

Secondary endpoints: surrogate interest or supplementary table?

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Provenance: This is a Guest Editorial commissioned by Section Editor Jianrong Zhang, MD (Department of Thoracic Surgery, First Affiliated Hospital of Guangzhou Medical University, Guangzhou Institute of Respiratory Disease, Guangzhou, China).

Comment on: Matthews JH, Bhandari S, Chapman SJ, *et al.* Underreporting of Secondary Endpoints in Randomized Trials: Cross-sectional, Observational Study. *Ann Surg* 2016;264:982-6.

Submitted Mar 07, 2017. Accepted for publication Mar 15, 2017.

doi: 10.21037/atm.2017.03.87

View this article at: <http://dx.doi.org/10.21037/atm.2017.03.87>

The article by Matthews and colleagues (1) emphasizes the potential impending consequences of underreporting secondary endpoints in studies addressing surgical site infection rates. Generally speaking, this may be a very crucial question about clinical trial methodology and rigor.

The value of the present study lies in the originality of their hypothesis and uniqueness of findings showing that secondary endpoint assessment (for surgical site infection) was associated with a significant reduction of accuracy and subsequent detection frequency compared with assessment as primary endpoint. According to their interpretation, such flaw may have severe effects on the interpretation of randomized studies and conducting meta-analysis.

Is the consequence of underreporting secondary endpoints a simple academic query or is it essential for research quality appraisal? In other words: “are secondary outcome measures really important in the global interpretation of a trial results, and should a reader rely on these outcomes in the decision-making process?”

To evaluate and justify if any new treatment may be adopted in clinical practice, physicians should ground their choice on the principles of evidence-based medicine, and strong evidences came from well-designed randomized trials. Among the numerous important methodological issues, the statistical power of a trial is fundamental to avoid underpowered findings and misleading analyses. The trail sample size has to be calculated on the primary endpoint and therefore, in this line of through, secondary outcomes may be of surrogate interest and ambiguous in the interpretation of evidences. In fact, a secondary endpoint

may result “significant” only because its incidence is higher than the primary outcome or vice versa not “significant” for a lower frequency. This substantially moderates the reliability of statistical calculation. However, there are opportunities for clinical interpretation. A secondary outcome should be judiciously evaluated and may be weighted if it is physiologically and clinically linked to the primary endpoint.

Another key issue is that the validity of any systematic review, such as this one (1), is mainly based on study inclusion and exclusion criteria. The authors selected the trials to be analysed on the impact factor (≥ 3) of the publishing journal. The question is whether we can fully trust the assumption—high impact factor journal equal to high quality randomized trial. By reading high impact factor journal it is not infrequent to find RCTs that are criticized for methodology or result interpretation in correspondence letters and invited comments. It is possible that well designed and conducted RCTs are published in low-ranking journal for several reasons that have nothing to do with quality. One for all is originality. An emblematic example is a trial designed to reproduce a previous study, with top-level originality, in order to validate or rebut earlier findings. A confirmative trial does not *per se* compromise the value of the study but the likelihood to be accepted in a high-ranking journal is quite low. It should be emphasized that only 17.5% (35/200) (2) of surgical journals have an impact factor ≥ 3 . Thus, this inclusion criterion of Matthews *et al.*, may have significantly limited the search strategy and trial selection. An additional hindrance is the policy of editors

to limit the length of manuscripts and number of tables and figures. Consequently, authors are often required to place secondary endpoints in supplementary materials, restricting the possibility of evaluation or interest of readers.

Nevertheless, we completely agree. Secondary endpoints should be described and reported with accuracy and highlighted in the main text of a manuscript because confidence in the overall positivity of a treatment may be enhanced if secondary outcomes also show benefit (or harm) and are consistent with the primary outcome measure.

As complementary to Matthews' review, we suggest reading a recent methodology article published in the *New England Journal of Medicine* by Pocock SJ and Stone GW (3). The authors suggest that the prespecified measure of success of a treatment merely based on the P value <0.05 of the primary endpoint of the trial, is not enough to evaluate the possible difference with a control arm. A more rational approach in the global interpretation of the results requires a careful examination of the totality of evidence, including secondary endpoints, safety issues, and size and quality of the trial. In this contest, the conclusions of Matthews and colleagues are commendable and stimulate

the upgrading of the quality of randomized trial reporting.

Acknowledgements

None.

Footnote

Conflicts of Interest: The authors have no conflicts of interest to declare.

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Cite this article as: Gianotti L, Sandini M. Secondary endpoints: surrogate interest or supplementary table? *Ann Transl Med* 2017;5(Suppl 1):S18. doi: 10.21037/atm.2017.03.87