SUPPLEMENT

Prolonged awake prone positioning vs usual care for non-intubated patients with COVID-19-related acute respiratory failure: a multicentre, randomised controlled trial

Prolonged awake prone positioning vs usual care for non-intubated patients with COVID-19-related acute respiratory failure: a multicentre, randomised controlled trial

STATISTICAL ANALYSIS PLAN

ClinicalTrials.gov registration number: NCT05677984

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Chief Investigators: Prof Ling Liu

Trial statisticians: Dr Tao Chen, Dr Bingwei Chen

SAP authors: Dr Tao Chen, Prof Ling Liu, Prof Bingwei Chen

SAP version history		
Version Date	SAP Version #	Details of Changes

	Signature	Date
Dr Tao Chen (Trial Statistician)	Tao Chen	
Prof Ling Liu (Chief Investigator)	Ling Liu	
Prof Linling Hu (DMC Chair)	Lin Ling Hu	

ABBREVIATIONS

Abbreviation	Explanation
AE	Adverse Event
APP	Awake Prone Positioning
CRRT	Continuous renal replacement therapy
HFNC	High Flow Nasal Cannula
NIV	Noninvasive ventilation
IMV	Invensive mechanical ventilation
ECMO	Extracorporeal Membrane Oxygenation
ITT	Intent-to-treat
ICU	Intensive Care unit
DMC	Independent Data Monitoring Committee
PP	Per-protocol
RR	Risk Ratio
GLM	Generalised linear model
SAP	Statistical Analysis Plan
S	Standard Deviation
TSC	trial steering committee
TMG	Trial Management Group

1. INTRODUCTION

1.1. Purpose of the statistical analysis plan

The purpose of this Statistical Analysis Plan (SAP) is to define the outcome variables, statistical methods, and analysis strategies to address the study's objectives in a multicentre, randomised controlled trial comparing prolonged awake prone positioning to usual care for non-intubated patients with COVID-19-related acute respiratory failure (Protocol version 1.0, 07/01/2023).

2. STUDY OBJECTIVES AND OUTCOMES

2.1. Study Objectives

2.1.1. Primary Objective

To assess the impact of awake prone positioning on intubation rate in patients with COVID-19-related acute respiratory failure at 28 days.

2.1.2. Secondary Objectives

- To determine the mortality rate by treatment.
- To determine the length of ICU or hospital days by treatment.
- To determine the need for respiratory support
- To assess the adverse events of interest.

2.2. Outcomes

2.2.1. Primary outcome

Endotracheal intubation rate within 28 days after randomization

2.2.2. Secondary outcomes

1. Hours of APP per day
2. Mortality (within 28 days of randomization)
3. ICU and hospital length of stay (within 28 days of randomization)
4. Need for respiratory support (HFNC, NIV, IMV, ECMO), CRRT, vasopressors (within 28 days of randomization)
5. Adverse events of interest (Nausea, Unintentional removal of intravenous access, Pressure ulser, Unexpected respiratory or cardiac arrest) associated with the prone position and duration of APP.

3. STUDY DESIGN

3.1. Design

This is a multicenter, unblinded, randomized controlled trial.

3.2. Trial Sites

Trial recruitment will take place at 12 hospitals in China.

3.3. Treatments

Control group
The patients in the control groups will be treated according to the same standard of care, and receive the same oxygenation support with Standard oxygen, high-flow nasal oxygen, mask noninvasive ventilation and invasive mechanical ventilation. Awake prone position is now standard of care in all the participating centers. Patients in control group will not be asked to not prone, but they will not be encouraged to remain in prone position for long time (>12h/day)

Intervention group
The patients in the intervention groups will turn in prone position with the help and under the supervision of a caregiver to ensure that they are predominantly on their chest rather than on their side. Patients will be asked to remain in prone position as long as they can and as close as possible to 12 hours or more per day.

3.4. Randomisation

Participants will be individually randomized to either control or intervention group with a 1:1 allocation using block randomization with randomly selected but undisclosed block sizes. The block sizes will not be disclosed, to ensure concealment. The randomisation sequence was generated by the trial statistician through SAS 9.4 (procedure 'PROC PLAN'). Randomization was stratified according to study centre.

Participants will be randomized using sealed envelopes and will be enrolled in the study after providing informed consent. Subsequently, they will open the envelope and determine whether the patient will be assigned to the experimental or control group.

However, due to the nature of the intervention in this trial, patients, physicians, and study investigators were impractical to be blinded to treatment allocation. However, the data inputting and analysis was performed by trained personnel who did not participate in patient care and were blinded to group allocation.

3.1. Sample Size

According to a previous study from Ehrmann 2021 LRM[1], we expected the intubation rate was 35% from the control group. If the prone position would reduce the intubation rate by 13%, using a two-sided a = 0.05 and 80% power, gave a sample size of 409 after allowing for withdrawals and losses to follow-up of up to 10%.

4. ANALYSIS POPULATIONS

4.1. Study population data sets

The principle of intention-to-treat (ITT) is the main strategy of the analysis adopted for the primary outcome and all the secondary outcomes.

The membership of each analysis set will be determined and documented and the reasons for exclusion will be given prior to database lock. A summary table will list the individual subjects sorted by treatment group and describe their protocol deviation/violation.

Intent-to-Treat (ITT) population: This participant population consists of all consented eligible participants, regardless of whether they are ineligible, prematurely discontinue treatment, or are otherwise protocol violators/deviators.

Per-protocol population

Per protocol population will be deemed as a sub-population of the ITT population and participants will be **excluded from the ITT population** if they:

1) Switch treatment (i.e., Patients in the usual care group who remained in APP for more than 12 hour in D1 or Patients in the prolonged prone positioning group who stayed in APP less than 12 hour in D1).
2) Refused endotracheal intubation after enrollment
3) Refused to receive the randomised treatment.

This population will be used for the supportive analyses.

Safety population

This will be defined as all study participants excluding those who did not perform any prone positioning

5. GENERAL CONSIDERATIONS FOR DATA ANALYSES

5.1. Reporting guidelines

We will follow the Consolidated Standards of Reporting Trials (CONSORT) 2010 statement: updated guidelines for reporting parallel group randomized trials (http://www.consort-statement.org/)[2].

5.2. Participant disposition and Flow chart

A flow chart will be drawn up showing the number of patients screened, enrolled, and followed up in each study arm, and the number contributing to the ITT, primary analysis, per-protocol and safety analysis.

The number screened and not enrolled and the reasons for non-enrolment will be reported, as well as the number and reasons of patients who were lost for follow-up, or who were withdrawn from the study for safety reasons, or who crossed over between study arms, or because of other reasons, et al.

A list of major protocol deviations will be presented after being blindly confirmed by the trial steering committee (TSC).

5.3. Data Summaries

The Shapiro-Wilk test was used to assess the normality of the continuous variables . normally distributed data were reported as means with standard deviations (SDs). Skewed continuous data were reported as medians and interquartile ranges (IQRs).

Categorical variables will be summarised according to the absolute frequency and percentage of subjects (%) in each category level. The denominator for the percentages is the number of subjects in the treatment arm with data available unless noted otherwise.

5.4. Planned Covariates

Covariate analyses will be performed, in particular the primary outcome on the ITT population. The prespecified covariates in this study will be:

- Age
- respiratory support
- Location at enrolment

5.5. Subgroup analysis

To further test the robusteness of the study result. A *priori* subgroups analysis will be performed for the following variables

- Age (<60, >=60 in years)
- respiratory support (Standard oxygen, Non-standard oxygen [including High-flow nasal oxygen and Mask noninvasive ventilation])
- Location at enrolment (General ward, non-general ward [including Intensive care unit, Intermediate care unit and])

The lack of a significant interaction will imply that the results are consistent across subgroups. The result for the subgroups analysis will be presented in a forest plot.

5.6. Missing data

Missing baseline covariates will be imputed using simple imputation methods in the covariate adjusted analysis based on the covariate distributions. For a continuous variable, missing values will be imputed from random values from a normal distribution with mean and SD calculated from the available sample. For a categorical variable, missing values will be imputed from random values from a uniform distribution with probabilities P_1, P_2, …, and P_k from the sample. For a count data, missing values will be imputed from random values from a Poisson distribution with λ from the sample. Seed for the imputation is set as 128.

Missing efficacy covariates will not be imputed for the primary analysis as we expect the missing rate will be low (<5%) during the short follow up. However, a series of sensitivity analyses may be performed as below.

- Worse case scenarios
- Best case scenarios
- Multiple imputation under the assumption of data missing at random.

5.7. Interim Analyses and early stopping guidelines

No interim unblinding and efficacy analysis is planned.

6. STATISTICAL ANALYSES

The analyses will be carried out by the trial statistician and the primary analysis will be reviewed by a second statistician. The principle of intention-to-treat (ITT) will be the main strategy of the analysis adopted for the primary outcome and all the secondary outcomes.

R will be used to perform all data analyses and generate the majority of data displays. STATA or SAS 9.4 may also be used for some data analyses.

6.1. Primary Outcome Analysis

6.1.1. ITT analysis of the primary outcome - the primary analysis

The primary endpoint will be summarised by number (%) of participants that have intubation by treatment group.
A generalised linear model (GLM) will be used. In the GLM model, the occurrence of intubation will be treated as the response variable following a binomial distribution and the treatment as fixed effect, center as covariates and identity link function. If the above identity-binomial regression model does not converge, the risk difference will be calculated directly without accounting for the covariates.

Meanwhile, we also presented the risk ratio (RR) together with their 95%CI through a log-binomial model on the basis of the above model but with a log link function.

6.1.2. Sensitivity analysis of the primary outcome

A series of sensitivity analyses will be performed to assess the robustness of the primary efficacy analysis.

- Covariate adjusted analysis after additionally including age, respiratory support, and location at enrolment into the model in the primary analysis
- Same analysis approach performed in primary analysis but in PP population
- Subgroup analysis by performing the primary analysis separately for each category of a subgroup covariate with the treatment, subgroup variable, and their interaction term as predictors (If treatment difference can not be estimable due to the small numbers within each category, the nearest category will be combined).
- Missing primary outcome using different imputed approaches(see above **section 5.6**)

Estimates of the treatment effect will be derived and then compared with the primary endpoint analysis in order to assess whether the estimate of the treatment effect would

substantially change in these alternate scenarios. The final conclusion will be from the primay analysis if any discrepency occurs.

6.2. Secondary Outcome Analysis

All secondary outcomes will be analysed as a superiority design and two-sided 95% CIs for the treatment differences in these outcomes between two treatment groups will be calculated and presented. Secondary outcome analyses will be based on the ITT population.

6.2.1. Analysis of binary outcomes

Similar approach will be adopted for other binary outcomes as it is performed for the primary outcome in primary analysis.
Relative risks and risk difference with their two-sided 95% confidence intervals comparing two treatment arms will be derived from the GLM models with log or identity link functions, respectively.

6.2.2. Analysis of time-to-event outcomes

Mortality or intubation will also be analysed as time-to-event outcomes (e.g. time from randomisation to the occurrence of death from any cause or intubation at the end of study) and will be summarised by number (%) of participants with event, person-years, and incidence rate by treatment arm.

The trial arms will be compared using the log-rank test, as a two-sided test. The Kaplan-Meier plots will be drawn by treatment arms. The Cox regression model will be used to derive the hazard ratio and its 2-sided 95% confidence interval for comparing two treatment groups.

6.2.3. Analysis of continuous outcomes

The continuous variables such as biochemical markers or days free from respiratory support will be summarised using number of subjects (n), mean, standard deviation (SD), median (IQR), minimum, and maximum by treatment group, and will be analysed by a GLM model with treatment as fixed effect with normal distribution and identity link function, if the data follows normal distribution. Mean differences with their two-sided 95% confidence intervals between two groups will be derived. However, when data was not normal distributed, treatment difference (location shift in median) and confidence interval were calculated from Hodges Lehmann method.

6.3. Exploratory Analysis

Other statistical methods may be used if deemed necessary but was considered as exploratrory.

7. SAFETY ANALYSES

7.1. Safety Variables

AEs will be summarised using the number of AEs, the number (%) of participants with AEs by treatment arms.

8. REFERENCES

1. Ehrmann, S., et al., *Awake prone positioning for COVID-19 acute hypoxaemic respiratory failure: a randomised, controlled, multinational, open-label meta-trial.* Lancet Respir Med, 2021. **9**(12): p. 1387-1395.
2. Schulz, K.F., et al., *CONSORT 2010 statement: updated guidelines for reporting parallel group randomised trials.* BMJ, 2010. **340**: p. c332.

Prolonged awake prone positioning vs usual care for non-intubated patients with COVID-19-related acute respiratory failure: a multicentre, randomised controlled trial

STATISTICAL ANALYSIS PLAN

ClinicalTrials.gov registration number: NCT05677984

Protocol version and date: Version 2.0, 15 Apr 2023

Chief Investigators: Prof Ling Liu ***Trial statisticians:*** Dr Tao Chen, Dr Bingwei Chen ***SAP authors:*** Dr Tao Chen, Prof Ling Liu, Prof Bingwei Chen

SAP version history		
Version Date	SAP Version #	Details of Changes
		Not applicable
	V2.0	1. *In case the GLM model with binormal with identity or log link function can not be convergent, marginal standardization based on the logistic regression model (GLM model but with logit function) will be used.* 2. *The Fine–Gray model was used as a sensitivity analysis for the time to intubation to account for the competing risk of death*

	Signature	Date
Dr Tao Chen (Trial Statistician)	Tao chen	
Prof Ling Liu (Chief Investigator)	Ling Liu	
Prof Linling Hu (DMC Chair)	Linling Hu	

ABBREVIATIONS

Abbreviation	Explanation
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CRRT	Continuous renal replacement therapy
HFNC	High Flow Nasal Cannula
NIV	Noninvasive ventilation
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ITT	Intent-to-treat
ICU	Intensive Care unit
DMC	Independent Data Monitoring Committee
PP	Per-protocol
RR	Risk Ratio
GLM	Generalised linear model
SAP	Statistical Analysis Plan
S	Standard Deviation
TSC	trial steering committee
TMG	Trial Management Group

9. INTRODUCTION

9.1. Purpose of the statistical analysis plan

The purpose of this Statistical Analysis Plan (SAP) is to define the outcome variables, statistical methods, and analysis strategies to address the study's objectives in a multicentre, randomised controlled trial comparing prolonged awake prone positioning to usual care for non-intubated patients with COVID-19-related acute respiratory failure (Protocol version 1.0, 07/01/2023).

10. STUDY OBJECTIVES AND OUTCOMES

10.1. Study Objectives

10.1.1. Primary Objective

To assess the impact of awake prone positioning on intubation rate in patients with COVID-19-related acute respiratory failure at 28 days.

10.1.2. Secondary Objectives

- To determine the mortality rate by treatment.
- To determine the length of ICU or hospital days by treatment.
- To determine the need for respiratory support
- To assess the adverse events of interest.

10.2. Outcomes

10.2.1. Primary outcome

Endotracheal intubation rate within 28 days after randomization

10.2.2. Secondary outcomes

6. Hours of APP per day
7. Mortality (within 28 days of randomization)
8. ICU and hospital length of stay (within 28 days of randomization)
9. Need for respiratory support (HFNC, NIV, IMV, ECMO), CRRT, vasopressors (within 28 days of randomization)
10. Adverse events of interest (Nausea, Unintentional removal of intravenous access, Pressure ulser, Unexpected respiratory or cardiac arrest) associated with the prone position and

duration of APP.

11. STUDY DESIGN

11.1. Design

This is a multicenter, unblinded, randomized controlled trial.

11.2. Trial Sites

Trial recruitment will take place at 13 hospitals in China.

11.3. Treatments

Control group
The patients in the control groups will be treated according to the same standard of care, and receive the same oxygenation support with Standard oxygen, high-flow nasal oxygen, mask noninvasive ventilation and invasive mechanical ventilation. Awake prone position is now standard of care in all the participating centers. Patients in control group will not be asked to not prone, but they will not be encouraged to remain in prone position for long time (>12h/day)

Intervention group
The patients in the intervention groups will turn in prone position with the help and under the supervision of a caregiver to ensure that they are predominantly on their chest rather than on their side. Patients will be asked to remain in prone position as long as they can and as close as possible to 12 hours or more per day.

11.4. Randomisation

Participants will be individually randomized to either control or intervention group with a 1:1 allocation using block randomization with randomly selected but undisclosed block sizes. The block sizes will not be disclosed, to ensure concealment. The randomisation sequence was generated by the trial statistician through SAS 9.4 (procedure 'PROC PLAN'). Randomization was stratified according to study centre.

Participants will be randomized using sealed envelopes and will be enrolled in the study after providing informed consent. Subsequently, they will open the envelope and determine whether the patient will be assigned to the experimental or control group.

However, due to the nature of the intervention in this trial, patients, physicians, and study investigators were impractical to be blinded to treatment allocation. However, the data inputting and analysis was performed by trained personnel who did not participate in patient care and were blinded to group allocation.

11.5. Sample Size

According to a previous study from Ehrmann 2021 LRM[1], we expected the intubation rate was 35% from the control group. If the prone position would reduce the intubation rate by 13%, using a two-sided a = 0.05 and 80% power, gave a sample size of 409 per arm after allowing for withdrawals and losses to follow-up of up to 10%.

12. ANALYSIS POPULATIONS

12.1. Study population data sets

The principle of intention-to-treat (ITT) is the main strategy of the analysis adopted for the primary outcome and all the secondary outcomes.

The membership of each analysis set will be determined and documented and the reasons for exclusion will be given prior to database lock. A summary table will list the individual subjects sorted by treatment group and describe their protocol deviation/violation.

Intent-to-Treat (ITT) population: This participant population consists of all consented eligible participants, regardless of whether they are ineligible, prematurely discontinue treatment, or are otherwise protocol violators/deviators.

Per-protocol population

Per protocol population will be deemed as a sub-population of the ITT population and participants will be **excluded from the ITT population** if they:

4) Switch treatment (i.e., Patients in the usual care group who remained in APP for more than 12 hour in D1 or Patients in the prolonged prone positioning group who stayed in APP less than 12 hour in D1).
5) Refused endotracheal intubation after enrollment
6) Refused to receive the randomised treatment.

This population will be used for the supportive analyses.

Safety population

This will be defined as all study participants excluding those who did not perform any prone positioning

13. GENERAL CONSIDERATIONS FOR DATA ANALYSES

13.1. Reporting guidelines

We will follow the Consolidated Standards of Reporting Trials (CONSORT) 2010 statement: updated guidelines for reporting parallel group randomized trials (http://www.consort-statement.org/)[2].

13.2. Participant disposition and Flow chart

A flow chart will be drawn up showing the number of patients screened, enrolled, and followed up in each study arm, and the number contributing to the ITT, primary analysis, per-protocol and safety analysis.

The number screened and not enrolled and the reasons for non-enrolment will be reported, as well as the number and reasons of patients who were lost for follow-up, or who were withdrawn from the study for safety reasons, or who crossed over between study arms, or because of other reasons, et al.

A list of major protocol deviations will be presented after being blindly confirmed by the trial steering committee (TSC).

13.3. Data Summaries

The Shapiro-Wilk test was used to assess the normality of the continuous variables . normally distributed data were reported as means with standard deviations (SDs). Skewed continuous data were reported as medians and interquartile ranges (IQRs).

Categorical variables will be summarised according to the absolute frequency and percentage of subjects (%) in each category level. The denominator for the percentages is the number of subjects in the treatment arm with data available unless noted otherwise.

13.4. Planned Covariates

Covariate analyses will be performed, in particular the primary outcome on the ITT population. The prespecified covariates in this study will be:

- Age
- respiratory support
- Location at enrolment

13.5. Subgroup analysis

To further test the robusteness of the study result. A *priori* subgroups analysis will be performed for the following variables

- Age (<50 , 50-69 , >=70 in years)
- respiratory support (Standard oxygen, High-flow nasal oxygen and Mask noninvasive ventilation)
- Location at enrolment (Intensive care unit, Intermediate care unit and General ward)

The lack of a significant interaction will imply that the results are consistent across subgroups. The result for the subgroups analysis will be presented in a forest plot.

13.6. Missing data

Missing baseline covariates will be imputed using simple imputation methods in the covariate adjusted analysis based on the covariate distributions. For a continuous variable, missing values will be imputed from random values from a normal distribution with mean and SD calculated from the available sample. For a categorical variable, missing values will be imputed from random values from a uniform distribution with probabilities P_1, P_2, …, and P_k from the sample. For a count data, missing values will be imputed from random values from a Poisson distribution with λ from the sample. Seed for the imputation is set as 128.

Missing efficacy covariates will not be imputed for the primary analysis as we expect the missing rate will be low (<5%) during the short follow up. However, a series of sensitivity analyses may be performed as needed.

- Worse case scenarios
- Best case scenarios
- Multiple imputation under the assumption of data missing at random.

13.7. Interim Analyses and early stopping guidelines

No interim unblinding and efficacy analysis is planned.

14. STATISTICAL ANALYSES

The analyses will be carried out by the trial statistician and the primary analysis will be reviewed by a second statistician. The principle of intention-to-treat (ITT) will be the main strategy of the analysis adopted for the primary outcome and all the secondary outcomes.

R will be used to perform all data analyses and generate the majority of data displays. STATA or SAS 9.4 may also be used for some data analyses.

14.1. Primary Outcome Analysis

14.1.1. ITT analysis of the primary outcome - the primary analysis

Since there are some patients who refused to incubation after randomisation, which makes it is impossible to get the incubation afterwards, our primary analysis for primary endpoint is based on the ITT analysis. The primary endpoint will be summarised by number (%) of participants that have intubation by treatment group.

A generalised linear model (GLM) will be used. In the GLM model, the occurrence of intubation will be treated as the response variable following a binomial distribution and the treatment as fixed effect, center as covariates and identity link function. If the above identity-binomial regression model does not converge, the risk difference will be calculated directly without accounting for the covariates.

Meanwhile, we also presented the risk ratio (RR) together with their 95%CI through a log-binomial model on the basis of the above model but with a log link function.

In case of the convergence issue from the above model, we will use the marginal standardization proposed through logistics regression[3].

14.1.2. Sensitivity analysis of the primary outcome

A series of sensitivity analyses will be performed to assess the robustness of the primary efficacy analysis.

- Covariate adjusted analysis after additionally including age, respiratory support, and location at enrolment into the model in the primary analysis
- Same analysis approach performed in primary analysis but in PP population
- Subgroup analysis by performing the primary analysis separately for each category of a subgroup covariate with the treatment, subgroup variable, and their interaction term as predictors (If treatment difference can not be estimable due to the small numbers within each category, the nearest category will be combined).
- Missing primary outcome using different imputed approaches(see above **section 5.6**)

Estimates of the treatment effect will be derived and then compared with the primary endpoint analysis in order to assess whether the estimate of the treatment effect would substantially change in these alternate scenarios. The final conclusion will be from the primay analysis if any discrepency occurs.

14.2. Secondary Outcome Analysis

All secondary outcomes will be analysed as a superiority design and two-sided 95% CIs for the treatment differences in these outcomes between two treatment groups will be calculated and presented. Secondary outcome analyses will be based on the ITT population.

14.2.1. Analysis of binary outcomes

Similar approach will be adopted for other binary outcomes as it is performed for the primary outcome in primary analysis.
Relative risks and risk difference with their two-sided 95% confidence intervals comparing two treatment arms will be derived from the GLM models with log or identity link functions, respectively. If not convengent, margninal standardization proposed through logistics regression[3].

14.2.2. Analysis of time-to-event outcomes

Mortality or intubation will also be analysed as time-to-event outcomes (e.g. time from randomisation to the occurrence of death from any cause or intubation at the end of study) and will be summarised by number (%) of participants with event, person-years, and incidence rate by treatment arm.

The trial arms will be compared using the log-rank test, as a two-sided test. The Kaplan-Meier plots will be drawn by treatment arms. The Cox regression model will be used to derive the hazard ratio and its 2-sided 95% confidence interval for comparing two treatment groups.

The Fine–Gray model was used as a sensitivity analysis for the time to intubation to account for the competing risk of death.

14.2.3. **Analysis of continuous outcomes**

The continuous variables such as biochemical markers or days free from respiratory support will be summarised using number of subjects (n), mean, standard deviation (SD), median (IQR), minimum, and maximum by treatment group, and will be analysed by a GLM model with treatment as fixed effect with normal distribution and identity link function, if the data follows normal distribution. Mean differences with their two-sided 95% confidence intervals between two groups will be derived. However, when data was not normal distributed, treatment difference (location shift in median) and confidence interval were calculated from Hodges Lehmann method.

14.3. Exploratory Analysis

Other statistical methods may be used if deemed necessary but was considered as exploratrory.

15. SAFETY ANALYSES

15.1. Safety Variables

AEs will be summarised using the number of AEs, the number (%) of participants with AEs by treatment arms.

16. REFERENCES

1. Ehrmann, S., et al., *Awake prone positioning for COVID-19 acute hypoxaemic respiratory failure: a randomised, controlled, multinational, open-label meta-trial.* Lancet Respir Med, 2021. **9**(12): p. 1387-1395.
2. Schulz, K.F., et al., *CONSORT 2010 statement: updated guidelines for reporting parallel group randomised trials.* BMJ, 2010. **340**: p. c332.
3. Naimi, A.I. and B.W. Whitcomb, *Estimating Risk Ratios and Risk Differences Using Regression.* Am J Epidemiol, 2020. **189**(6): p. 508-510.