0.794	0.374	0.583	0.053	0.035
Superiority	0.006	0.000	0.002	0.000	0.000

The non-COVID-19 groups demonstrate a modest loss in power compared to the Null Superiority scenario, but the borrowing with the COVID-19 group only increases its type I error rate slightly.

3.2.5 Good COVID-19 Scenario

For this scenario, the desired result in each group is futility except COVID-19, which should be superior.

	Non-Hyp	COPD	Immuno	APE	COVID-19
Futile	0.967	0.988	0.982	0.999	0.003
Non-Inferiority	0.033	0.012	0.018	0.001	0.559
Superiority	0.000	0.000	0.000	0.000	0.438

Compared to the Null Noninferiority scenario, the non-COVID-19 groups show a modest increase in type I error rate due to the borrowing with the COVID-19 group, where HPNC is effective. The COVID-19 group nearly always reaches non-inferiority but has an expected loss in power compared to the All Moderate scenario due to some borrowing with other groups.

3.2.6 BAD APE Scenario

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

	Non-Hyp	COPD	Immuno	APE	COVID-19
Futile	0.161	0.354	0.263	0.999	0.053
Non-Inferiority	0.827	0.645	0.732	0.001	0.930
Superiority	0.012	0.001	0.005	0.000	0.018

Results for this scenario are comparable to the Null Superiority scenario, except the APE group is rarely declared non-inferior.

3.2.7 Down-Flat Time Scenario

This scenario should be roughly equivalent to the Null Superiority scenario, since the only difference is the early decreasing intubation rate, followed by a constant rate.

	Non-Hyp	COPD	Immuno	APE	COVID-19
Futile	0.145	0.309	0.240	0.948	0.048
Non-Inferiority	0.843	0.690	0.755	0.052	0.936
Superiority	0.012	0.002	0.005	0.000	0.016

The results are nearly identical to Null Superiority scenario.

3.2.8 Down-Up Time Scenario

This scenario should be roughly equivalent to the Null Superiority scenario, since the only difference is the early decreasing intubation rate, followed by slow increase in the rate.

	Non-Hyp	COPD	Immuno	APE	COVID-19
Futile	0.145	0.310	0.243	0.951	0.059
Non-Inferiority	0.842	0.688	0.753	0.049	0.924
Superiority	0.013	0.002	0.004	0.000	0.017

Again, the results are nearly identical to Null Superiority scenario.