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PHARLAP Study Statistical Analysis Plan Version 1

Study Outcome Measures: The primary outcome is the number of ventilator free days at day 28 post randomisation, and will be defined as the total number of days from day 1 to day 28 on which a patient is alive and receives no assistance from mechanical ventilation, if any period of ventilator liberation lasts at least 48 consecutive hours. Study day 1 is the day of enrolment and will continue until the end of the daily ICU chart used at that site, or the end of the calendar day if electronic data collection systems are used. If patients are on mechanical ventilation for any portion of the study day they will be classified as being on mechanical ventilation for that entire study day. To be considered truly liberated from mechanical ventilation, the patient will need to have at least 48 consecutive hours where they are liberated from mechanical ventilation. This means that if, for example, they have 47 consecutive hours liberated from mechanical ventilation and then receive mechanical ventilation, none of this time will be considered as ventilator free. But if, for example, they have 49 consecutive hours liberated from mechanical ventilation and then receive mechanical ventilation, all of this time will be considered as ventilator- free, to contribute to classification of the ventilator-free status for each study day. Non-invasive mechanical ventilation will not be considered assistance if it is provided by face or nasal mask, but will be considered assistance if it is provided by tracheostomy. Any patient who dies before weaning from mechanical ventilation will be allocated the value of 0 ventilator free days. Any patient who dies after weaning from mechanical ventilation (i.e. they have at least 48 consecutive hours off mechanical ventilation) but before day 28 will not have the days after their death until day 28 considered as a ventilator free day.

The secondary outcome measures include (1) physiological outcomes such as the PaO_2/FiO_2 ratio, the static lung compliance (2) clinical outcomes such as the use of rescue therapies for severe hypoxaemia (specifically inhaled nitric oxide, inhaled prostacyclin, prone positioning, high frequency oscillatory ventilation and extracorporeal membrane oxygenation), ICU and hospital length of stay, (3) patient-centered outcomes including quality of life assessment measured using the EQ-5D at 6 months, mortality at ICU and hospital discharge, 28 days, 90 days and 6 months, cause of death and (4) safety outcomes including the rate of barotrauma, severe hypotension and serious adverse effects (SAEs). Specified incremental cost-effectiveness ratios will be reported using an analytic timeframe of 6 months, including the cost per additional quality adjusted life year (QALY) and cost per additional ventilator-free day compared to standard care. The EQ5D-5L, performed at 6 months following randomisation, will enable utilities to be determined and subsequent calculation of QALYs. Hospital costs will be determined using clinical costing systems at each participating site.

There are two planned sub-studies, including a study that aims to evaluate the change in inflammatory markers measured at baseline to day 3 in IL-8 and IL-6 concentrations in broncho-alveolar lavage fluid and plasma in a subgroup of patients and to investigate the effect of the intervention compared to standard care on inflammatory markers in different subtypes of ARDS (based on CXR).

Power calculations and sample size: With 282 subjects this study will have an 80% power to detect a difference equal to 33% of a standard deviation (equal to3VFD's) with a two-sided p-value of 0.05.[8] To account for likely occurrence that VFD will not follow a normal distribution, the sample size has been inflated by 15% to 324 in accordance with Lehmann.[12] Allowing for up to a 5% rate for withdrawal or loss to long term follow up, 340 patients will be enrolled.

Data management: All study-related data will be collected by trained staff at each study site using a paper source document (case report form) developed by the coordinating centre. Data will then be entered into an internet-based database hosted by Monash University. Data queries will be automatically generated as they are entered into this database.

Enrolled patients will be followed up to death or 6 months post-enrolment. Data will be collected in all patients including those where the study is discontinued prior to the end of the study period (Table 3). Patients who are alive at 6 months after enrolment will be interviewed by a trained follow-up assessor from the coordinating centre. This follow-up assessor will use a standardized structured telephone questionnaire to measure the QOL assessments EQ-5D13 and SF- 36v214,15.

Statistical analysis plan

Independent senior statisticians at Monash University will perform data analysis.
All data will initially be assessed for normality and log-transformed as required.
Baseline and outcome variables will be compared using Chi-square tests for categorical variables, Student's t-test for normally distributed continuous variables and Wilcoxon rank-sum tests otherwise, with results presented as frequency (%), mean (standard deviation) and median (interquartile range) respectively. To account for survival bias, duration variables and lengths of stay will be analysed using Cox-Proportional Hazards regression with all patients censored at the last known point of contact. Results will be presented as Kaplan Meier curves with a log-rank test for survival equality. For increased transparency, between group results will also be reported non-parametrically with additional stratification by survival status.
Where possible, to ensure that observed results were not due to heterogeneity between sites or baseline imbalance, additional hierarchical multivariable sensitivity analysis will be conducted adjusting for site and imbalanced variables.
Where outcome data is collected on multiple occasions, (e.g. PaO_2/F_IO_2 ratio) repeat measure mixed modelling will be employed fitting main effects for treatment and time and an interaction between treatment and time to determine if groups behave different over time.
All analyses will be conducted on an intention-to-treat [MB1] basis using SAS version (.4 (SAS Institute Inc., Cary, NC) and a two sided p-value of 0.05 will be used to indicate statistical significance.

Interim analysis: One midpoint interim analysis (after primary outcome data is available for 170 patients) will be performed to assess accumulated safety data. This will be reported to the Data Safety Monitoring Committee, but will not be made available to the Management Committee or to study sites.

Subgroup analyses: We plan to compare study outcomes in the following pre-specified subgroups:
(a) Patients with severe ARDS (PaO2/FiO2 < 100) versus patients with moderate ARDS (PaO_2/FiO_2 100-200 mmHg) at enrolment.
(b) Patients with diffuse ARDS versus patients with focal ARDS at enrolment (determined by independent radiologists).
(c) Patients who are responders to the open lung strategy versus patients who are non-responders (defined as meeting lack of improvement in static lung compliance definition).