Statistics in Medicine

(wileyonlinelibrary.com) DOI: 10.1002/sim.6581 Published online in Wiley Online Library

Use of composite endpoints in clinical trials

We thank Drs Guadalupe Gomez and Mateu Gomez (henceforth refer to as Gomez and Gomez) for their insightful retrospection into our paper on the use of composite endpoints in clinical trials regarding one of the major issues with the use of composite endpoints to address multiple endpoint problems in clinical trials.

From a theoretical viewpoint, we acknowledge that it is always possible to construct a test statistic that could show incremental gain in efficiency/power by combining highly correlated endpoints with homogeneous treatment effect versus individual ones. But from a practical clinical trial perspective (where the expectation is that highly correlated endpoints should exhibit similar treatment effect sizes), it would seem the natural and relevant question is 'is there an optimal correlation size (i.e. a point of inflexion) for optimal gain in efficiency of a test statistic?' Sankoh *et al.* [1] and Offen *et al.* [2] offered some examples that could provide some insight into the answer.

Sankoh *et al.* [3] clearly made the point that among the clinical expectations for the use of composite endpoints in clinical trials is that the composite endpoint result is not driven by what is considered to be the softest of the components. To some extent, Gomez and Gomez seem to ignore this point by focusing on the following: (1) the pairwise correlation between the softest of the components and the harder ones in their examples and (2) the one with even better treatment effect over what is already very strong treatment effect for the harder components. How does one know that the depicted incremental gain in efficiency is not purely the result of what looks like consistently strong treatment effect among the three components (i.e. not driven by the high correlation)? To answer that question, one needs to look at a simple (counter) example, one with heterogeneous treatment effects (at least where the softest of the components performs relatively worst compared with the harder ones). For even under the strong homogenous treatment effect examples considered by Gomez and Gomez, the figures provided no doubt show steady decrement in efficiency of the test as the (pairwise) correlation between the softest and harder components increases.

This is consistent with the statement by Sankoh *et al.* [3] that 'highly correlated components do not add much to trial efficiency compared with disparate or independent components'. The fact that the addition of a highly correlated component with better treatment effect provides incremental gain in the efficiency of the test does not contradict that statement, but rather more plausibly that the added component has a stronger treatment effect than the existing (and more clinically relevant) components.

So, to summarize, we do not see any contradiction between the statement in [3] and what Gomez and Gomez are saying. That is, we agree that to ascertain the clinical and statistical utility of components of a primary composite endpoint, one must (1) take into account the clinical relevance or meaningfulness of the components; (2) ensure the outcome on the composite endpoint is not primarily driven by the softer component(s); and (3) ascertain that for highly correlated components, homogeneous real treatment benefit is expected across the components for optimal test efficiency.

Abdul J. Sankoh
Synageva BioPharma
33 Hayden Avenue
Lexington, MA 02421, USA

Haihong Li
Merrimack Pharmaceuticals
One Kendall Square
Cambridge, MA 02139, USA

Ralph B. D'Agostino, Sr.
Boston University
111 Cummington Street
Boston, MA 02215, USA

References

1. Sankoh AJ, D'Agostino RB, Huque MF. Efficacy endpoint selection and multiplicity adjustment methods in clinical trials with inherent multiple endpoint issues. *Statistics in Medicine* 2003; **22**:3133–3150.
2. Offen W, Chuang-Stein C, Dmitrienko A, Littman G, Maca J, Meyerson L, Muirhead R, Stryszak P, Baddy A, Chen K, Copley-Merriman K, Dere W, Givens S, Hall D, Henry D, Jackson JD, Krishen A, Liu T, Ryder S, Sankoh AJ, Wang J, Yeh C-H. Multiple co-primary endpoints: medical and statistical solutions: a report from the multiple endpoints expert team of the pharmaceutical research and manufacturers of America. *Drug Information Journal* 2007; **41**:31–46.
3. Sankoh AJ, Li H, D'Agostino RB. Use of composite endpoints in clinical trials. *Statistics in Medicine* 2014; **33**:4709–4714.