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Effective sample size estimation for a mechanical ventilation trial through Monte-Carlo simulation: Length of mechanical ventilation and Ventilator Free Days

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ABSTRACT

Randomised control trials have sought to seek to improve mechanical ventilation treatment. However, few trials to date have shown clinical significance. It is hypothesised that aside from effective treatment, the outcome metrics and sample sizes of the trial also affect the significance, and thus impact trial design.

In this study, a Monte-Carlo simulation method was developed and used to investigate several outcome metrics of ventilation treatment, including 1) length of mechanical ventilation (LoMV); 2) Ventilator Free Days (VFD); and 3) LoMV-28, a combination of the other metrics. As these metrics have highly skewed distributions, it also investigated the impact of imposing clinically relevant exclusion criteria on study power to enable better design for significance. Data from invasively ventilated patients from a single intensive care unit were used in this analysis to demonstrate the method.

Use of LoMV as an outcome metric required 160 patients/arm to reach 80% power with a clinically expected intervention difference of 25% LoMV if clinically relevant exclusion criteria were applied to the cohort, but 400 patients/arm if they were not. However, only 130 patients/arm would be required for the same statistical significance at the same intervention difference if VFD was used.

A Monte-Carlo simulation approach using local cohort data combined with objective patient selection criteria can yield better design of ventilation studies to desired power and significance, with fewer patients per arm than traditional trial design methods, which in turn reduces patient risk. Outcome metrics, such as VFD, should be used when a difference in mortality is also expected between the two cohorts. Finally, the non-parametric approach taken is readily generalisable to a range of trial types where outcome data is similarly skewed.

1. Introduction

Mechanical ventilation (MV) is a core intensive care therapy for patients suffering from respiratory failure or acute respiratory distress syndrome (ARDS) [1]. While it is a relatively straightforward treatment, optimising mechanical ventilation without causing damage to the lung is complex in practice. A range of randomised control trials (RCTs) have been carried out to assess methods of improving patient MV care. However, many have had non-significant [2–5] findings, and the field remains uninformed about consistent action that might improve outcomes.

Respiratory failure is often a secondary symptom from a range of diseases, many causing lung damage that is mixed in effect and severity [6]. Thus, the generalised treatment proposed in some

Abbreviations: ARDS, acute respiratory distress syndrome; ICU, intensive care unit; KS-test, Kolmogorov–Smirnov test; LoMV, length of mechanical ventilation; LoMV-28, length of mechanical ventilation - 28 Days; MV, mechanical ventilation; RCT, randomised control trial; RS-test, Wilcoxon-Ranksum test; VFD, Ventilator Free Days.

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Table 1
Summary of several randomised control trials assessing LoMV and VFD.

Study	No. patients	Metric used	Groups (number of patients) (in mean ± standard deviation or median [interquartile range])		p-value
ARDSNet [5]	861	VFD	Low Vt+ (432) 12 ± 11	High Vt (429) 10 ± 11	**0.0070**
ALVEOLI [2]	549	VFD	Lower PEEP# (273) 14.5 ± 10.4	Higher PEEP (276) 13.8 ± 10.6	**0.5000**
EXPRESS [4]	767	VFD	Minimal distension (382) 3 [0–17]	Increased recruitment (385) 7 [0–19]	**0.0400**
LOVS [3]	983	LoMV	Control (507) 10 [6–16]	Lung open (475) 10 [6–17]	**0.9200**
Meta-analysis [14]	2299	VFD	Lower PEEP (1136) 11 [0–21]	Higher PEEP (1163) 13 [0–22]	**0.1000**
Individualised PEEP [12]	70	VFD	Control (36) 0 [0–15.75]	Intervention (34) 1 [0–18]	**0.1600**
Sedation study [13]	113	VFD	Control (58) 18.0 [0–24.1]	No Sedation (55) 6.9 [0–20.5]	**0.0191**

Table 2
Outcome metrics to be used in study.

1.	**LoMV**	The total duration of mechanical ventilation.
2.	**VFD**	The number of days free of MV within a 28 day period. VFD is defined by [7] as: • VFD = 0: if the patient dies before 28 days • VFD = (28 LoMV): if the patient is successfully weaned from MV within 28 days. • VFD = 0: if the patients requires MV for 28 days or more
3.	**LoMV-28**	Length of MV within 28 days, where: • LoMV-28 = 28: if the patient dies before 28 days • LoMV-28 = LoMV: if the patient is successfully weaned from MV within 28 days • LoMV-28 = 28: if the patients required MV for 28 days or more.

RCTs may not provide the best possible treatment for all patient types. In addition, non-significant RCT results may also be partly due to difficulty in determining the efficacy of mechanical ventilation therapy. Aside from patient mortality, other metrics used to assess the quality of mechanical ventilation treatment include cardiopulmonary and haemodynamic responses, patients physiological or acuity scores, and patients ventilator dependency such as length of mechanical ventilation (LoMV) and Ventilator Free Days (VFDs) [7]. However, all these metrics have limitations.

LoMV or VFD are the two most common metrics that were used to assess MV efficacy. These metrics consider patient ventilator dependency and how early patients are weaned from the ventilator along with the mortality rate for the cohort [7]. They also assess the economic impact, as ventilator dependency is associated with higher cost [8].

For a clinical trial to be successful, it must have both useful results and statistical significance [9]. While a trial may have useful clinical results, it is unable to make a meaningful statement without sufficient statistical significance or power. Thus, determining the necessary effective trial sample size to reach a sufficient power is critical. Table 1 shows a range of mechanical ventilation RCTs that use LoMV or VFD as one of their outcome metrics [2–5,10–13]. These studies ranged in size from 70–2300 patients, with only three able to reach a statistical significance of $p < 0.05$.

When clinical significance was not found, it was often due to ineffective treatment or inability to effectively treat all patients. However, high levels of patient variability as well as insufficient sample sizes can significantly impact the ability of a clinical study to achieve significance [15,16]. In an earlier study by Chiew et al. [17], it was also noted that the commonly used sample size estimation methods for a powered study [18] were not feasible for LoMV clinical data that were heavily skewed with a very long upper tail. Thus, it is not possible to truly assess whether trial design or numbers, or trial inefficacy are the course of failure. Hence, a simulation-based method using retrospective clinical cohort data may provide a better estimation of a well-powered sample size for a desired outcome metric and patient cohort [19].

This study presents a Monte-Carlo simulation-based method to estimate sample sizes for a powered and significant RCT for a range of outcome metrics relating to ventilator dependency. The outcome metrics investigated in this study were LoMV, VFD and a modified LoMV. A case study for determining the sample sizes of a planned RCT is also presented, where patient selection criteria are simulated to replicate the planned RCT as closely as possible [20]. Overall this study presents a non-parametric simulation based method that is readily generalisable for trial design, and presents it in terms of a sample size study design involving LoMV and VFD, their potential limitations, including a case example which also demonstrates how this method can effectively pre-test a cohort when designing the trial.

2. Methods

2.1. Sample size analysis metric

Three outcome metrics for sample size estimation were investigated: 1) Length of mechanical ventilation (LoMV); 2) Ventilation Free Days (VFD) [7]; and 3) Length of mechanical ventilation within 28 days (LoMV-28). VFD and LoMV-28 are modified LoMV distributions that also include mortality information where deceased patients have 0 VFD or 28 days of LoMV. Table 2 shows a more detailed description of each outcome metric used in this study.

2.2. Retrospective patient cohort data (Cohort A)

Retrospective data from 5176 patients admitted to the Christchurch Hospital Intensive Care Unit (ICU) from 2011 to 2014

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