Statistical Analysis Plan

Protocol Number: IRC-005

A Randomized Double-Blind, Phase 3 Study Comparing the Efficacy and Safety of High-Titer versus Low-Titer Anti-Influenza Immune Plasma for the Treatment of Severe Influenza A

Version 1
(Based on Protocol Version 1 dated September 4, 2015)

ClinicalTrials.gov Identifier: NCT02572817

Introduction

This document describes the content proposed for the final primary statistical analysis of IRC 005. The focus is on analyses that address the major randomized comparisons for key safety, tolerability and efficacy outcome measures, including those needed to address the study's primary and secondary objectives.

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Protocol Summary

Full Title: A Randomized Double-Blind, Phase 3 Study Comparing the Efficacy and Safety of High-Titer versus Low-Titer Anti-Influenza Immune Plasma for the Treatment of Severe Influenza A

Short Title: IRC-005

Clinical Phase: 3

IND Sponsor: OCRPRO, NIAID

Conducted by: NIAID Influenza Research Collaboration (NIRC)

Sample Size: 150

Accrual Ceiling: 300 subjects will be screened to randomize 150 subjects

Study Population: Subjects aged two weeks or older, including children and pregnant women, hospitalized with severe influenza A infection

Study Duration: November 2015 – November 2018

Study Design: This randomized, double-blinded, multicenter phase 3 trial will assess the efficacy and safety of anti-influenza immune plasma as an addition to standard of care antivirals in subjects hospitalized with severe influenza A infection (as defined in the inclusion criteria). Up to 40 sites in the United States will participate in this protocol. Adults and children may participate. There is no exclusion for pregnancy. A total of 150 eligible subjects will be randomized in a 2:1 ratio to receive either high-titer anti-influenza plasma or control (low-titer) plasma. All subjects will receive standard care antivirals. Randomization will be stratified by:

- severity: in the intensive care unit (ICU), non-ICU hospitalization requiring supplemental oxygen, or non-ICU hospitalization not requiring supplemental oxygen
- age category (child/adult).

Subjects will be assessed on Day 0 (baseline) and on Days 1, 2, 3, 7, 14, and 28. For subjects who are not hospitalized on Days 2, 14, and 28, contact with the subject for the purpose of study data collection on those days may be performed by telephone.

All subjects will undergo a series of efficacy, safety, and hemagglutination inhibition (HAI) assessments during the study. Blood samples will be collected on Day 0, 1, 3, and 7. Oropharyngeal (OP) swabs for influenza PCR will be obtained on Days 0 and 3.

Study Agent: All plasma is from male donors to minimize the risk of transfusion-related acute lung injury (TRALI). The high-titer arm will receive 2 units of human plasma (FFP or FP24, 250-350 mL per unit, or pediatric equivalent) with influenza A/H1N1 and A/H3N2 HAI titers of at least 1:80. The sponsor will try to supply units with as high a HAI as possible. The antigens for the HAI will be for Protocol IRC005 contemporary strains defined as strains contained within that year's seasonal trivalent influenza vaccine.

The control (low-titer) arm will receive 2 units of human plasma (FFP or FP24, 250-350 mL or pediatric equivalent) with influenza A/H1N1 and A/H3N2 HAI titers of 1:10 or less.

Primary Objective: Evaluate the efficacy of treatment with high-titer versus low-titer anti-influenza immune plasma as an addition to standard care in subjects hospitalized with severe influenza A by clinical status at Day 7.

Primary Endpoint: Subjects clinical status at Day 7 (6-point ordinal scale):

1. death;
2. in ICU;
3. non-ICU hospitalization, requiring supplemental oxygen;
4. non-ICU hospitalization, not requiring supplemental oxygen;
5. not hospitalized, but unable to resume normal activities; or
6. not hospitalized with full resumption of normal activities.

Secondary Objectives:

1. Evaluate the efficacy and safety of treatment with high-titer versus low-titer anti-influenza immune plasma plus standard care, using the following parameters:
   - Subject clinical status (6-point ordinal scale) at Days 1, 2, 3, 14, and 28
   - Duration of initial hospitalization
   - 28-day mortality
   - In-hospital mortality during initial hospitalization
   - Composite of mortality and hospitalization at Days 7, 14, and 28
   - Change from baseline to Day 3 and Day 7 in National Early Warning (NEW) score
   - Duration of supplemental oxygen use among those requiring oxygen at randomization
   - Incidence of new oxygen use during the study
   - Duration of ICU stay among those requiring ICU admission at randomization
   - Incidence of new ICU admission during the study
   - Duration of mechanical ventilation use among those requiring mechanical ventilation at randomization
   - Incidence of new mechanical ventilation use during the study
   - Duration and severity of acute respiratory distress syndrome (ARDS) among those meeting definition of ARDS at randomization

- Incidence and severity of new ARDS during the study
- Duration of extra corporeal membrane oxygenation (ECMO) use among those requiring ECMO at randomization
- Incidence of new ECMO use during the study
- Change from baseline to Day 3 and Day 7 in sequential organ failure assessment (SOFA) score for age ≥18 years, and pediatric logistic organ dysfunction (PELOD) score for age <18 years
- Disposition (home, rehabilitation, chronic nursing facility, initial hospitalization ongoing at 28 days, died in hospital) following the initial hospitalization
- Percent of subjects with influenza virus detectable in OP sample at Day 3

2. Compare the plasma and control groups for HAI titers at Days 1, 3, and 7.

3. Evaluate the safety of high titer anti-influenza plasma as compared to low titer plasma as assessed by:
   - Cumulative incidence of grade 3 and grade 4 adverse events (AEs)
   - Cumulative incidence of serious adverse events (SAEs)

1. General analysis considerations

Unless otherwise specified, data summaries and analyses will be presented overall and by randomized arm. For tables with categorical variables, the number (%) will be presented. For tables with continuous variables, the mean, standard deviation, median, 25th and 75th percentiles, min and max will be presented. The number with missing values will also be shown. In calculation of percentages, subjects with missing data will not be included in the denominator.

Unless otherwise stated, analyses will be restricted to subjects with non-missing data or available follow-up time for the endpoint of interest. Tables/figures will show the number of subjects included in the analysis. Sensitivity analyses may be undertaken using (1) the last available measurement carried forward, and (2) extreme scenarios in which subjects are assigned in the worst status in one randomized arm and the best in the other (and vice versa) to illustrate the sensitivity of conclusions to any incompleteness in the data.

Appendices to the report will provide tables and figures for adults (age ≥18 years) and children (age <18 years) separately.

To help protect participant confidentiality, listings of individual patient level data will be minimized as much as possible. Dates will also not be presented in listings; instead, for example, listings will present details as days since randomization.

2. Application validation

All study-specific programs for creation of derived datasets defined in this document will require application validation and verification per written Standard Operating Procedures as appropriate.

3. Visit and Evaluation Schedule

The expected schedule for clinic visits (per protocol) is shown in **Table 1** below. The visit windows are often small with the goal of better data. Visits outside these windows are considered deviations. However, to allow use of data collected outside these windows, the visit windows have been expanded for analysis purposes as indicated. If there are multiple measurements within a window, then the one closest to the scheduled time will be used in analysis.

Table 1. IRC005 study days and analysis windows

	Days since randomization						
Visit	*Day 0 (Baseline)*	*Day 1*	*Day 2*	*Day 3*	*Day 7*	*Day 14*	*Day 28*
Per protocol (Days)	*0*	*1*	*2*	*3*	7±1	14±2	*28*±3
Analysis (Days)	*0*	*1*	*2*	*3-4*	*5-9*	*10-18*	*22-36*

4. Analysis Populations

All tables and figures will note the analysis population used:

- Enrolled Population includes all subjects who had a signed informed consent form for screening.
- Modified Intention To Treat (mITT) Population includes all subjects who were randomized and who had the study plasma infusion started (as defined in Section 12.1 of the protocol).

5. Study population

5.1 Screening, screen failures, and exclusion of subjects (Enrolled Population)

The purpose of this section is to describe the number enrolled (i.e. signed an informed consent form for screening), account for screen failures to give the number randomized, and then to account for exclusion of randomized subjects from subsequent analyses because they did not have infusion of study plasma started.

a. Table: Number screened: overall and by month/year. Dates of first and last subjects screened.
b. Table: Screen failures: Number by reason (including any due to screening eligibility violations).
c. Table: Number randomized in each arm, showing number excluded from analysis population because they did not have a plasma infusion started.
d. Table of demographic characteristics: Age at randomization and associated age group (adult versus child); sex; pregnancy status; self-reported NIH race/ethnicity (major category race, minor category ethnicity).
e. List of reasons plasma infusion never started: Randomized arm, subject ID, site, age, sex, pregnancy status, reason (including reasons due to randomization eligibility violations), subject's study status (completed 28 days, died, discontinued early from study, reason for discontinuation). [Sort by randomized arm and subject ID].
f. For enrolled subjects who were not randomized or who were randomized but did not receive plasma:
    i. List of deaths: Subject ID, whether randomized or not (and randomized arm if randomized), site, age, pregnancy status, days from enrollment to death, primary cause of death. [Sort by subject ID].
    ii. List of SAEs: Subject ID, whether randomized or not (and randomized arm if randomized), site, age, pregnancy status, days from enrollment to SAE, SAE (MedDRA SOC and PT, and verbatim description), ICH seriousness criterion met, severity grade, outcome. [Sort by subject ID, MedDRA SOC and PT].
g. List describing deviations/violations of eligibility criteria (for screening or randomization): Randomized arm, subject ID, site, age, pregnancy status, deviation/violation, description of deviation/violation, subject's study status (completed 28 days, died, discontinued early from study, reason for discontinuation). [Sort by randomized arm and subject ID].

6. Baseline characteristics (mITT population)

Baseline characteristics are those recorded as Day 0; if values are missing but are available from screening assessments, then these will be used instead. Tables in this section will show number (%) for categorical variables, and median, 25^{th} and 75^{th} percentiles, min and max for the ordinal/continuous variables; number with missing values. No statistical comparison will be undertaken between randomized arms (instead, the impact of any imbalance may be evaluated in adjusted analyses—see efficacy analyses section).

a. Table: Number randomized: overall and by month/influenza season (generally November – March, but for grouping will be August – July). Dates of first and last randomizations.
b. Table: Number randomized by site.
c. Table of demographic characteristics: Age at randomization and associated age group (adult versus child, with children classified as <2 years, ≥2 to<8 years, and ≥8 to <18 years); sex;

pregnancy status; self-reported NIH race/ethnicity (major category race, minor category ethnicity).

d. Table of body mass index (BMI) and BMI group (adults only, using standard U.S. categories for underweight, etc.).
e. Table of influenza disease status: Influenza vaccination in the current season; days from onset of influenza symptoms to randomization; influenza antivirals taken through to randomization (number (%) for each specific drug or combination of drugs, and number (%) taking any antivirals);influenza status by site testing (negative versus positive, type of testing), influenza status from central lab from Day 0 (negative versus positive) and subtype from central laboratory testing; viral shedding in OP sample by qPCR at central laboratory testing.
f. Table of days hospitalized prior to randomization
g. Table of chronic medical conditions and allergies (defined as starting >30 days prior to randomization), by MedDRA SOC and PT.
h. Table of vital signs, including SaO_2.
i. Table of clinical status: Study 6-point ordinal scale; measures of clinical support (hospitalization, oxygen requirement, mechanical ventilator requirement, ICU requirement, ECMO requirement), ARDS (yes/no, and by severity)
j. Table of respiratory status: PaO2/ FiO2 Ratio, SpO2/ FiO2 Ratio [excluding those on ECMO as these criteria are erroneous in this population).
k. Table of clinical status scores: NEW Score and SOFA Score for adults; PEW Score and PELOD Score for children.
l. Table of chest X-ray findings (only reported if performed for clinical indications): Obtained: yes/no; if yes, % with each abnormal finding.
m. Table of CBC results: White cell count and differential white cell count (neutrophil and lymphocyte percentages), hemoglobin, hematocrit, and platelets; PT and INR.
n. Table of blood chemistry results: Creatinine, glucose, total protein, ALT/GPT, AST/GOT, total bilirubin.

7. Study Execution (mITT population)

7.1 Study status of subjects and losses to follow-up.

a. Table: Number (%) for the following categories:
   - Completed Day 28 visit, categorized by whether at <25 days versus 25-31 days (protocol-specified window) versus >31 days
   - Died prior to completing Day 28 visit
   - Lost to follow-up before completing Day 28 visit (with subcategories showing reason for loss)

b. List of subjects lost to follow-up before completing Day 28 visit showing: Randomized arm, days from randomization to last study visit, subject ID, site, age, pregnancy status, reason for loss [Sort by randomized arm, days from randomization, subject ID).

7.2 Anti-influenza plasma receipt

[Note: Subjects who did not start study plasma are not included in analysis population].

a. Table showing number (%) in following categories
   - Full planned treatment
   - Partial treatment
   - More than full planned treatment

b. Table of HAI titers in plasma infused

c. Table of plasma volumes.
   - Adults – combined volume for first and second unit.
   - Children – combined volume for first and second unit (of applicable) per kg body weight.

d. For subjects who did not receive full planned treatment, or received more than full planned treatment: randomized arm, subject ID, site, age, pregnancy status, type of departure from full planned treatment (partial treatment versus more than full planned treatment), reason for not receiving full planned treatment. [Sort by randomized arm, subject ID].

e. Table of hours from randomization to start of initial plasma infusion among those documented as having received one or more infusions: median, 25^{th} and 75^{th} percentiles, min and max, number (%) starting at >24 hours after randomization.

f. Table of hours between first and second infusion among those documented as having received two or more infusions: median, 25^{th} and 75^{th} percentiles, min and max.

g. Table: median, 25^{th} and 75^{th} percentiles, min and max (and sample size) for HAI titer in first infusion; and similarly for second infusion.

h. Listing of subjects that received units that were not assigned by randomization including site, subject ID, randomized treatment arm, HAI titer in unit(s) received, ABO blood type, ABO of units received, and description of deviation

7.3 Use of influenza antivirals

a. Table of influenza antivirals taken between study enrollment and Day 28: number (%) for each specific drug or combination of drugs, and number (%) taking any antivirals (note: per protocol, subjects should be taking an antiviral).

8. Safety Endpoints (mITT Population)

8.1 Mortality

a. List of deaths: Randomized arm, days from randomization to death, subject ID, site, age, pregnancy status, days from start of first infusion to death, whether or not death occurred in-hospital during initial admission, primary cause of death, relatedness to study intervention List to include all deaths reported, irrespective of time from randomization to the date of death (i.e.

including any deaths reported after the Day 28 evaluation). [Sort by randomized arm, days from randomization to death and subject ID].

b. Table: Number (%) dying during initial hospitalization; p-value from Fisher's Exact Test. The denominator for this analysis will be the number of subjects who have an infusion started (and so included in all analyses). A sensitivity analysis will be performed using the ITT population.

c. Figure and analysis of mortality occurring between randomization and the date/time of the Day 28 evaluation: Kaplan-Meier plot of time from randomization to death (censoring at earlier of Day 28 evaluation if completed follow-up, or at date of last contact if lost to follow-up prior to Day 28 evaluation), with associated table showing: number censored, number dying; p-value from log-rank test. The estimated hazard ratio and associated 95% confidence interval comparing randomized arms will be obtained using a proportional hazards model applied to the times of death with censoring as above. For clarity, the date/time of the Day 28 evaluation for this analysis is defined to be the date/time of the Day 28 assessment of the 6-point clinical status. A death occurring on the same day as this Day 28 evaluation but after this date/time (or on a subsequent day) will not be included in this analysis (as reporting of such deaths is not required by the protocol). This also means that a death which is included in this statistical analysis which occurred on the day of the Day 28 evaluation should also show as the "result" of the Day 28 assessment of the 6-point clinical status.

8.2 Serious adverse events (SAEs)

a. Table: Number (%) of subjects with an SAE by MedDRA System Organ Class (SOC) and Preferred Term (PT); number (%) of subjects with any SAE. This table will include all SAEs, irrespective of time from randomization to the date of onset of the SAE (i.e. including any SAEs reported after the day of the Day 28 evaluation). A second table will be generated including only SAEs with onset dates through to the day of the Day 28 visit. In these tables, subjects with SAEs will be counted (e.g. counting a subject with multiple SAEs with the same PT only once for that PT).

b. Table: Number of SAEs by MedDRA System Organ Class (SOC) and Preferred Term (PT); number (%) of SAEs. This table will include all SAEs, irrespective of time from randomization to the date of onset of the SAE (i.e. including any SAEs reported after the day of the Day 28 visit). A second table will be generated including only SAEs with onset dates through to the day of the Day 28 visit. In these tables, SAEs will be counted (e.g. counting multiple SAEs with the same PT within the same subject).

c. List of SAEs: Randomized arm, subject ID, site, age, pregnancy status, days from randomization to Day 28 visit, days from randomization to SAE, days from start of first infusion to SAE, SAE (MedDRA SOC and PT, and verbatim description), ICH seriousness criterion met, severity grade, relatedness to study intervention, outcome (sort by randomized arm, subject ID, days from randomization to SAE, MedDRA SOC and PT).

8.3 Adverse events (AEs)

Note: The protocol requires reporting of Grade 3 or higher AEs.

a. Table: Number (%) of subjects with an AE by MedDRA System Organ Class (SOC) and Preferred Term (PT) and severity grade; number (%) of subjects with any AE. This table will include all AEs through to the Day 28 visit. In this table, subjects with AEs will be counted (e.g. counting a subject with multiple AEs with the same PT only once for that PT).

b. Table: Number of AEs by MedDRA System Organ Class (SOC) and Preferred Term (PT) and severity grade; number (%) of AEs. This table will include all AEs through to the Day 28 visit. In this table, AEs will be counted (e.g. counting multiple AEs with the same PT within the same subject).

c. List of AEs: Randomized arm, subject ID, site, age, pregnancy status, days from randomization to Day 28 visit, days from randomization to AE, days from start of first infusion to AE, AE (MedDRA SOC and PT, and verbatim description), severity grade, relatedness to study intervention (sort by randomized arm, subject ID, days from randomization to AE, MedDRA SOC and PT).

8.4 Changes in laboratory test values and vital signs

The protocol requires the collection of the following at Days 0, 1, 3 and 7:

- CBC: White cell count and differential white cell count (neutrophil and lymphocyte percentages), hemoglobin, hematocrit, and platelets.
- Blood chemistries: creatinine, glucose, total protein, ALT/GPT, AST/GOT, total bilirubin.
- Vital signs, including SaO_2.
- PT, INR.

a. Figure and associated Table: For each test: median, 25^{th} and 75^{th} percentiles at each required measurement time (min, max and sample size also in table).
b. Figure and associated Table: For each test: median, 25^{th} and 75^{th} percentiles change from Day 0 at each required measurement time (min, max and sample size also in table).

Note –laboratory abnormalities that are clinically significant, or require an intervention, are captured as AEs above.

8.5 Pregnancies

a. List of pregnancies including: randomized arm, subject ID, site, age of woman, gestational age at first infusion, gestational age at pregnancy outcome, type of outcome, narrative of outcome; infants' birth weight; narrative of complications if any, and presence of pre-term labor. (Sort by randomized arm, subject ID).

9. Pharmacokinetic analysis

a. Figure and associated table for each strain tested: geometric mean HAI titer with 95% CI on study Days 0, 1, 3 and 7.

b. Figure and associated table for HAI from infecting strain (H1 or H3): geometric mean HAI titer with 95% CI on study Days 0, 1, 3 and 7.
(note – this is the PK from the plasma as well as the natural development of antibodies occurring after an infection)
c. Figure and associated table for HAI from non-infecting strain (H1 or H3): geometric mean HAI titer with 95% CI on study Days 0, 1, 3 and 7. *(note – this is the PK from the plasma and should not be significantly affected from development of antibodies to a different strain)*
d. Figure and associated table for each strain tested: geometric mean HAI titer ratio (versus Day 0 titer) with 95% CI on Days 1, 3 and 7.
e. Figure and associated table from infecting strain (H1 or H3): geometric mean HAI titer ratio (versus Day 0 titer) with 95% CI on Days 1, 3 and 7.
f. Figure and associated table from non-infecting strain (H1 or H3): geometric mean HAI titer ratio (versus Day 0 titer) with 95% CI on Days 1, 3 and 7.

10. Efficacy Analysis (mITT population)

10.1 Primary endpoint: Clinical status at Day 7

The primary endpoint is the subject's clinical status at Day 7 on a 6-point ordinal scale:

1. death;
2. in the ICU;
3. non-ICU hospitalization, requiring supplemental oxygen;
4. non-ICU hospitalization, not requiring supplemental oxygen;
5. not hospitalized, but unable to resume normal activities; or
6. not hospitalized with full resumption of normal activities.

a. Table: Number (%) of subjects in each category of the 6-point scale, showing also number with missing values. Analysis of the primary endpoint will use a proportional odds model with an indicator variable for randomized treatment. The Wald test will be used to generate a p-value comparing treatments, as well as the estimated proportional odds ratio comparing treatments with associated 95% CI. A sensitivity analysis will be undertaken using the score test (the score test of the treatment effect from a proportional odds model is equivalent to a Wilcoxon rank sum test even if the proportional odds assumption does not hold). If there are missing data for the primary endpoint, then a sensitivity analysis will be undertaken to evaluate the sensitivity of study conclusions to the handling of the missing data using the last known status of the subject. A sensitivity analysis will be performed using the ITT population. The proportional odds model will be extended to undertake comparison of randomized treatments adjusted for the clinical status at baseline (this will use two indicator variables to reflect the three possible categories at baseline [categories 2, 3 and 4 in the list above]); other adjusted analyses may also be taken for any baseline variables about which there might be concern about an imbalance at baseline.

b. Subgroup analyses: For each subgroup variable a table will be generated showing the number (%) of subjects in each category of the 6-point scale and the number with missing values for each level of the subgroup variable. The proportional odds model will be extended to evaluate

possible differences in the comparison of randomized treatments between subgroups of subjects (including subgroup indicator variable(s) for the main effect and indicator variables(s) for the treatment by subgroup interaction). The following subgroup variables are pre-specified for analysis: sex (male/female), age (adult/child), race/ethnicity (based on IRC 002, this is anticipated to be white/black/other), clinical status at baseline (the three possible categories), NEW/PEW score at baseline (categorized as above/below median separately for adults and children), and days since onset of influenza symptoms to randomization (≤4 versus 5-6).

10.2 Secondary endpoints: Clinical status outcomes

a. Table of ordinal outcome during follow-up: Number (%) of subjects in each category of the 6-point scale on each study Day, showing also number with missing values (for completeness the table will also show the status at Day 0 and Day 7). At each study Day, the table will also show the p-value comparing treatments (Wald test from the proportional odds model), as well as the estimated proportional odds ratio comparing treatments with associated 95% CI. A sensitivity analysis will be performed using the ITT population.

b. Table of composite of mortality and hospitalization: Number (%) of subjects died prior to, or still in hospital on each of Days 7, 14 and 28, showing also number with missing values due to loss to follow-up. At each study Day, the table will also show the p-value comparing treatments (Wald test from a logistic regression model) as well as the estimated odds ratio comparing treatments with associated 95% CI.

10.3 Disposition

a. Table of disposition following initial hospitalization (home without assistance, home with home health care, rehabilitation, chronic nursing facility, initial hospitalization ongoing at 28 days, died during initial hospitalization): Number (%) of subjects in each disposition category, showing also number with missing values (eg due to withdrawal of consent during initial hospitalization). The table will also show the p-value comparing treatments (Wald test from the proportional odds model), as well as the estimated proportional odds ratio comparing treatments with associated 95% CI.

10.4 Secondary endpoints: Hospitalization, intensive care/support and ARDS

The protocol specifies the following secondary endpoints:

- Duration of initial hospitalization
- Duration of all hospitalizations
- Duration of admission to an ICU among those in an ICU at randomization
- Incidence of new ICU admission among those not in an ICU at randomization
- Duration of supplemental oxygen use among those requiring oxygen at randomization
- Incidence of supplemental oxygen use among those not requiring oxygen at randomization
- Duration of mechanical ventilation use among those requiring mechanical ventilation at randomization
- Incidence of new mechanical ventilation use among those not requiring mechanical ventilation at randomization

- Duration of ECMO use among those on ECMO at randomization
- Incidence of new ECMO use among those not on ECMO at randomization
- Duration of ARDS among those with ARDS at randomization
- Incidence of new ARDS among those not having ARDS at randomization

Notes:

i. Each of these measures will be evaluated through to the Day 28 visit and so will reflect the use of interventions (or of ARDS) during the study follow-up period.
ii. Deaths and losses to follow-up may affect the interpretation of the results for these endpoints (e.g. deaths, losses to follow-up). Sensitivity analyses may be undertaken to assess how the interpretation of formal analyses might be affected by these issues.

a. Table showing durations of interventions: n (will be overall sample size for hospitalizations, and number receiving intervention at randomization for other interventions and ARDS), median, 25^{th} and 75^{th} percentiles and min, max. Difference in medians between treatments, p-value from Wilcoxon's test and associated 95% CI for difference.
b. Table showing incident use of intervention (or new development of ARDS): n (will be number not receiving intervention or not having ARDS at randomization), number (%) with incident use of intervention (or new development of ARDS), difference in %'s between treatments, and odds ratio comparing treatments with p-value and associated 95% CI from exact logistic regression.

10.5 Secondary endpoints: NEW/SOFA Scores in adults, and PEW/PELOD Scores in children

The NEW and SOFA Scores are evaluated in subjects of age ≥18 years, and the PEW and PELOD Scores are evaluated in subjects of age <18 years. The Scores are evaluated at Day 0, and Days 3 and 7.

Notes:

- If a subject has a missing Score at Day 0, the subject will be excluded from the analysis. If a subject has a missing Score at Day 3 (or at Day 7) for reason other than death, then the last available Score will be used instead.
- If a subject was on ECMO on Day 0, the subject will be excluded from the analysis as these scores are affected by the ECMO intervention.
- For a subject who dies without having a Score obtained at Day 3 (or at Day 7), then the Score and change in Score will be assumed to be (ie ranked) worse than any Score and change in Score for a subject who has a Score at Day 3 (or at Day 7).
- For a subject who starts ECMO during follow-up, then the Score and change in Score on those days when on ECMO will be assumed to be (ie ranked) worse than any Score and change in Score for a subject who has Score on that day (but ranked better than a subject who died before that day).

a. Table: Completeness of evaluations for Score showing number (%) at each visit who:

i. have all of the evaluations necessary to calculate the Score
ii. have some but not all evaluations necessary to calculate the Score
iii. died prior to the visit
iv. were lost to follow-up prior to the visit
v. were in follow-up but on ECMO
vi. were in follow-up but have missing values for all of the evaluations necessary to calculate the Score.

b. Table: median, 25th and 75th percentiles, min and max Score at each of Days 0, 3 and 7, showing also number missing.

c. Table: median, 25th and 75th percentiles, min and max of change in Score at each of Days 3 and 7, showing also number missing. At each of Days 3 and 7: difference in medians between treatments, p-value from Wilcoxon's test and associated 95% CI for difference. Wei-Johnson Test will be used to provide a comparison between treatments combining over Days 3 and 7.

d. Sensitivity analysis: The sensitivity of the results to the handling of missing values at Days 3 and/or 7 (for reasons other than death) will be evaluated by considering the above analysis under more extreme scenarios than carrying forward the last available measurement: specifically by ranking subjects in one treatment group as having unfavorable changes (same rank as subjects who die) and subjects in the other treatment group as having favorable outcomes (equal to the best change); and vice versa.

10.6 Secondary endpoint: Detectable influenza virus in OP sample at Day 3

a. Table: Number (%) with positive result at Day 3, number not evaluated by reason (death, prior loss to follow-up, in follow-up but no result), difference in %'s between treatments, and odds ratio comparing treatments with p-value and associated 95% CI from exact logistic regression.