Reducing the Length of Mechanical Ventilation with Significance

A Case Study of Sample Size Estimation Trial Design using Monte-Carlo Simulation

Yeong Shiong Chiew[1], Christopher Pretty[1], Elena Molchanova[2], Carl Scarrott [2], Daniel Redmond[1], Geoffrey M Shaw[3], J. Geoffrey Chase[1]

[1] Department of Mechanical Engineering, University of Canterbury, Christchurch, New Zealand

[2] School of Mathematics and Statistics, University of Canterbury, Christchurch, New Zealand

[3] Intensive Care Unit, Christchurch Hospital, Christchurch, New Zealand

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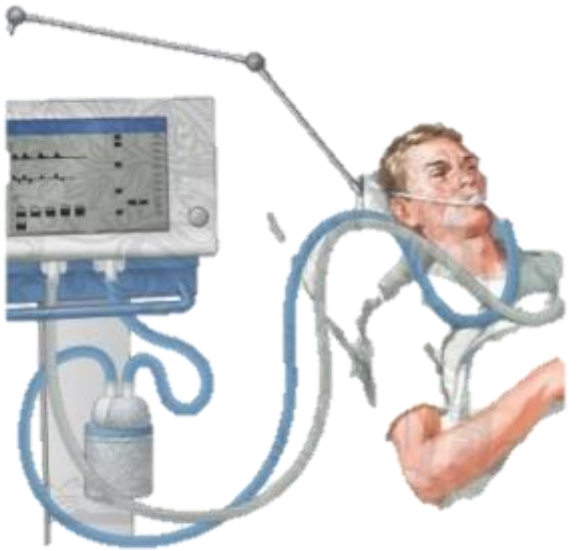
Mechanical Ventilation

- Primary support for patients with respiratory failure
  - Maintaining lung recruitment
  - Effective O2 delivery
  - Provide good patient-ventilator interaction without inducing further stress



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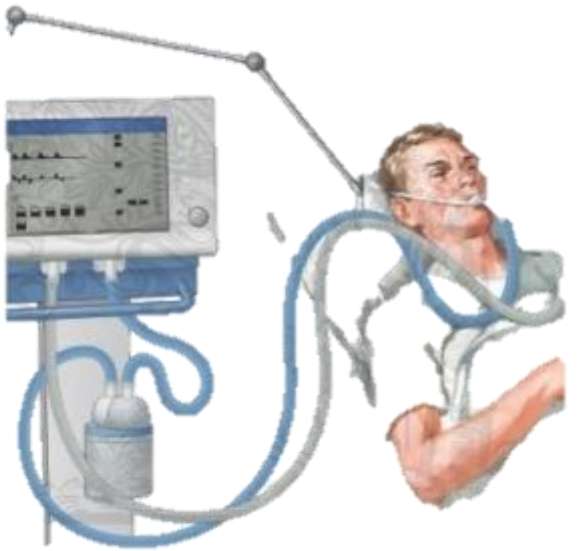

- What is considered as effective ventilation?
  - No further injuries
  - Patient receiving sufficient O_2
  - Good patient interaction with ventilation
  - Recovery

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- What is the surrogate of an effective mechanical ventilation?

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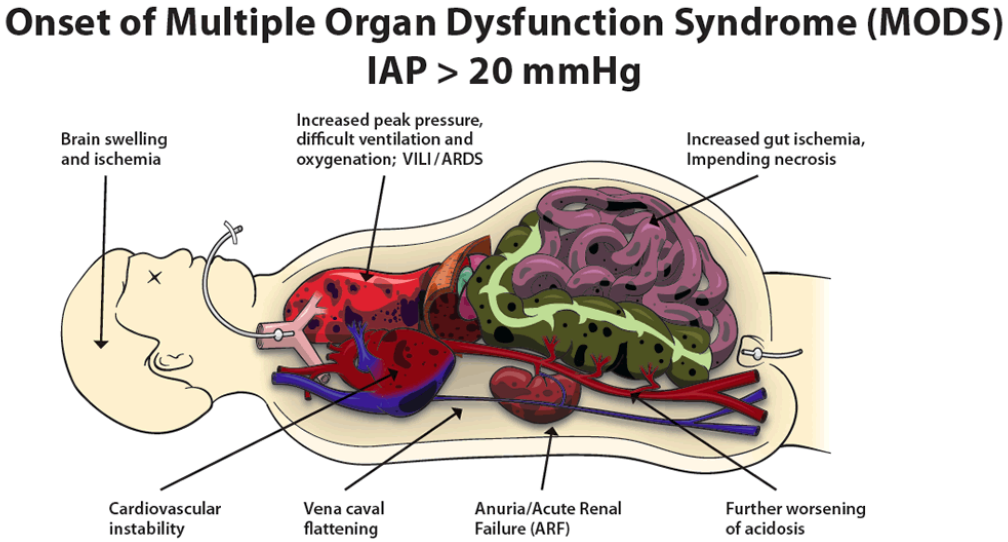

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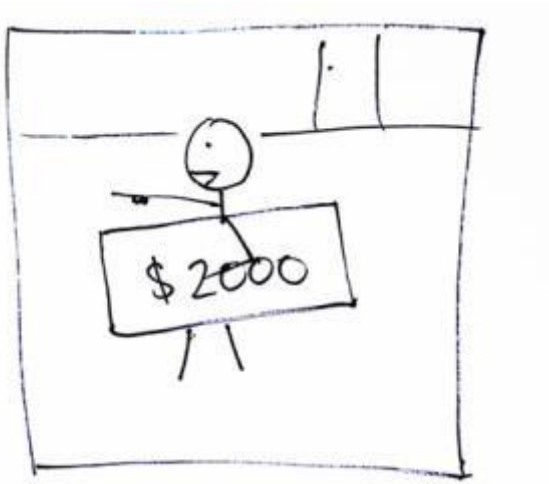
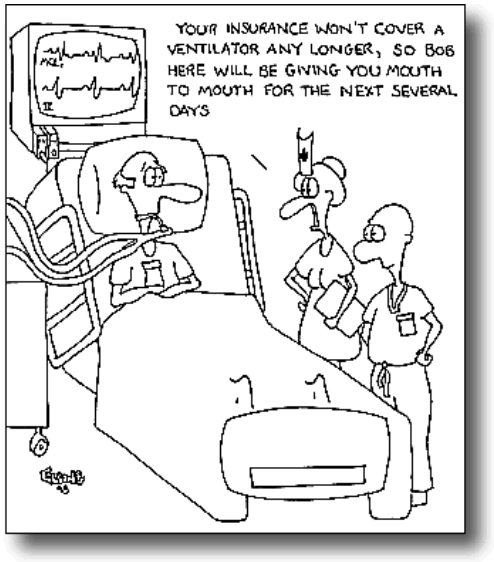
- Why Ventilator Free Days (VDF) or Length of Mechanical ventilation (LOMV)?





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Existing studies with LoMV as primary or secondary outcome

Study	No. Patient	Outcome	Groups (Number of patient) LoMV or Vent Free Days (in mean ± standard deviation or median [interquartile range])		p-value
ARDSNet (The Acute Respiratory Distress Syndrome Network, 2000)	861	VFD*	Low Vt+ (432) 12±11	High Vt (429) 10±11	0.0070
ALVEOLI (Brower et al., 2004)	549	VFD	Lower PEEP# (273) 14.5±10.4	Higher PEEP (276) 13.8±10.6	0.5000
EXPRESS (Mercat et al., 2008)	767	VFD	Minimal distension (382) 3 [0-17]	Increased recruitment (385) 7 [0-19]	0.0400
LOVS (Meade et al., 2008)	983	LoMV	Control (507) 10 [6-16]	Lung open (475) 10 [6-17]	0.9200
Meta-Analysis (Briel et al., 2010)	2299	VFD	Lower PEEP (1136) 11 [0-21]	Higher PEEP (1163) 13 [0-22]	0.1000
Individualised PEEP (Pintado et al., 2013)	70	VFD	Control (36) 0 [0-15.75]	Intervention (34) 1 [0-18]	0.1600
Sedation Study (Strøm et al., 2010)	113	VFD	Control (58) 18.0 [0-24.1]	No Sedation (55) 6.9 [0-20.5]	0.0191

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This study aimed to:

- Estimate the sample size required for a randomised controlled trial for mechanical ventilation.
  - Sample size for the change in LoMV detection
- We compare two methods
  - Using model-based method (Altman-nomogram)
  - Using simulation-based method (Monte-Carlo)
- Using ICU patients data from a single hospital Intensive care unit (From 2011-2013)

Christchurch ICU Record

- Age, Apache diagnostic code, ICU mortality, length of mechanical ventilation, ventilation modes.
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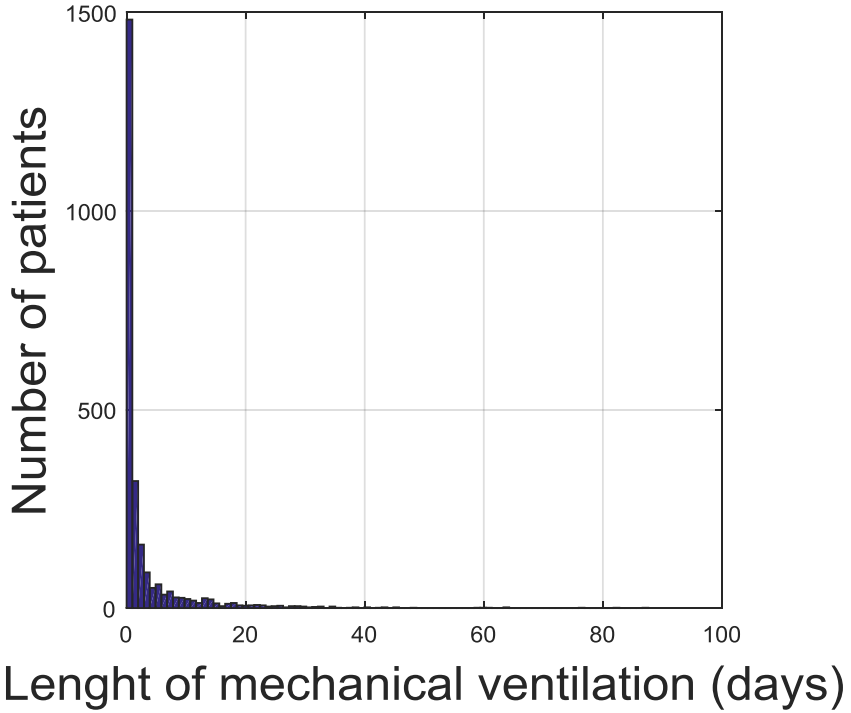

- Cohort A LoMV mean (± SD) LoMV for Cohort A is 3.23 ± 7.03 days (median = 0.72 days [IQR: 0.24-2.62]).

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Altman Nomogram

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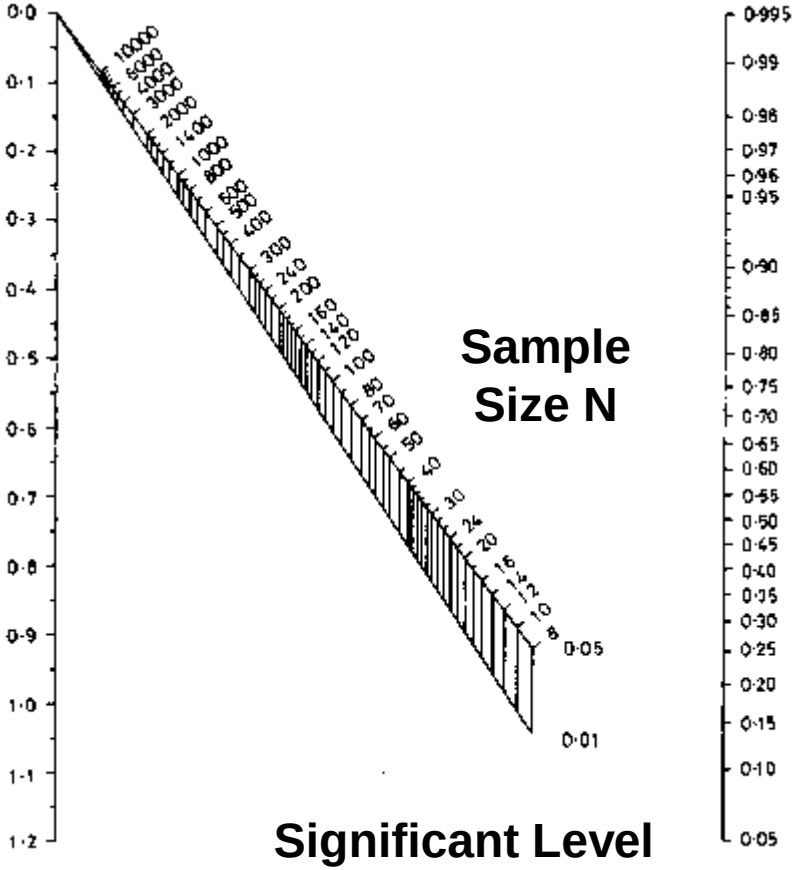
Standardised Difference = Δmean/ SD



Sample Size N

Power

Significant Level

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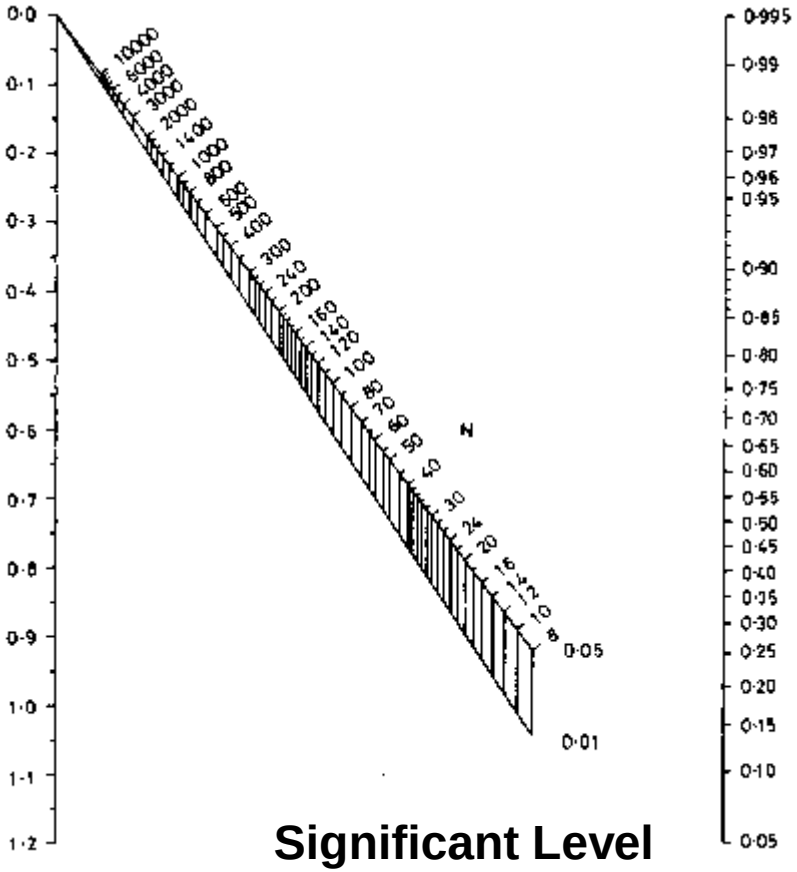
Altman Nomogram

3 day difference

Standardised Difference



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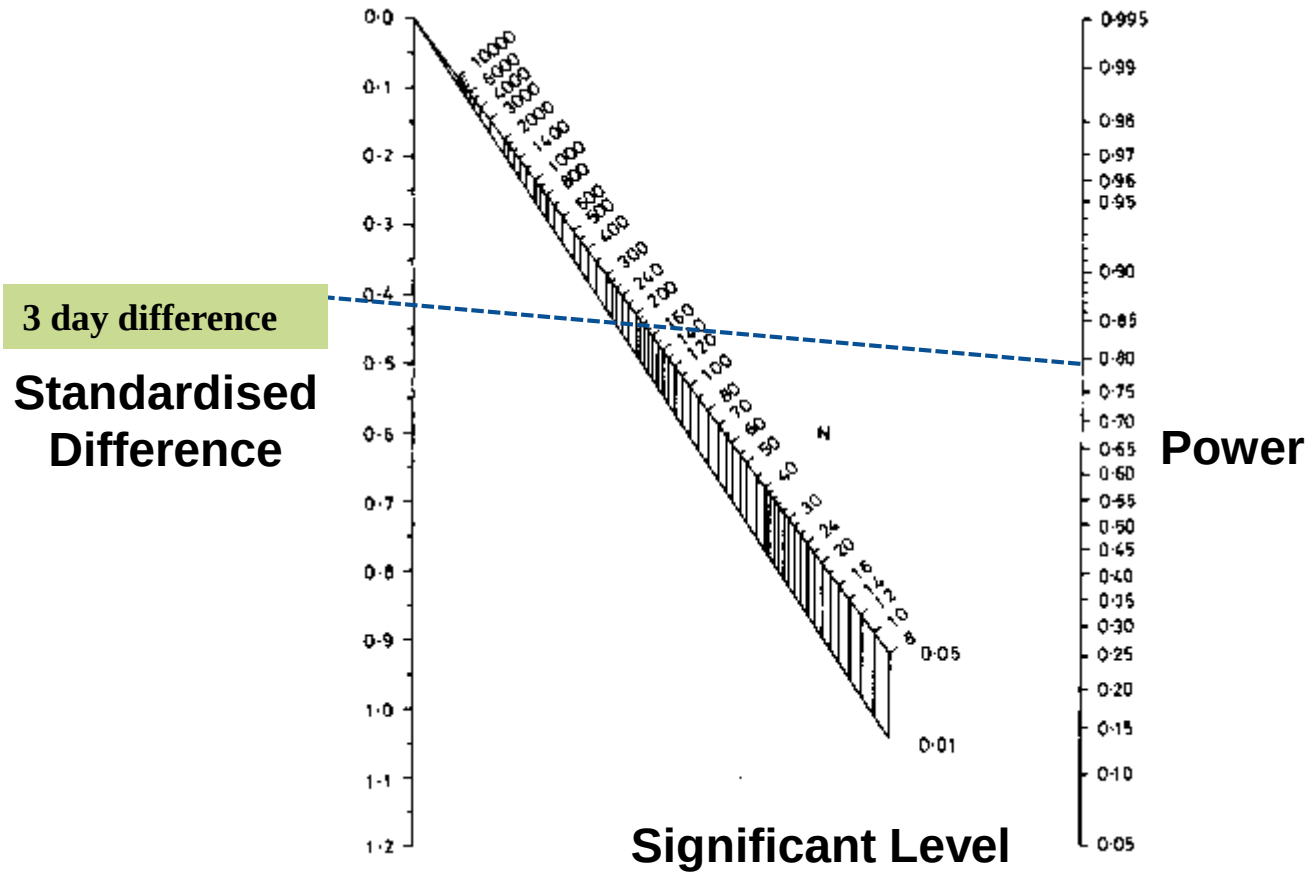

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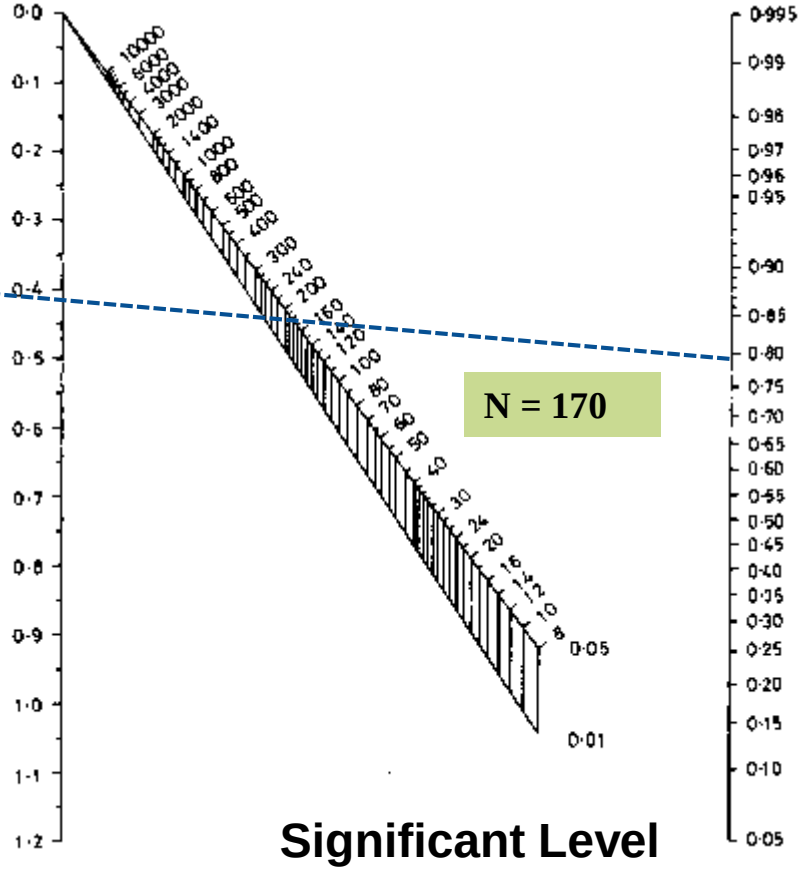

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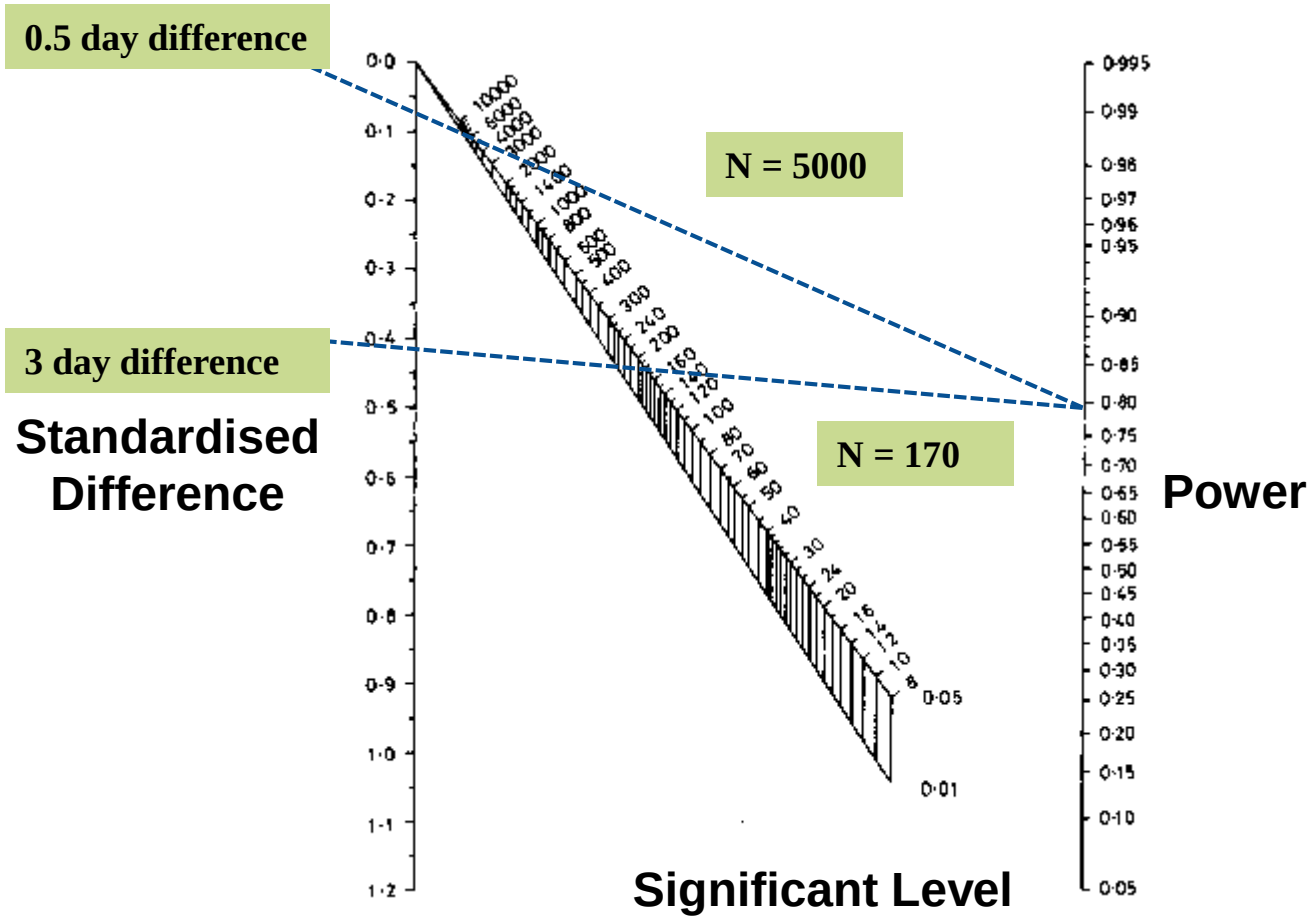

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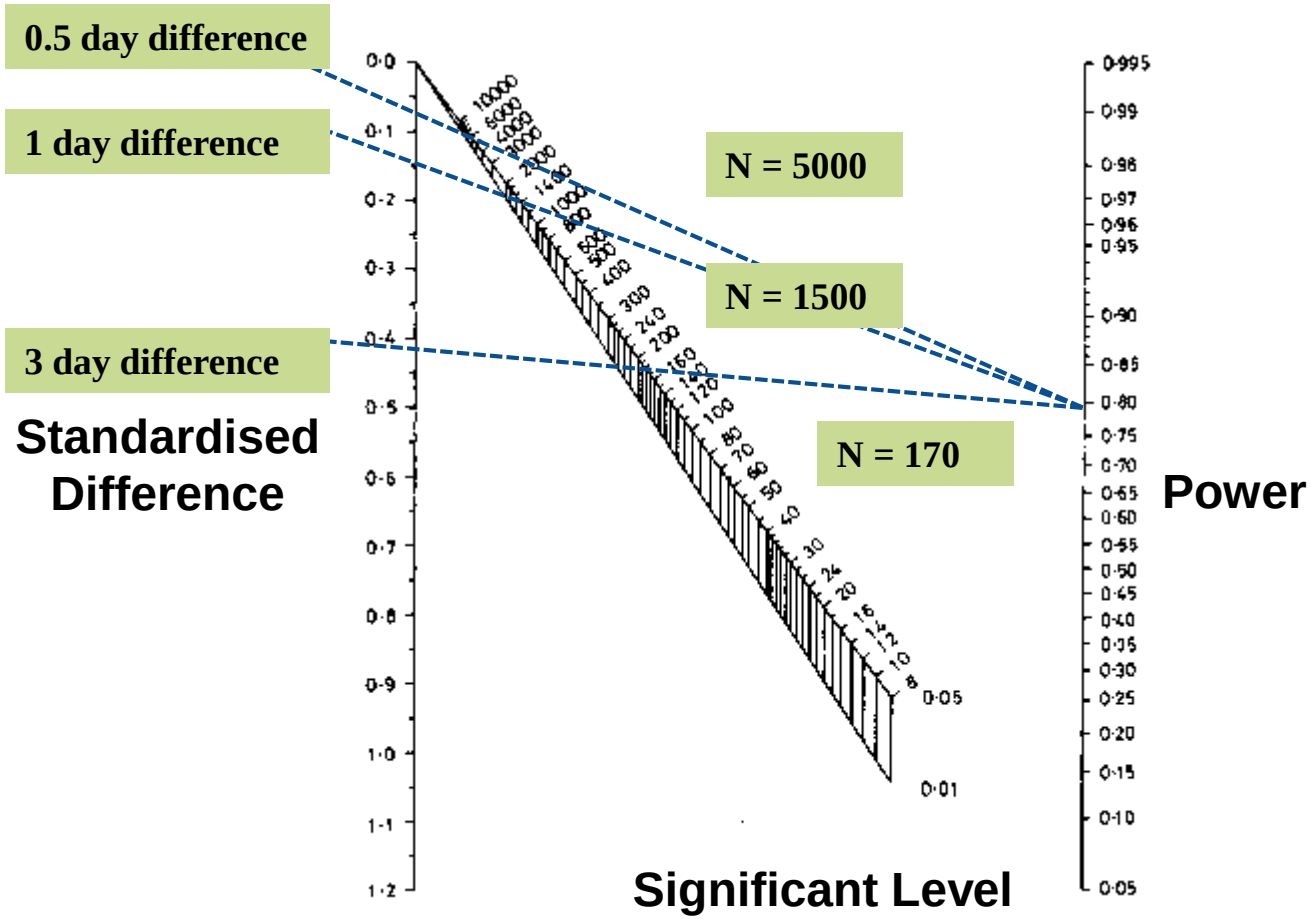

Monte-Carlo Simulation

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- Using Simulation based approach, we are able to impose a selection criteria on patients
  - (1) Patients who are likely to be discontinued from MV within 24 hours
  - (2) Patients with increase intracranial pressure
  - (3) Patients who have significant weakness from any neurological disease
  - (4) Patients who have asthma as the primary presenting condition or a history of significant chronic obstructive pulmonary disease, and
  - (5) Patients who are pregnant

- How do we know which patient? APACHE II Diagnostic codes

Christchurch ICU Record

	Code	Description		Code	Description
Non - Operative	100	Cardiovascular	Post - Operative	1200	Cardiovascular
	200	Respiratory		1300	Respiratory
	300	Gastrointestinal		1400	Gastrointestinal
	400	Neurological		1500	Neurological
	500	Sepsis		1600	Trauma
	600	Trauma		1700	Renal/ Genitourinary
	700	Metabolic		1800	Gynaecological
	800	Haematology		1900	Musculoskeletal
	900	Renal disorder		2100	Haematological
	1000	Other medical disorders		2200	Metabolic
	1100	Musculoskeletal/ Skin disease			
	0	No diagnosis entered			

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Monte-Carlo Simulation

- Non-operative neurological (400)
- Post-operative neurological (1500)
- Chronic obstructive pulmonary disease (206)
- Asthma (209)
- Head trauma with or without multi trauma (601)
- Multi trauma with spinal injury (604)
- Isolated cervical spine injury (605)
- Post operation patients: head trauma with or without multi trauma (1601)
- Post operation patients: multi trauma with spinal injury (1604)
- Post operation patients: isolated cervical spine injury (1605)
- Pregnancy-related disorder (1802).
- Patients with LoMV less than 1 day and more than 30 days were also excluded.

These exclusion criteria were chosen based the clinical implication that these patient may not benefit from a MV intervention, or could be harmed in some cases.

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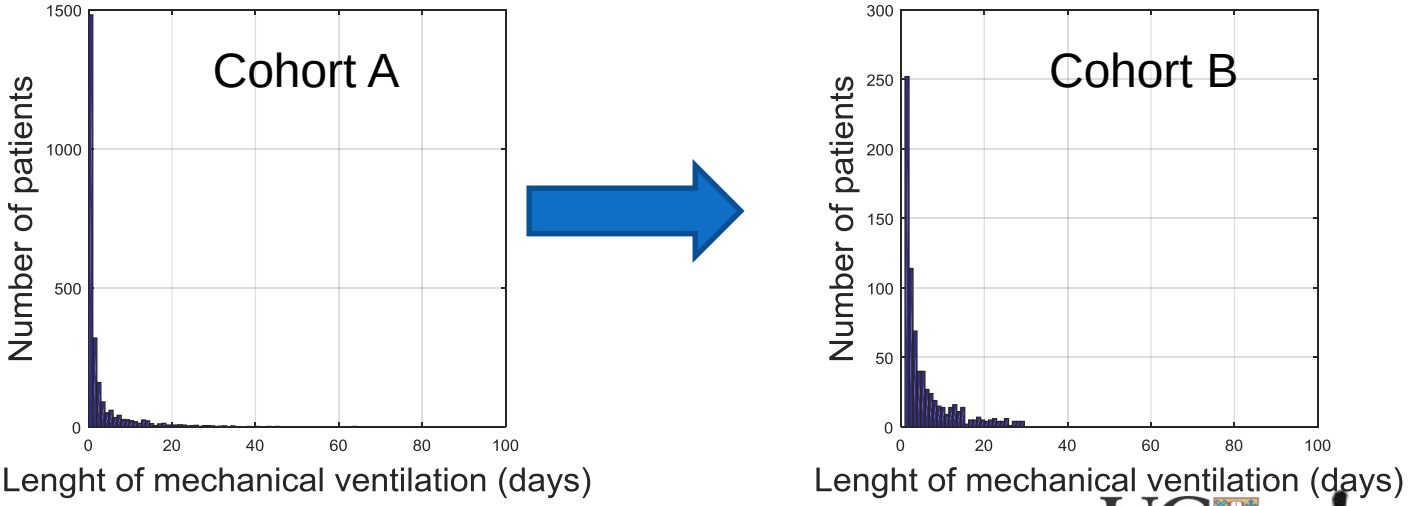

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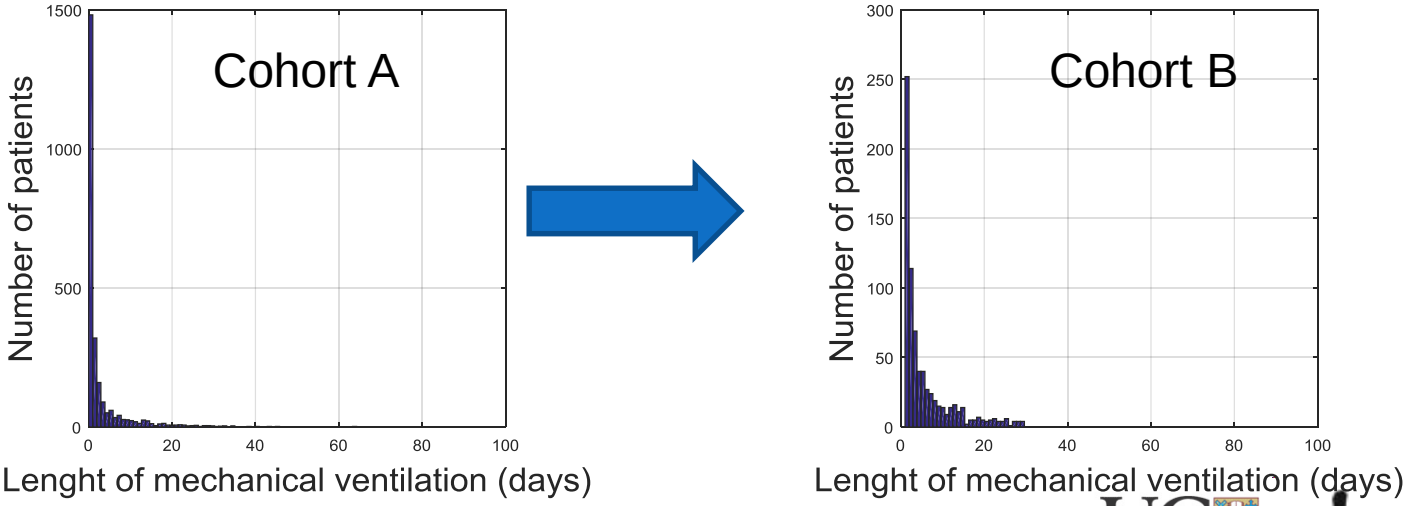
- Cohort B mean LoMV was 5.81 ± 6.30 days (median = 2.92 days [IQR: 1.67-7.38]),
- Significantly different from Cohort A ($p < 0.05$ using Student *t*-test and Wilcoxon ranksum test and Kolmogorov-Smirnov test).



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1.	Patient Cohorts	• Select a patient cohort: 1) Cohort A includes all invasively ventilated patients. 2) Cohort B is created from Cohort A by imposing exclusion criteria.	• Cohort A • Cohort B

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4.	Statistical Test	• Perform statistical test comparing the LoMV between two groups. • Using parametric and non-parametric tests. • A value of $p < 0.05$ is indicates that LoMV for intervention group is significantly different from control group.	• Student t-test • Student t-test (log scale) • Wilcoxon Ranksum test • Kolmogorov-Smirnov test

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5.	Power Analysis	• Each Monte-Carlo simulation iteration will generate a p-value for each statistical test. • For a given sample size and significance level α, statistical power is evaluated as the proportion of iterations for which the $p < \alpha$.	• E.g. for 10000 Monte-Carlo iterations, if $p < \alpha$ for 84% (8400 iterations), Power = 0.84.

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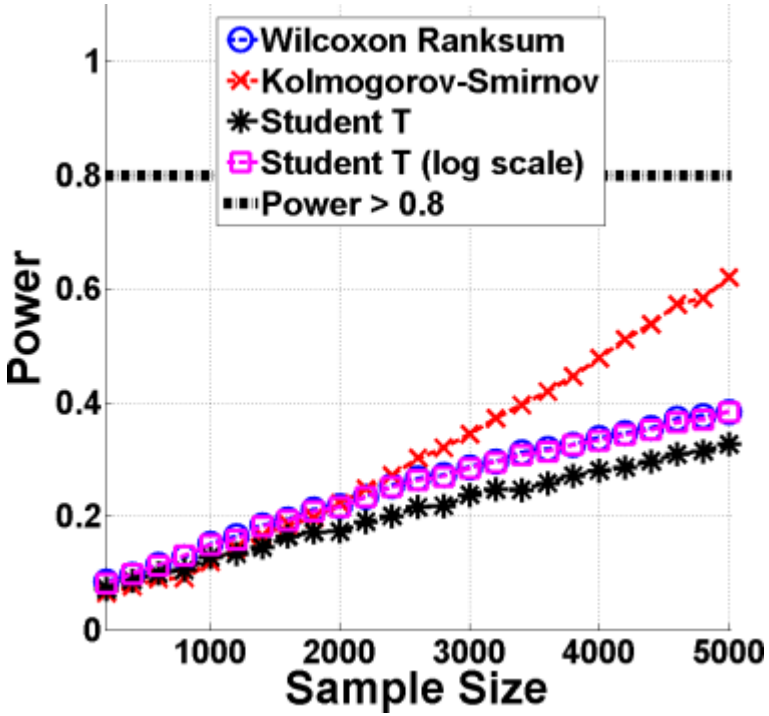

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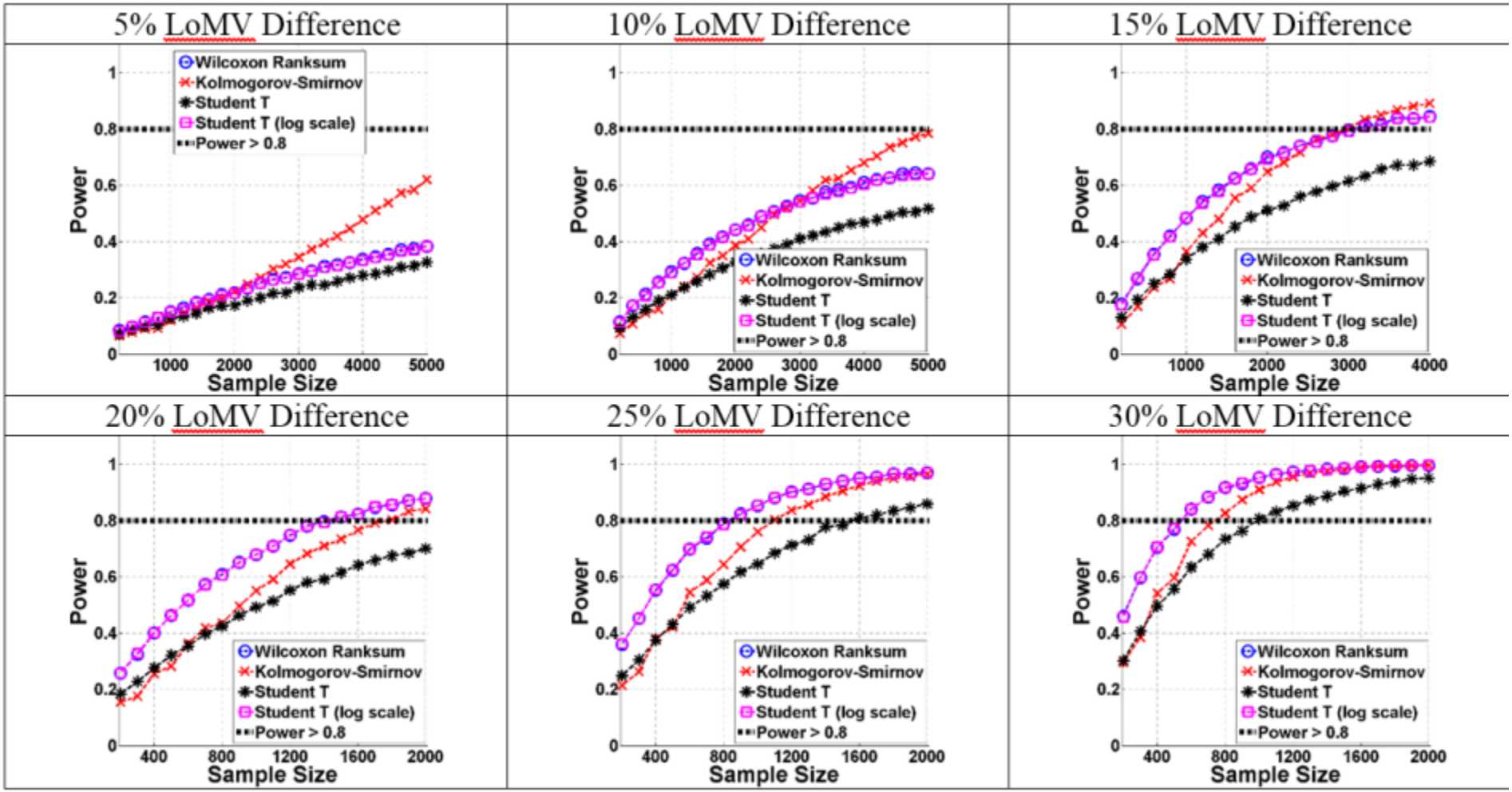

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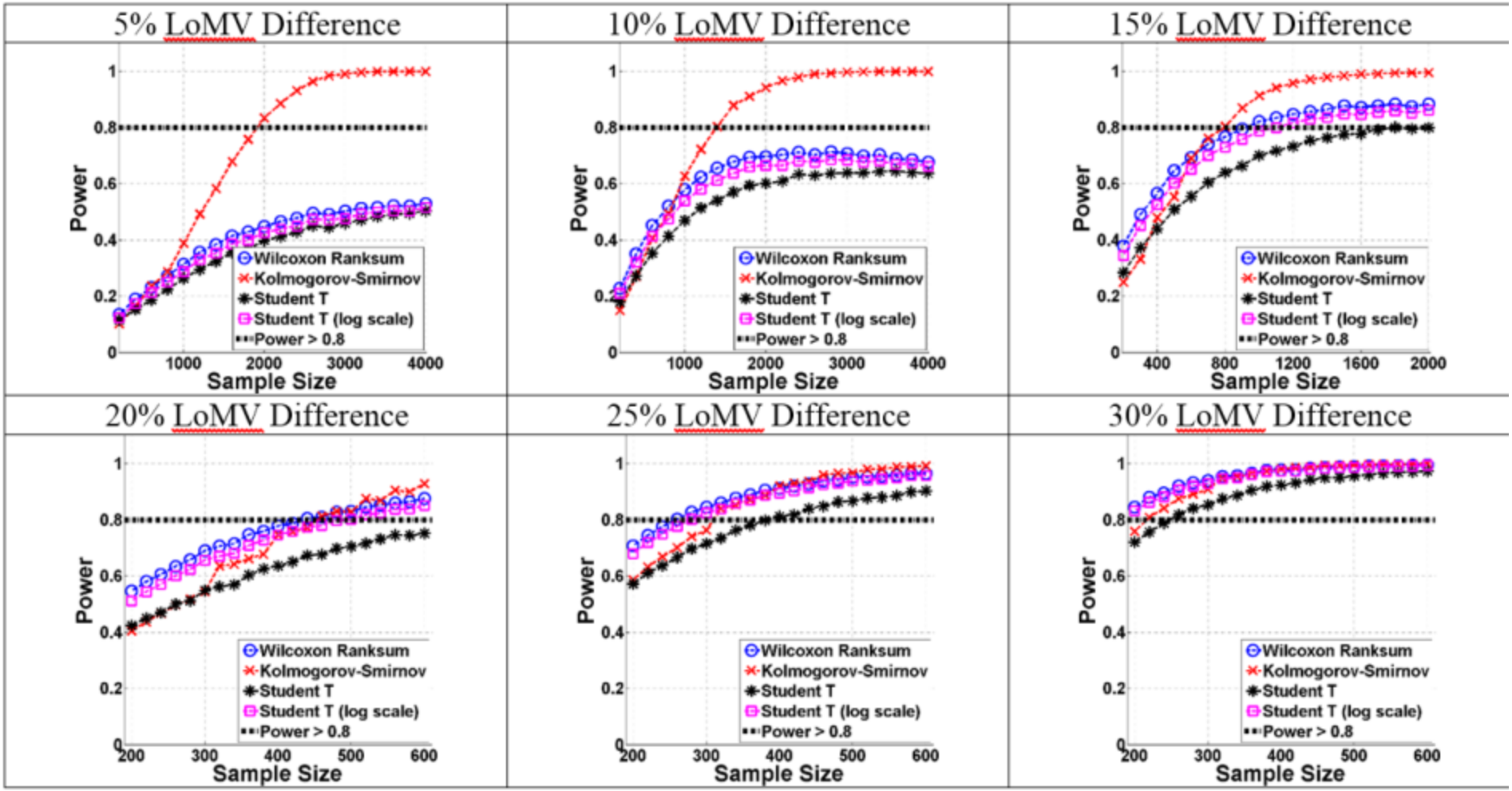

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Discussion

- One of the ideal inclusion criteria in other studies is to focus on patients with a more severe form of respiratory failure, such as the acute respiratory distress syndrome (ARDS).
- LoMV distributions may vary between centres (Van Der Lee et al., 2009). This variability in patient distribution means that the N_{total} derived from this study may only be applicable to the participating centre or other regional centres that have similar characteristics (Van Der Lee et al., 2009).
- The changes of LoMV used in this study were arbitrarily chosen and may not represent the true possible LoMV change for any given intervention (Schulz and Grimes, 2005).
- Thus, given the effective sample size and percentage difference in LoMV needed, the results suggest that the clinical outcome (LoMV) requires a large sample size due to the high variability in the population.

Final Thoughts

- Trial inclusion and exclusion criteria is important to capture the targeted group.
  - A specific group or,
  - A generalised group
- There are other co-founding factors that can affect MV deliveries.
  - Intention to treat
  - Protocol deviation
  - Effective protocol
  - MV is a supporting therapy

Acknowledgement

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Dankie Gracias
Спасибо شكراً Merci Takk
Köszönjük Terima kasih
Grazie Dziękujemy Dėkojame
Ďakujeme Vielen Dank Paldies
Kiitos Täname teid 谢谢
Thank You Tak
感謝您 Obrigado Teşekkür Ederiz
Σας Ευχαριστούμ 감사합니다
ขอบคุณ
Bedankt Děkujeme vám
ありがとうございます
Tack

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