Composite End Points of Death and Hospitalization Are the Only Appropriate Option for Most Trials

To the Editor:

We read with great interest the article by Collard et al in a recent issue of CHEST (November 2014) regarding the usefulness of composite end points of death or hospitalization in idiopathic pulmonary fibrosis. The authors highlight the large impact of the use of composite end points on statistical power and subsequent trial sample size.

Aside from statistical power considerations, we would like to comment on other methodologic aspects that deserve attention. Indeed, the use of hospitalization rather than hospitalization or death would result in very similar power because of the much higher hospitalization rates compared with mortality rates. In addition, the use of composite end points remains a matter of controversy. For instance, Montori et al suggested certain criteria required for their appropriate use, including the clinical relevance of individual components, the frequency of each component, as well as treatment effects on each component. Hence, why not use hospitalizations rather than composite end point, which would result in very similar power and would facilitate conclusions regarding treatment effect?

First, in keeping with previous reports from the clinical trial literature, since the conclusion of a trial is solely based on the primary end point, the latter should capture a treatment effect that is relevant to clinical practice. Importantly, trialists should fear treatment effects in the opposite direction. Since the decrease in hospitalization rates would hardly indicate clinical benefit if their reduction is gained at the expense of higher mortality rates, only the assessment of hospitalization and death is clinically relevant.  

Second, the high methodologic value of composite end points is related to competing risks. Indeed, when hospitalization alone is considered, noninformative censoring of death is hypothesized, which is an unverifiable and probably dangerous assumption. As highlighted in previous reports, traditional survival analysis overestimates the risk of morbidity event rates when the mortality rate is high. In this setting, the appropriate strategy is to model both events at the same time—a survival analysis strategy called the competing risk approach, such as the competing risk regression of Fine and Gray. Nonetheless, this strategy is more technically challenging and does not overcome the problem that arises from treatment effect in the opposite direction.

As a result, we strongly advocate for the use of composite end points in clinical trials when targeting all-cause death is not feasible. From our viewpoint, composite end points are the only appropriate option for most trials, which eventually prompted their use in several fields of medicine, including oncology and cardiology.

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FINANCIAL/NONFINANCIAL DISCLOSURES: The authors have reported to CHEST that no potential conflicts of interest exist with any companies/organizations whose products or services may be discussed in this article.

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DOI: 10.1378/chest.14-3246

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