EDITORIAL

# Composite Outcomes for Clinical Trials in Critical Care: The Devil is in the Detail

Saptharishi Lalgudi Ganesan[1], Narayanan Parameswaran[2]

**Keywords:** Acute respiratory distress syndrome, Clinical trials, Composite outcome measures, Ventilator-free days.
*Indian Journal of Critical Care Medicine* (2020): 10.5005/jp-journals-10071-23641

A composite outcome measure (COM) combines two or more distinct end points called component end points into a single outcome. As intensive care mortality dropped over the years, it became apparent that future randomized controlled trials (RCTs) would require a sample size of several thousands to be able to identify a mortality benefit. In the last three decades, researchers have been choosing COMs, which are continuous measures, as the primary end point for RCTs to decrease sample size requirements and improve precision.[1–3] For research on respiratory therapies and mechanical ventilation in critically ill patients with acute respiratory distress syndrome (ARDS), the COM of choice is the "ventilator-free days (VFD)". VFD combines survival and length of mechanical ventilation. However, there is significant heterogeneity in how VFD has been defined, described, and analyzed by researchers.[4] One of the important drawbacks of VFD is that it tries to combine a binary outcome measure (survival) with a continuous measure (duration of ventilation) and like any other COM does not adequately distinguish between the component risks. Therefore, it can give the erroneous impression that the intervention reduces both mortality and duration of ventilation which may be far from the truth in many cases. In addition, although it is often reported as "days", this is not the most accurate unit of VFD measurement. As the numerical value of VFD is a merger of the probabilities of death or ventilation on the defined day (day 28) with days free of ventilation among patients alive and free of the ventilator on the designated day (day 28),[5] some experts prefer to use the term VFD score instead of VFD.[5]

In this issue, Baranwal et al. utilize data from seven Indian pediatric RCTs to compare sample size requirements based on a primary outcome of VFD at 14 days and 28 days.[6] The authors elegantly argue that in low- and middle-income countries (LMICs), the early mortality from critical illness is still high and contributes to the bulk of the mortality, and therefore 14-day VFDs are more relevant to RCTs from LMICs. It is true that the time frame for assessing VFD should be such that most subjects will experience the outcome event within the time frame to minimize data skew. In that context, the time horizon chosen by Baranwal et al. may be appropriate for RCTs in LMICs, where a significant proportion of the reported mortality still occurs within the first week or so and the duration of ventilation is typically less than 2 weeks. To support their argument, they have performed *post hoc* analyses on these RCTs to evaluate the time-to-event and recalculated sample sizes with 14-day VFD as the primary outcome of interest.

The authors must be commended for choosing an unconventional yet important area of research. Clinician researchers in LMICs often do not question research methods, outcomes, and standards established and agreed upon by the developed, resource-rich countries. This may occur at the cost of feasibility, economic prudence, and good science. It is indeed refreshing to see that we have begun critically evaluating nuances of research methods, statistical approaches, and clinical outcomes as applicable to LMICs.

We must temper this enthusiasm with a modicum of caution while interpreting the results of this study. First, there could be diverging behavior of components of the COM in some cases. VFD operate under the assumption that interventions that improve respiratory physiology will decrease duration of ventilation and improve mortality. This assumption is particularly fragile in the context of LMICs where mortality is affected by a host of factors that may not impact length of mechanical ventilation such as healthcare associated infections. Second, mortality in critically ill patients continues to be high in LMICs and this component outcome is likely to unduly influence the COM, VFDs.

In this context, in LMICs, the RCTs on interventions in critically ill patients with ARDS may consider continuing to target survival as the primary outcome. If researchers determine that VFD is the most suitable primary outcome after careful deliberation, they should consider using a 14-day VFD, assigning weights to components, considering differential impact within a single event type and providing details of component end points in the final paper. In addition, when researchers are comparing VFDs in LMICs (as well as in other parts of the world), the distribution is likely to be skewed given zero inflation of VFDs. Therefore, it is important to use competing risk regression to assess VFDs as more than one mutually exclusive endpoint is possible with the use of such COMs.[1,7,8] Another approach is to use hierarchical composite end points, like alive and ventilator-free (AVF) score.[5] Hierarchical

[1]Department of Paediatrics, Schulich School of Medicine and Dentistry, Western University, London, Canada; Children's Hospital of Western Ontario, London Health Sciences Centre, London, Canada

[2]Department of Paediatrics, Jawaharlal Institute of Postgraduate Medical Education and Research, Puducherry, India

**Corresponding Author:** Narayanan Parameswaran, Department of Paediatrics, Jawaharlal Institute of Postgraduate Medical Education and Research, Puducherry, India, e-mail: narayanan.p@jipmer.edu.in

**How to cite this article:** Lalgudi Ganesan S, Parameswaran N. Composite Outcomes for Clinical Trials in Critical Care: The Devil is in the Detail. Indian J Crit Care Med 2020;24(10):903–904.

**Source of support:** Nil

**Conflict of interest:** None

outcomes address certain failings of simpler composite outcomes such as VFD through improved face validity and interpretability. AVF can facilitate more efficient performance of ARDS clinical trials without appreciable loss of power and may yield higher power when compared to the non-hierarchical composite outcomes, like the VFD.[5]

## References


1. Yehya N, Harhay MO, Curley MAQ, Schoenfeld DA, Reeder RW. Reappraisal of ventilator-free days in critical care research. Am J Respir Crit Care Med 2019;200(7):828–836.
2. Bodet-Contentin L, Frasca D, Tavernier E, Feuillet F, Foucher Y, Giraudeau B. Ventilator-free day outcomes can be misleading. Crit Care Med 2018;46(3):425–429.
3. Schoenfeld DA, Bernard GR, ARDS Network. Statistical evaluation of ventilator-free days as an efficacy measure in clinical trials of treatments for acute respiratory distress syndrome. Crit Care Med 2002;30(8):1772–1777.
4. Contentin L, Ehrmann S, Giraudeau B. Heterogeneity in the definition of mechanical ventilation duration and ventilator-free days. Am J Respir Crit Care Med 2014;189(8):998–1002.
5. Novack V, Beitler JR, Yitshak-Sade M, Taylor Thompson B, Schoenfeld DA, Rubenfeld G, et al. Alive and ventilator free: a hierarchical, composite outcome for clinical trials in the acute respiratory distress syndrome. Crit Care Med 2020;48(2):158–166.
6. Baranwal AK, Kumar-M P, Gupta PK. Comparison of ventilator-free days at 14 and 28 days as a clinician trial outcome in low- and middle-income countries. Indian J Crit Care Med 2020;24(10):960–966.
7. Andersen PK, Geskus RB, de Witte T, Putter H. Competing risks in epidemiology: possibilities and pitfalls. Int J Epidemiol 2012;41(3):861–870.
8. Wolkewitz M, Cooper BS, Bonten MJM, Barnett AG, Schumacher M. Interpreting and comparing risks in the presence of competing events. BMJ 2014;349:g5060.